

Handbook of Clinical Neurophysiology

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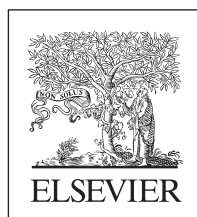
Volume 6

Clinical Neurophysiology of Sleep Disorders

Volume Editor

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Note

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Foreword

Clinical neurophysiology encompasses the application of a wide variety of electrophysiologic methods to the analysis of normal function and to the diagnosis and treatment of diseases involving the central nervous system, peripheral nervous system and muscles. The steady increase in growth of subspecialties in neurology has led to a need for a compilation of the whole range of physiologic methods applied in each of the major categories of neurologic disease. While some of these methods are applied to a single category of disease, most are useful in multiple clinical settings.

Each volume will be designed to serve as the ultimate reference source for academic clinical neurophysiologists and as a reference for subspecialists in the area. They will provide the information needed to fully understand the physiology and pathophysiology of disorders in their patients. As such these volumes will also serve as a major teaching text for trainees in that subspecialty.

The Handbook volumes will cover all of the clinical disorders served by clinical neurophysiology, including the epilepsies, autonomic dysfunction, peripheral nerve disease, muscle disease, motor system disorders, somatosensory system disorders, behavioral disorders, visual and auditory system disorders, and monitoring neural function. Each will focus on the advances in one of these major areas of clinical neurophysiology.

Each volume will include critical discussion of new knowledge in basic neurophysiology, approaches to characterization of disease type, localization, severity and prognosis with detailed discussion of advances in techniques to accomplish these. It is recognized that some techniques will be discussed in more than one volume, but with different focuses in each of them.

Each volume will include an overview of the field, followed by a section that includes a detailed description of each of the CNP techniques used in the category of disorders, and a third section discussing electrophysiologic findings in specific diseases. The latter will include how to evaluate each disorder along with a comparison of the relative contribution of each of the methods. A final section will discuss ongoing research studies, and anticipated future advances.

Our recognition of the high prevalence of sleep disorders and our increasing understanding of their variety of presentations make them a particularly appropriate early volume in this series. We are privileged to have one of the world's leaders in the clinical neurophysiology of sleep disorders as the volume editor. He has done a superb job of assembling other world leaders in the description of the neurophysiologic methods of testing and in their application to individual categories of disorders.

This volume defines the role of clinical neurophysiology in the study of disorders of sleep. It includes the physiology of sleep, and the role of clinical neurophysiology in assessing sleep with common and less common methods of testing. The epidemiology of sleep disorders and the wide range of neurophysiologic abnormalities associated with them are described, including disorders associated with other neurologic diseases.

Jasper R Daube
François Mauguière
Series Editors

Preface

Within the past 30 years, sleep medicine has emerged as a new medical discipline. Most of the technology used in sleep medicine is the same as that used by clinical neurophysiologists on a daily basis. The development of the electroencephalogram (EEG) and other polygraphic techniques as the primary descriptor of sleep and wakefulness was extraordinarily important in establishing the field of sleep medicine. These same techniques are used for our own current research.

The many neurons in our brain fire differently; not only during wakefulness compared to sleep but also between the two distinct sleep states (non-rapid eye movement (NREM) and rapid eye movement (REM) sleep). This suggests that what these many and varying neuronal networks control is different during each of these states. It is really important for all of us, particularly physicians, to understand the changes occurring with the different sleep states since the basic nervous system controls of vital functions may vary depending on the physiologic state of the brain. We must have a clear understanding of the normal processes of wakefulness and sleep to be in a better position to assess pathological conditions.

Historically, Henri Pieron's book *Le problème physiologique du sommeil* in 1913 and Nathaniel Kleitman's monograph *Sleep and wakefulness*, which was first published in 1939 and revised in 1963, are the first scholarly and comprehensive works in the field of sleep research. Investigations of pathology linked to sleep came out of two European clinical neurophysiology conferences. The first was under the guidance of Henri Gastaut and the French Society of EEG and Clinical Neurophysiology and resulted in publication of *Le sommeil de nuit normal et pathologique: études électroencéphalographiques* in 1965. The second conference was the 15th European EEG Society meeting organized in Bologna, Italy by Elio Lugaresi in 1967, which resulted in publication of the book *Abnormalities of sleep in man* in 1968.

These stepping stones led to the recognition of the importance of the dysfunction of sleep states and their impact on our health. We were able to recognize the many negative changes that sleep may bring to a sick patient. The recognition of the dependence of humans on an internal biological clock and awareness of chronopathology generated by modern society has added an important new element in sleep medicine.

The field is now well recognized. Epidemiological studies based on representative samples of the general population from the European and North America communities are available. Asian communities have started similar research. We have deciphered the genetic basis for circadian disorders such as long and short sleepers, and for advanced and delayed sleep phase syndromes. The genetic investigations of canine narcolepsy led to the discovery of a new modulating system distributed throughout the brain: the hypocretin/orexin system. We have progressed in the understanding of sleep in all age groups. The first normative data based on meta-analysis articles on sleep duration were published in 2004. Sleep medicine specialists along with sleep medicine training programs exist in different countries. In addition, clinical neurophysiology training programs in North America and Europe include education of sleep and its disorders.

This book has the problem of all textbooks: it is already outdated compared to the newest research. However, it represents a solid base on which to build. The contributors are internationally recognized specialists that deal on a daily basis with the clinical problems that they address here. We hope that this volume will be helpful not only to clinical neurophysiologists and sleep medicine specialists but also to all individuals who want to have an understanding of the fundamentals of sleep and its pathology.

Christian Guilleminault

Volume Editor

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CHAPTER 1

The physiology of sleep

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1.1. Introduction

1.1.1. Stages of sleep and wakefulness

First and foremost sleep is a brain process. Sleep is often described as a reversible state in which an individual has little or no response to environmental stimuli. Regardless of whether sleep is conceptualized as a process or as a state, it is multidimensional. That is, sleep is not just one process (or state); there are different kinds of sleep. Each type of sleep has its own regulatory mechanisms and presumably different functions. For example, selective deprivation of one type of sleep leads to preferential recovery of that type of sleep when sleep is permitted. The different types of sleep can be thought of as different overall organizational states of the nervous system, some involving increased brain activity and some involving decreased brain activity. While this may sound like neo-dualism, we are not implying that sleep is unimportant to the body. Some bodily processes depend completely on the brain entering one state of sleep or another. Moreover, as the nervous system's organizational state changes during the different states of sleep, concomitant physiological changes occur in the body. In the present chapter we will first describe alterations in brain activity associated with sleep. This will be followed by a description of physiological alterations in various organ systems associated with the different types of sleep.

1.1.2. Regulation of sleep

There are three basic mechanisms coordinating and governing sleep and wakefulness: (1) autonomic nervous system balance, (2) homeostatic sleep drive, and (3) circadian rhythms. These mechanisms maintain sleep and wakefulness in a dynamic balance. This active equilibrium provides the system with some extent of flexibility. Thus when the balance is upset, these mechanisms provide an avenue for the system to adjust and recover. This arrangement of regulatory mechanisms also provides a means by which an individual can adapt to sudden shifts in the time and duration of sleep.

1.1.3. Difference from stupor, coma and delirium

Like sleep, coma may result from diminished arousal and impairment of cognitive functions. Coma is the result of passive loss of function and metabolic depression in brain stem and cerebral cortex. Ironically, early theories of sleep postulated this process as responsible for sleep. We now know that sleep is an active process involving the interaction of brainstem and cerebral cortex characterized by continued brain oxygen utilization. Notably, sleep can be distinguished from coma by the rapid and complete reversal of any awareness deficit or consciousness impairment when the individual awakens.

Stupor is a state in which consciousness is diminished. It is now realized that alterations in consciousness may involve level, content, or both. Delirium represents a change in the content of consciousness whereas stupor usually involves reduced level of consciousness. The continuum for level of consciousness runs from wakefulness to drowsiness to stupor and finally to coma. Changes in content characteristically arise from diffuse cortical dysfunction; for example,

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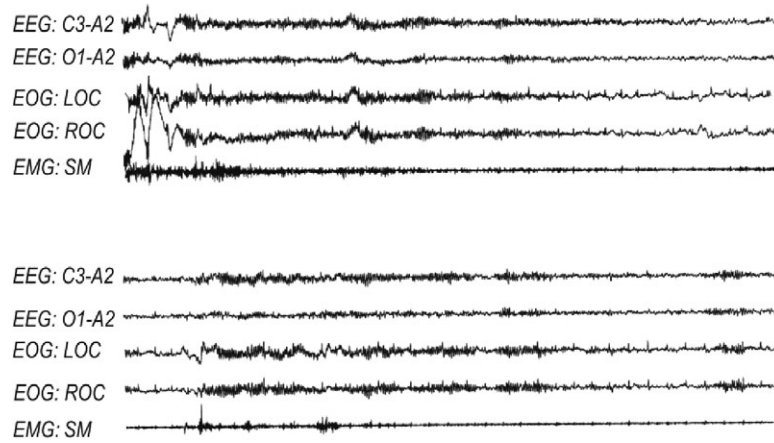


Fig. 1.1. Sleep-onset. Two examples of 30-second epochs showing sleep onset (at approximately three-quarters of the way through the tracing). Electroencephalogram (EEG) is shown from central monopolar mastoid-referenced (C3–A2) and occipital monopolar mastoid referenced (O1–A2) derivations. Electro-oculogram (EOG) is shown from left outer canthus (LOC) and right outer canthus (ROC) derivations. Electromyogram (EMG) from submentalis is also shown (SM).

metabolic encephalopathies. By contrast, changes in the level of consciousness can arise from brainstem lesions.

1.2. Central nervous system

1.2.1. Sleep vs wakefulness

1.2.1.1. EEG correlates

Before brain-recording techniques became available, sleep was mainly discussed in scientific and theoretical texts in terms of behavior. Generally, sleep was associated with rest and wakefulness with activity and these two states alternated. This theoretical construct was formalized by Kleitman as the Basic Rest Activity Cycle (BRAC) and continued as a fundamental construct even long after brain activity recording techniques developed. However, as soon as brain activity recording became possible, sleep was described in electroencephalographic terms by none other than Hans Berger (1930). He noted alpha rhythm disappearance when his test subject fell asleep. The operational definition for sleep-onset remains unchanged to this day: alpha EEG disappearance, generally recorded from an occipital derivation, defines the transition from wakefulness to sleep in a person whose eyes are closed and who is not engaged in challenging mental activity. Thus, the waking brain can be distinguished from the sleeping brain. This differential electroencephalographic (and presumably brain activity) correlate of sleep and wakefulness sets up the basic paradigm for studying human sleep and sleep disorders.

It was, however, noted early on that some individuals do not have clear alpha EEG activity. This makes determining sleep-onset more difficult. In such cases, other correlated electrophysiological activity must be used, including: EEG slowing, occurrence of a vertex sharp wave, cessation of blinking, presence of slow rolling eye movements, and/or diminution of submentalis electromyogram (EMG). Figure 1.1 shows examples of sleep-onset. Overall, regardless of the preceding activity, sleep-onset is marked by sustained low-voltage, mixed frequency EEG activity which is classified as Stage 1 sleep.

1.2.1.2. Neurophysiologic regulation

Hypothalamically generated motivation directs behavioral systems to perform actions designed to reduce drive. In this manner, homeostatic regulation of sleepiness parallels that for thirst, hunger and sex. Thus, sleepiness increases as a function of the duration of prior wakefulness (sometimes called process S) (Borbely, 1994). In general, the longer an individual remains awake, the sleepier he or she becomes. Prolonged wakefulness eventually makes sleep irresistible. The specific site underlying sleep's homeostatic process has not been identified; however, many models have been proposed. Kleitman, the dean of American sleep research, proposed that there was a build-up of neurotoxins during wakefulness that were removed by sleep. The complementary model was that neurotransmitters are used up during wakefulness and must be replenished by sleep, an idea harkening back to Shakespeare's notion of sleep 'knitting up the raveled sleeves

of care'. Of course, the battery is a popular metaphor with sleep playing the role of a recharging process.

Modern scientific investigation of specific models began with Bremer (1935) demonstrating sleep in response to lesioning cortical inputs. This 'deafferentation' model stood for 15 years until the Reticular Activation System (RAS) was described. The RAS's key maintenance of wakefulness role was demonstrated (Moruzzi and Magoun, 1949). These researchers also showed that RAS could promote wakefulness even without cortical inputs, thereby refuting the 'deafferentation' model. Subsequent work mapped out collateral sensory pathways providing RAS input and two main pathways through which the RAS activation is transmitted to forebrain and cortex. The first pathway is the nonspecific thalamocortical projection system, the second is the subthalamus, hypothalamus and basal forebrain route. The first pathway begins dorsally in medulla and connects locus coeruleus (LC) (noradrenergically mediated) to substantia nigra and then (dopaminergically mediated) to the ventral tegmental area and then (serotonergically mediated) to dorsal and median raphe. Projections continue to the laterodorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT) via cholinergic neurons. This pathway continues to nonspecific thalamic nuclei and diffusely to cortex. The second pathway begins ventrally in medulla, connecting to midbrain, subthalamus and hypothalamus and then continues on to basal forebrain, preoptic area and finally cerebral cortex.

Von Economo (1931) observed patients with 'encephalitis lethargica' and severe insomnia had extensive anterior hypothalamic lesions. Subsequent electrical stimulation and ablation studies identified anterior hypothalamus and the hypothalamic preoptic area as sleep-promoting and autonomic (parasympathetic) areas. The GABAergic VLPO connects with the histaminergic TMN (Sherin et al., 1998). Activity in the TMN also inhibits VLPO neuronal firing.

Most people pulling 'all nighters' (i.e., staying awake all night) describe a surge of energy at day-break. This common experience violates the homeostatic principle that sleepiness increases as a function of prior wakefulness duration. Specifically, when staying awake all night, at 8:00 a.m. a person has been awake longer than they were at 4:30 a.m.; nonetheless, they feel less sleepy. This reveals another factor governing sleep and wakefulness: the circadian rhythm (sometimes called process C) (Borbely and Achermann, 1992). The circadian rhythm is an approximate day-long rhythm (from the root 'circa' + 'dias' [approx-

mately a day]). The circadian pacemaker controlling the sleep-wake cycle is located in the suprachiasmatic nucleus (SCN). Because the core body temperature cycle is usually entrained to this sleep-wake oscillator, temperature is often used as a surrogate marker for circadian phase. Usually maximum alertness occurs at temperature peak with ensuing drowsiness as temperature begins falling. When temperature reaches its nadir, sleepiness can be overwhelming. Alertness improves as temperature starts rising. The cycle begins anew upon temperature reaching its peak (Ashcroft, 1965; Moore-Ede et al., 1982).

1.2.1.3. Neurobehavioral and neurocognitive correlates

Wakefulness is normally marked by responsiveness to the environment, consciousness, and the full array of cognitive abilities. Posture can be recumbent, seated, or erect and mobility is normal. Eyes can be open or closed. Perceived sensorium is a representation of the external reality. During sleep an individual has reduced or absent responsiveness to environmental stimuli. However, if a stimulus is of sufficient magnitude or if it is meaningful to the sleeper, it will likely provoke arousal and subsequent return to wakefulness. However, during sleep there may also be some responsiveness even below the arousal threshold. Consciousness and self-awareness are generally suspended during sleep; however, anxiety level can alter sleep-state perception. Posture during normal sleep is recumbent and eyes are closed. Perceived sensoriums vary greatly depending on what stage of sleep is occurring.

Sleep deprivation studies attempt to explore sleep's function by examining deficits produced by its loss. Not surprisingly, sleep loss increases sleepiness. Sleep loss also seems to diminish coping. Sleep-deprived individuals are notoriously irritable and easily frustrated. Sleep deprivation also adversely affects attention and leads to performance lapses (Dinges, 1992). Very prolonged sleep deprivation can, on rare occasion, produce seizures and may be associated with hallucinations, paranoia and mood swings. Because sleep deprivation is stressful, catecholamine turnover increases and cortisol level rises (Horne, 1988).

1.2.1.4. Neuropharmacology

The regulation of sleep and wakefulness can be viewed as a dynamic balance between alertness-promoting and sleep-promoting neurochemical systems. Two well-established hypothalamically based path-

ways underlying wakefulness promotion involve histaminergic and orexinergic (hypocretin) neurones. Tubulomammillary nucleus histaminergic neurons and lateral hypothalamus perifornical area orexinergic neurons have ascending projections to cortex, basal forebrain and midline thalamus (Vanni-Mercier et al., 1984; Lin et al., 1999; Xi et al., 2001). Descending pathways, especially from orexin neurons, connect to noradrenergic LC, serotonergic raphe and cholinergic LDT and PPT areas (Peyron et al., 1998).

The critical RAS ascending pathways to thalamus, hypothalamus and basal forebrain involve cholinergic, noradrenergic, dopaminergic, and histaminergic neurons. The LDT and PPT cholinergic cells fire at their highest rate during wakefulness. Dopaminergic neurons, especially in the forebrain bundle, appear to increase alertness. Overall, dopamine agonists (especially reuptake inhibitors) are somnolytic. By contrast, GABAergic cell complexes promote sedation and sleep. By contrast, GABA-A receptor agonists are generally somnogenic.

1.2.1.5. Imaging

Overall, imaging studies verify decreased cerebral blood flow, diminished brain oxygen consumption, and lower glucose metabolism associated with sleep onset compared to wakefulness. Brain metabolism on average declines 20–35% during nonrapid-eye-movement sleep. Sleep-related brain reduction in oxygen consumption far exceeds that in the rest of the body (by a factor of 5:1).

1.2.2. Sleep stage differences

1.2.2.1. EEG correlates

The human sleep pattern based on all-night, continuous electrophysiological recordings was first described in 1937 by Loomis, Harvey and Hobart (1937). The technological feat of recording all-night sleep EEG was accomplished using a specially designed 8-foot-long drum polygraph. To summarize miles of paper tracings these researchers created a data-reduction scheme called sleep staging. The sleep stage classification system (stages A, B, C, D and E) was largely based on predominant EEG activity within a fixed time domain, or epoch. EEG activity includes beta activity (>13 Hz), sleep spindles (12–15 Hz bursts), alpha rhythm (8–13 Hz, sometimes slower), theta rhythm (4–7 Hz, more common in adolescents than adults), saw-tooth theta waves (4–7 Hz, with notched appearance), delta rhythm (<4 Hz), and slow

waves (<2 Hz). As polygraph technology improved and scoring systems evolved, many variations of the 'Loomis system' were developed. The current Standardized System was developed by an ad hoc committee that included a veritable pantheon of prominent sleep researchers under the chairmanships of Drs Allan Rechtschaffen and Anthony Kales (1968). For the most part, the rules for scoring already existed as the Dement–Kleitman system and the Williams–Karacan system. Modifications simplified recording and improved scoring reliability. In the end, however, the critical ingredient was consensus.

In the Standardized System, EEG activity is recorded from central (C3 or C4) derivations, EOG activity from right and left eye (recorded from the outer canthi), and EMG from submentalis. In standard practice, each 30 seconds of recording is considered as 1 epoch. Often, occipital (O3 or O4) is added to the recording montage. The Standardized System defines stage 1 sleep as an epoch containing low-voltage mixed-frequency EEG with no K complexes, spindles or rapid eye movements. It is a non-alpha, state with EEG activity that is deltaless and spindleless; however, vertex sharp waves may be present. Stage 2 sleep is characterized by sleep spindles or K-complexes but high-amplitude (75 micro-volts, or greater) delta EEG activity may be present but for less than 20% of the epoch. Stage 3 is scored when 20–50% of an epoch has high-amplitude delta EEG (or slow-wave activity). Stage 4 is defined by predominant delta EEG (or slow-wave) activity, occupying 50%, or more, of an epoch (see Figure 1.3).

Eugene Aserinsky (1953), while working in Nathaniel Kleitman's laboratory in the early 1950s, noticed EOG activity suggesting rapid, jerky eye movements occurring during stage 1 when it naturally recurred after 90–100 minutes of sleep. Initially, this EOG finding was dismissed as recording artifact; however, continued efforts verified that actual eye movements were occurring. These jerky eye movements (JEMs, as Aserinsky called them) eventually became known as REMs (rapid eye movements) and lent its name to a unique sleep state. REM sleep is scored when rapid eye movements and muscle atonia accompanying a stage 1 EEG pattern. In addition to REMs, other electrophysiological correlates associated with REM sleep include saw-tooth theta EEG, middle ear muscle activity (MEMA), periorbital integrated potentials (PIPs) and sleep-related erections (SREs). Some REM sleep epochs have intense eye movement activity; at other times, few or no eye

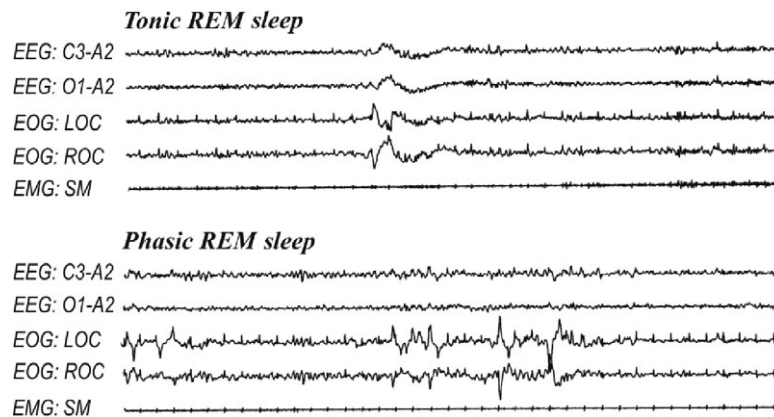


Fig. 1.2. Rapid eye movement (REM) sleep. An example of one 30-second epoch for tonic REM sleep and for phasic REM sleep. Electroencephalogram (EEG) is shown from central monopolar mastoid-referenced (C3–A2) and occipital monopolar mastoid referenced (O1–A2) derivations. Electrooculogram (EOG) is shown from left outer canthus (LOC) and right outer canthus (ROC) derivations. Electromyogram (EMG) from submentalis is also shown (SM).

movements occur. These two faces of REM sleep are called phasic REM sleep and tonic REM sleep (see Figure 1.2).

Sleep stage scoring involves dividing the recording into epochs and classifying each as wake or sleep stage 1, 2, 3, 4 or REM. Epoch length is a convention left over from procedures developed for paper polysomnographic tracings. These tracings were usually recorded at a chart speed of 10 mm/s; therefore, each resulting polygraph page was 30 s in duration. Because each polygraph page is numbered, it was a matter of convenience to summarize sleep state for each 30-s page. Notwithstanding the ability of computerized polysomnographic systems to easily resize pages and alter temporal resolution, the 30-s epoch remains.

Stages 1, 2, 3 and 4 are sometimes collectively referred to as NREM or non-REM sleep. Stages 1 and 2 are sometimes referred to as light sleep (LS) while stages 3 and 4 are often combined and called slow-wave sleep (SWS) or deep sleep (see Figure 1.3). Table 1.1 summarizes EEG–EOG–EMG characteristics for wakefulness and the different sleep stages.

A healthy young adult sleeper will have a 90–95% sleep efficiency; that is, 5–10% or less of the total time in bed will be spent awake. Sleep onset should occur swiftly (less than 15 minutes) and nocturnal awakenings should be few and brief. Stage 2 sleep usually accounts for approximately half the night's sleep and REM sleep will account for another 20–25%. A nightly total of 1–5% of stage 1 sleep will be distributed at the wakefulness–sleep transition and at light sleep transitions. The remaining sleep will be distrib-

uted between slow-wave sleep stages 3 and 4. Only minor differences are found for sleep stage distributions between young adult men and women. Figure 1.4 shows the nightly percentages for each stage.

The normal pattern involves repeated 90–120-minute-long cycles of NREM and REM sleep. With each cycle reoccurrence, systematic alterations in cycle properties occur. The progression and continuity of sleep through the sleep cycles on a given night is called sleep architecture. Figure 1.5 shows a typical night with normal sleep architecture in a healthy young adult. In general, (1) adult sleep begins with NREM sleep, (2) NREM and REM sleep alternate approximately every 90–120 minutes, (3) slow-wave sleep predominates in the first third of the night, (4) REM sleep predominates in the last third of the night, and (5) REM sleep occurs in 4–6 discrete episodes each night with episodes generally lengthening as sleep period progresses.

Sleep pattern changes as a function of aging. Total sleep time gradually declines over the lifespan. REM sleep percentage (of total sleep time) decreases from more than 50% at birth to 20–25% at adolescence. REM sleep then stabilizes; additional decline may occur after age 65 years. By contrast, slow-wave sleep begins declining post-adolescence and continues declining as a function of age, disappearing completely in some elderly individuals. Greater wakefulness intermixed with sleep (fragmentation) increases with age and the elderly spend more time in bed but less time sleeping than younger subjects. Some of the sleep disturbances associated with aging are pro-

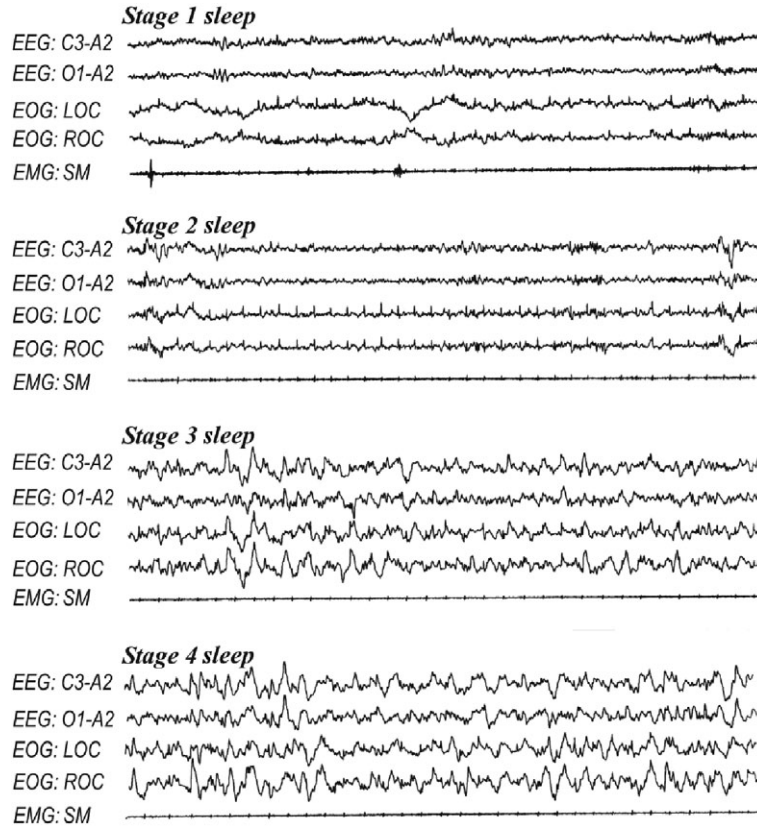


Fig. 1.3. NREM sleep. An example of one 30-second epoch for each NREM sleep stage (stage 1, stage 2, stage 3 and stage 4). Electroencephalogram (EEG) is shown from central monopolar mastoid-referenced (C3–A2) and occipital monopolar mastoid referenced (O1–A2) derivations. Electrooculogram (EOG) is shown from left outer canthus (LOC) and right outer canthus (ROC) derivations. Electromyogram (EMG) from submental is also shown (SM).

Table 1.1

EEG-EOG-EMG characteristics of sleep and wakefulness.

State or stage	Beta EEG	Alpha EEG	Spindle Activity	Delta EEG	Other EEG features	EOG	EMG muscle activity
Wakefulness	+	>50% of epoch	–	–		Slow and rapid	High
Stage 1 sleep	–	–	–	–	Vertex sharp waves	Slow	Decreased from W
Stage 2 sleep	–	–	+	<20% of epoch	K complexes	None	Decreased from W
Stage 3 sleep	–	–	+	20–50% of epoch		None	Decreased from W
Stage 4 sleep	–	–	+	>50% of epoch		None	Decreased from W
REM	+	+ bursts	–	–	saw-tooth theta waves	Rapid	Nearly absent

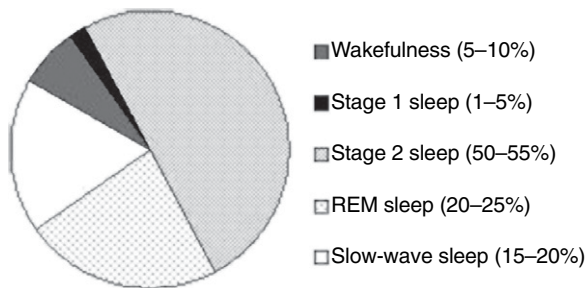


Fig. 1.4. Sleep stage percentages in a healthy young adult.

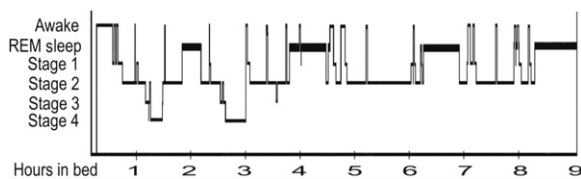


Fig. 1.5. Sleep stage histogram for a healthy young adult.

duced by increasing sleep-related pathophysiology (for example, arousals from sleep apnea). However, some proportion of age-associated sleep deterioration may directly relate to neurophysiological processes and not to secondary factors compromising sleep.

1.2.2.2. Neurophysiologic regulation

Sleep spindles, delta waves and slow cortical waves are the three waveforms characteristic of NREM sleep. Sleep spindles appear to be generated by GABAergic reticulothalamic neurons that create inhibitory postsynaptic potentials on thalamocortical neurons. By contrast, delta waves are cortically generated with input from thalamus. During NREM sleep RAS activation diminishes in response to thalamocortical hyperpolarization. Thus, NREM is marked by functional deafferentation produced by thalamocortical inhibition. Slow waves arise from cortical cells after prolonged depolarization and hyperpolarization and are prominent in frontoparietal regions (McCarley, 1994).

Jouvet and colleagues' transection studies demarcated REM-generating neurons as located in the pons. Through a series of brain-slicing studies it was concluded that the pons is sufficient and necessary to generate all signs of REM sleep (Jouvet et al., 1959; Siegel, 2000). Subsequent work discovered REM-on neurons in LDT and PPT (Mitani et al., 1988). LDT and PPT project to areas involved in PGO (pontine-lateral geniculate-occipital cortex) spike

generation (related to eye movement activity during REM sleep) (McCarley and Ito, 1983) and to thalamic, basal forebrain and cortical areas thought to produce REM-related EEG desynchronization.

1.2.2.3. Neurobehavioral and neurocognitive correlates

Slow-wave sleep is marked by very low responsiveness to the environment and very little consciousness. In all stages of sleep, posture is recumbent and eyes are closed. NREM sleep sensorium is fairly impoverished, except at the sleep-wake transition when elaborate hypnagogic or hypnapompic images may be present. At other times, simple images or shapes may appear.

During REM sleep, dreaming occurs. When referring to dreams here we mean visualized or narrated stories with characters, actions and plot. When REM sleep was first discovered, awakenings from REM sleep revealed dreaming on 20 of the 27 trials (Aserinsky and Kleitman, 1953). And thus, the EEG correlates of dreaming were established, arming researchers with a laboratory tool to unlock the mysteries Freud had called the 'the royal road to the unconscious', or so it was thought.

After many hundreds of studies attempted to exploit the REM-dreaming paradigm; no unified 'dream theory' emerged. Some Freudian concepts were verified (e.g., daytime residue) while others were not. The major competing modern theories are (1) the neurophysiologically based activation-synthesis hypothesis and (2) cognitive dream theory. The activation-synthesis hypothesis considers dreaming epiphenomenologic, created by a cortex trying its best to interpret incoming random subcortical activity. By contrast, the cognitive theories consider dreaming an extension of daytime thought albeit governed by different grammar and looser rules (Hobson and McCarley, 1977; Foulkes, 1982).

Jouvet introduced the concept that REM sleep was an important third state of nervous system organization and not just another component of the basic rest activity cycle (BRAC). During wakefulness the nervous system supports an active brain in an active body. Under normal circumstances, an individual is conscious of the surroundings and responsive to the environment. During sleep, for the most part, we lose our environmental responsiveness and become unconscious. Therefore, sleep was traditionally regarded as a deactivated (or inactive) brain in an inactive body. With the discovery of REM sleep muscle atonia (presumably accompanying dreaming), another organiza-

tional state could be postulated: an active brain in an inactive body.

1.2.2.4. Neuroparmacology

LDT/PPT neurons are cholinergic and act as REM-on cells. Serotonergic dorsal raphe nuclei and noradrenergic locus ceruleus (LC) neurons act as REM-off controllers. REM sleep atonia is mediated by the release of glycine which inhibits alpha motor neurons. PRF 'REM-on' neurones slowly activate 'REM-off' cells of the dorsal raphe (serotonergic), LC (aminergic) that then inhibit REM-on cells, thus producing the cyclical REM sleep pattern (McCarley, 1994). Orexin knockout mice and dogs manifest narcolepsy. Orexin neurons project to VLPO which may coordinated REM-NREM transitions.

At a cerebrocortical level, aminergic activity is high during wakefulness, decreases during NREM sleep, and reaches a very low level during REM sleep. In contrast to this stepwise reduction in activity from wakefulness to NREM to REM sleep, cholinergic activity is high during wakefulness and during REM sleep. It reaches its low point during NREM sleep.

1.2.2.5. Imaging

In general, cerebral blood flow, whole brain absolute CGMR, and oxygen consumption are lower during NREM sleep compared to wakefulness or REM sleep. Imaging also shows a correlation between increasing EEG slow-wave activity and brain metabolic rate. The largest decreases in brain activity during NREM sleep occur in frontal cortex, thalamus, brainstem reticular formation and cingulate gyrus.

Although whole brain metabolism for wakefulness and REM sleep are similar, localized patterns differ. Interestingly, REM sleep is associated with greater activity (compared to wakefulness) in limbic structures (especially cingulate and amygdala) and less activity in prefrontal cortex. Finally, cerebral glucose metabolism in oculomotor systems correlates with REM activity.

1.3. Autonomic Nervous System (ANS)

1.3.1. Sleep vs wakefulness

The solitary tract nucleus (NTS) arising from dorso-lateral medullary reticular formation and projecting to limbic forebrain structures is thought to modulate ANS activity during sleep. In general, sleep requires decreased sympathetic activation and increased

parasympathetic balance. Consequently, anything that increases sympathetic outflow can disturb sleep. The net effect is the same regardless of whether the sympathetic activation originates endogenously or exogenously (Hirshkowitz et al., 1997). That is, sleeplessness can result from drinking coffee at bedtime (exogenous) or anxious rumination (endogenous). This feature of autonomic regulation has survival value. When emergencies occur in the middle of the night, there needs to be a mechanism to promote quick response and sustained alerting. The survival value may be why autonomic activations commence rapidly but dissipates slowly. Unfortunately this mechanism may go awry and contribute to insomnia. If an individual gets 'worked up' about something right before bedtime, they may toss and turn for hours. 'Winding down' rituals can promote progressive relaxation with gradual reorientation away from daytime stressors. In children that sleep well, elaborate pre-sleep rituals are common. The ritual may include a bedtime story, a light snack, teeth brushing, prayers and having a favorite stuffed animal toy, pillow and blanket. The toy animal, pillow and blanket also provide stimulus cues for sleep-onset and likely facilitate conditioning. As an autonomic process, sleep-onset is amenable to classical conditioning. Pavlov was able to condition a dog to salivate by repeatedly pairing a ringing bell with food presentation (canines automatically salivate when food is present). Conditioning sleep-onset to the bed, pillow, blanket (or stuffed animal toy for children) occurs. However, in some cases a bedroom stimulus will cue an alerting response (producing psychophysiological insomnia). Similarly, if a parent becomes the child's stimulus cue for sleep-onset, the parent may have to rock the baby back to sleep at any and all times of the night.

1.3.2. Sleep stage differences

If we consider sympathetic and parasympathetic activity balance during the wake state, sleep-onset is marked by increasing parasympathetic tone. The overall autonomic tone increases parasympathetically as NREM sleep progresses. This process continues through tonic-REM sleep. By contrast, during phasic REM sleep, intermittent bursts of sympathetic activation occur, producing swings in blood pressure, irregular breathing, and overall cardiovascular instability. The progressive increase in parasympathetic activation can be observed using surrogate measures, such as pupillary constriction. During phasic REM sleep,

the transient sympathetic bursts are associated with pupillary dilation. Interestingly, direct measurement of sympathetic motor neurons reveal REM-related increased sympathetic activation. By contrast, skin sympathetic activation using electrodermal activity reveals activation during slow-wave sleep with a complete cessation during REM.

1.4. Endocrine

Endocrine function has been extensively studied during wakefulness and sleep. Endocrine function is affected both by the circadian and homeostatic mechanisms (Van Cauter, 2000). The following section summarizes endocrine changes during sleep.

1.4.1. Corticotrophin axis

ACTH and cortisol regulation is under circadian control. Cortisol's highest levels occur in early morning hours. During the day, cortisol levels remain low with the minimum level occurring in late evening and during the early part of sleep. This overall corticotropic axis activity pattern is not affected by the presence or absence of sleep; however, the sleep–wake homeostatic mechanism can change the amplitude of the activity by 15% (Van Cauter, 2000). Initiation of sleep can elongate the nadir period while awakening at the end of sleep period may increase the amplitude of the peak cortisol level (Weitzman et al., 1983). Therefore, a reverse effect is expected and seen during sleep deprivation. That is, sleep deprivation delays the return of corticotropic activity to its nadir and results in higher than baseline corticotropic activity the following night. Furthermore, sleep fragmentation and awakenings interrupting sleep are associated with corticotropic activity.

1.4.2. Growth hormone (GH)

GH secretion is stimulated by GH-releasing hormone (GHRH) and suppressed by somatostatin. Therefore, the balance between these two hormones determines the GH release. The GH secretion pattern is characterized by a low baseline level with abrupt pulses. GH regulation is primarily sleep-dependent. Sleep onset is associated with a GH secretion pulse regardless of its time of occurrence (Van Cauter and Plat, 1996). GH level and amount of slow-wave sleep correlate strongly. GH release, like slow-wave sleep, diminishes with advancing age (Mullington et al., 1996; Van

Cauter and Plat, 1996; Van Cauter, 2000). Furthermore, because GH is strongly sleep-dependent, awakenings and sleep fragmentation inhibit GH secretion. Nonetheless, circadian oscillation can affect GH secretion. GH secretion is higher during the early evening, even before sleep onset. This elevation reflects GHRH and somatostatin balance (Jaffe et al., 1995).

1.4.3. Thyroid function

Thyroid hormone secretion is controlled by thyrotropin (TSH). TSH secretion is under both circadian and sleep–wake homeostatic control (Brabant et al., 1990). TSH level is low during the day and it gradually rises in the evening and at the beginning of sleep (Chokroverty, 1999; Van Cauter, 2000). Afterwards it declines, returning to its low daytime level. In response to sleep deprivation, night-time TSH rises above the normal level suggesting that sleep suppresses TSH level; however, this effect is not sleep stage dependent (Chokroverty, 1999).

1.4.4. Prolactin secretion

Prolactin is regulated through a dopaminergic system, has sleep-dependent secretion, reaches its highest level during the sleep, and is lowest during the wake hours. Prolactin level begins rising after sleep onset and peaks in the early morning hours (5:00–7:00 a.m.). Prolactin secretion is temporally related to delta wave sleep. Morning awakening and sleep interruption during the night is accompanied by prolactin inhibition. Circadian oscillation also affects prolactin levels, albeit to a much lesser degree than sleep (Parsch et al., 1995). Circadian oscillation presents as the progressive prolactin level increases during the late afternoon and before sleep onset and is more pronounced in females than males (Desir et al., 1982; Waldstreicher et al., 1996). Maximal prolactin secretion occurs when the sleep and circadian effects are superimposed.

1.4.5. Glucose regulation

Sleep in humans represents a relatively long period of fasting, however, blood glucose level is usually maintained (Van Cauter, 2000). Studies of glucose regulation during sleep show a marked decrease in glucose tolerance during nocturnal sleep. With initiation of sleep, this tolerance decreases and reaches minimum level around the middle of the sleep period. After reaching minimum, glucose tolerance gradually increases

towards the awake level (Simon et al., 1987; Van Cauter et al., 1989). Decreased brain and peripheral glucose uptake is the main reason for the altered glucose tolerance (Boyle et al., 1994). Restoration of glucose tolerance in the second half of the sleep period is due to increased REM sleep (therefore increased glucose uptake by brain) and increased insulin sensitivity (resulting from low cortisol level) (Van Cauter, 2000).

1.4.6. *Other hormones*

A clear relationship between sex hormones and the sleep–wake cycle has not been found, however, gonadotropin levels rise during sleep in prepuberty and puberty stages (Wu et al., 1996). Testosterone's pulsatile release appears to have peaks near the NREM–REM transition. Parathyroid secretion is linked with cycles of slow-wave sleep and with peak occurrence every 100 minutes (Kripke et al., 1978). Hormones involved in salt and water metabolism include aldosterone, vasopressin and the renin–angiotensin system. Aldosterone level rises before awakening but vasopressin secretion appears unrelated to the sleep–wake cycle. By contrast, plasma renin level increases with slow-wave sleep.

1.5. The Respiratory System During Sleep

1.5.1. *Overview*

The major functions of respiratory system are to provide the body with the required oxygen and remove carbon dioxide produced during metabolism. In addition, the respiratory system is involved in acid–base regulation. Because O_2 and CO_2 are critical for survival, levels of these two gases are closely regulated. This regulation operates through a negative feedback loop. For example, elevated CO_2 increases ventilation, while hypocapnia decreases ventilation. The loop consists of gas exchange units (lungs), a pump (respiratory muscles including diaphragm, upper airway muscles and intercostal muscles), a controller (central nervous system), and the sensory and afferent elements relaying information from the respiratory system and blood to the controller.

Sensory elements of the respiratory system are divided to chemoreceptors and non-chemoreceptor components. The chemoreceptor component consists of peripheral and central chemoreceptors. The peripheral chemoreceptors in human are located in the carotid body that responds to changes in O_2 and CO_2

level in the blood. An estimated 30% of CO_2 chemosensitivity is provided by the peripheral chemoreceptors (Honda and Tani, 1999). The carotid body response to change in arterial pressure of CO_2 ($PaCO_2$) is linear. With hypercapnia, the firing rate of the carotid body increases. In contrast, the peripheral chemoreceptor provides 90–95% of hypoxic chemosensitivity (Honda and Tani, 1999). The carotid body response to reduction of arterial pressure of O_2 (PaO_2) is not linear. Instead, it responds linearly to arterial blood oxygen saturation. Concomitant hypercapnia and hypoxia have an additive effect on carotid body response. Furthermore, acidosis can stimulate the carotid body and augment the effect of hypercapnia and/or hypoxia on the carotid chemosensor.

The carbon dioxide level is mainly regulated by central chemoreceptors. These are located in the superficial layers of the ventral medulla (Mitchell, 1969). Furthermore, other deeper areas responsible for CO_2 chemosensitivity have been considered. The central chemoreceptor areas are sensitive to changes in H^+ concentration in the cerebrospinal fluid (CSF) and the medullary interstitial tissue. Carbon dioxide is a lipid-soluble gas and can pass through the blood–brain barrier. In CSF CO_2 reacts with H_2O to produce H^+ and HCO_3^- . Carbonic anhydrase accelerates this reaction. Change in the CO_2 concentration in blood affects the CSF H^+ concentration and through that stimulates or suppresses the respiratory generator. Therefore, by increasing the H^+ concentration in CSF, hypercapnia increases the rate and depth of breathing. The opposite effect is produced by hypocapnia.

The rhythmogenicity of the central respiratory controller is not known and is out of the scope of this chapter (Remmer, 1999). However, extensive research localizes the respiratory controller in the medulla oblongata and pons (Berger et al., 1977a, 1977b, 1977c; Mitchell and Berger, 1977; Von Euler, 1986). The rhythmic respiratory activity is generated by the central pattern generator (CPG) in the medulla. The CPG is defined as a neural circuit that generates a periodic rhythm with defined spatiotemporal characteristics in the absence of phasic sensory input. The medullary respiratory area consists of (1) the dorsal respiratory group (ventrolateral nucleus of tractus solitarius (NTS)) (Berger et al., 1977b, 1977c), and (2) the ventral respiratory group. The NTS is mainly involved with inspiration and its activity increases during inspiration. The ventral respiratory group consists of a group of neurons with inspiratory or expiratory activity. For example, nucleus ambiguus

innervates the muscles of upper airway. The pontine respiratory group is not necessary for generating respiration; however, it is involved in processing of vagal afferent and upper brain inputs (e.g., hypothalamus and cerebral cortex) (Von Euler, 1986). These inputs are integrated in the pontine respiratory group and then relayed to medullary centers.

Finally, the efferent arm of the feedback loop consists of motor output to the upper airway (especially the pharyngeal area), diaphragm, intercostal and abdominal muscles through phrenic and intercostal nerves. In summary, the respiratory system under control of the CPG in the medulla oblongata sustains ventilation and maintains O_2 and CO_2 within a normal range in the blood and tissue environment. The central controller through chemoreceptor and non-chemoreceptor sensors monitors O_2 , CO_2 and H^+ concentration in blood. Alterations in the level of these gases adjust ventilatory output. In situations with increased O_2 , CO_2 or H^+ demand, the respiratory controller increases ventilation. This in turn will restore the normal level of these gases. This negative feedback loop is the basis for automatic control of respiratory activity. The automatic control of ventilation is maintained regardless of the sleep or awake state of the animal. However, the respiratory controller activity can be affected by behavioral and voluntary input from a higher area of the brain, like cortex during the awake state and possibly rapid eye movement (REM) of sleep.

Activity of the respiratory controller differs in wakefulness and different stages of sleep. It is also affected by different disease conditions like cardiovascular or respiratory disorders. In the following sections we will review changes in respiratory system function with sleep.

1.5.2. Wakefulness vs NREM and REM sleep

With transition from wakefulness to NREM and REM sleep, alveolar ventilation and therefore, CO_2 and O_2 concentrations change. Ventilation is under automatic control during sleep. With initiation of sleep minute ventilation falls about 0.5–1.5 liters per minute (Hudgel et al., 1984; Chokroverty, 1999). The minute ventilation change with sleep is due to reduced CO_2 production and O_2 uptake, absence of wakefulness stimulus, reduced chemosensitivity and increased upper airway resistance. A similar reduction in minute ventilation is reported in REM sleep. The reduction of minute ventilation results in a 2–8 mmHg elevation of partial pressure of carbon dioxide ($PaCO_2$) up to

10 mmHg reduction in partial pressure of oxygen (PaO_2); and less than 2% reduction of oxygen saturation (Douglas et al., 1982; Chokroverty, 1999).

1.5.2.1. Upper airway

Upper airway patency depends on multiple factors, including anatomical characteristics, tonic and phasic upper airway muscle activity (Kuna and Remmers, 2000), and thoracic volume (Begle et al., 1990). Phasic upper airway muscle activity is regulated by the respiratory center. By contrast, tonic activity is independent of the respiratory center, depending instead on the general muscle tone (Krieger, 2000). With transition from wakefulness to NREM and from NREM to REM sleep, upper airway resistance increases. This increase is mainly in the palatal or hypopharyngeal areas (Lopes et al., 1983; Hudgel and Hendricks, 1988), is greater in snorers and obese subjects (Skatrud and Dempsey, 1985; Dempsey et al., 1996), is highest during REM sleep (Orem and Lydic, 1978), and is induced by diminished upper airway muscle phasic activity and loss of upper airway protective reflexes (Dempsey et al., 1996; Krieger, 2000). With transition into REM sleep, the tonic activity of the upper airway muscles diminishes further. Hence, upper airway occlusion is usually more prominent in REM sleep. In addition to reduced upper airway muscle activity, there is a breath-to-breath variation in the upper airway resistance during sleep. This variation is mainly due to change in sleep state and lung volume with sleep (Dempsey et al., 1997).

1.5.2.2. Lower airway

Lower airway resistance shows a circadian variation, especially in patients with asthma. In these patients, mild bronchoconstriction during sleep is reported (Kerr, 1973). Cough due to stimulation of airways is suppressed with sleep and only occurs with arousals (Douglas, 2000).

1.5.2.3. Respiratory pump

Input to respiratory muscles is controlled by the respiratory center in the brain stem through phrenic and intercostal nerves. The phasic activity of the respiratory pump is state dependent and therefore diminishes with initiation of sleep; however, phasic activity of the diaphragm is maintained. With progression of sleep into REM, the tonic component of the respiratory muscle pump decreases. The changes in muscle activity result in increased upper airway resistance and decreased minute ventilation.

1.5.2.4. Chemoreceptors

The hypoxic ventilatory response diminishes during sleep (Hedemark and Kronenberg, 1982). In NREM sleep, men show more reduction from wakefulness than women (White et al., 1982). This difference is mainly due to higher ventilatory drive during wakefulness in men. With progression to REM sleep, the hypoxic ventilatory drive further falls in both men and women (Douglas, 2000).

The hypercapnic ventilatory response diminishes about 50% with the transition from wakefulness to NREM sleep (Bulow, 1963; Douglas et al., 1982; Douglas, 2000). In REM sleep the ventilatory response falls even further; therefore, the lowest ventilatory response to hypercapnia occurs during REM sleep (Douglas et al., 1982).

Overall, with transition from wakefulness to NREM sleep, the wakefulness stimulus and voluntary control of ventilation are lost, leaving automatic control to prevail. In addition, CO₂ production and O₂ uptake diminish, upper airway resistance increases, chemoreceptor response to hypercapnia and hypoxia falls, and operating lung volume decreases. Subsequently, PaCO₂ rises and PaO₂ falls. Combination of these changes can produce respiratory instability and predispose to periodic breathing and obstruction of the upper airway during sleep. Loss of muscle tone with REM makes the upper airway more prone to obstruction.

1.6. The Cardiovascular System During Sleep

1.6.1. Overview

The cardiovascular system is closely regulated by the autonomic nervous system (ANS). The sympathetic nervous system (SNS) innervates atria, ventricles, sinoatrial and atrioventricular nodes and vasculature. SNS increases the heart rate, the ventricular contractility, and the peripheral vascular resistance, and reduces the atrioventricular conduction delay. The overall effect of the SNS is tachycardia, increased cardiac output, and increased systemic blood pressure. The parasympathetic (vagal) nervous system mostly innervates the atrium, and sinoatrial and atrioventricular nodes. Therefore, vagal stimulation reduces the heart rate, prolongs atrioventricular conduction, but does not have an appreciable effect on ventricular contractility or peripheral vascular resistance. The effect of the autonomic nervous system on cardiovascular function is the net balance of the two components of

ANS (Schlant et al., 1998). Changes in the cardiovascular system during sleep therefore, are mostly subsequent to alterations in ANS activity.

1.6.2. Wakefulness vs NREM vs REM sleep

1.6.2.1. Cardiac changes

With transition from wakefulness to NREM sleep, the SNS activity diminishes and parasympathetic (vagal) nervous system predominates (Mancia, 1993; Somers et al., 1993; Cherniak, 1999). As sleep deepens the vagal dominance increases.

1.6.2.2. Rhythm changes

NREM sleep is characterized by heart rate reduction due to vagal predominance (Khatri and Freis, 1967). The lowest heart rate occurs during the deepest stages of NREM sleep (slow-wave sleep). In contrast to NREM, REM sleep is characterized by episodic increases in heart rate due to heightened SNS activity on a backdrop of vagal predominance (Verrier et al., 2000). Additionally, during tonic REM, episodes of heart rate deceleration due to episodic increased vagal activity are seen. Arrhythmias observed during normal sleep include sinus pauses longer than 2 seconds (in 4–10%), sinus bradycardia with heart rate less than 40 (in 24%), first-degree atrioventricular block (in 8–12%), and Wenckebach second-degree AV block (in 6–11%) (Brodsky et al., 1977).

1.6.2.3. Pump changes

Cardiac output decreases at sleep-onset in normal sleep and continues to drop as sleep deepens. This reduction is mainly due to slowing of heart rate rather than any appreciable change in stroke volume (Khatri and Freis, 1967). However, during REM sleep with episodic changes in SNS, cardiac output varies.

1.6.2.4. Vascular changes

The vascular bed, and therefore regional perfusion, is under autonomic and local control. Mean arterial pressure, the driving force moving the blood in the circulation, is determined by cardiac output and peripheral vascular resistance. Both cardiac output and peripheral vascular resistance are tightly controlled by the ANS. The peripheral vascular bed receives innervations from SNS. Various vascular beds respond differently to changes in SNS. Blood flow change in different organs is dependent on sleep state change while the cerebral blood flow changes are tied to its various functions during different sleep states (flow-metabolism coupling) (Franzini, 2000).

Cerebral and spinal blood flow is lower than wakefulness during NREM sleep. This reduction in cerebral blood flow is due to change in vascular resistance and is independent of systemic hemodynamic changes. With transition to REM, cerebral blood flow to brainstem, thalamus and basal forebrain, and spinal blood flow increase (Franzini, 2000). Cerebral blood flow to cortical areas is variable. In general, cerebral blood flow continuously decreases during the night and has the lower values after awakening compared to pre-sleep (Braun et al., 1997). This is consistent with the theory proposing a restorative action to sleep.

Blood flow in other organs mainly is affected by ANS changes. The local blood flow decreases with the transition from wakefulness to NREM sleep. With REM sleep episodic changes in SNS activity cause a fluctuation in local blood flow. Specifically, coronary blood flow increases with phasic episodes of sinus tachycardia seen during REM sleep. This indicates that coronary blood flow is controlled both by ANS activity and is responsive to local metabolic demand.

1.6.3. Cardiovascular–respiratory interaction

Control mechanisms that regulate cardiovascular and respiratory systems are connected and affected by each other. As described in the previous section, regulation of breathing is under a negative feedback loop control (Khoo, 2000). It is well known that heart failure results in unstable respiratory control and causes periodic breathing and other forms of sleep-related breathing disorders (Javaheri et al., 1998; Lanfranchi and Somers, 2003). Conversely, the effect of breathing on the heart rate (sinus arrhythmia) is well studied. The cardiovascular system affects respiration through both circulation and neural reflexes. Any change in alveolar gas tension should be transferred to peripheral and central chemoreceptors before producing any change in ventilation. Circulation time therefore can affect the phase delay with which the changes in alveolar gas tension will be sensed by the chemoreceptors. Both cardiovascular and respiratory neural centers are located in the dorsal area of the medulla oblongata. In addition, it is proposed that activation of cardiac vagal afferents may affect respiration centrally (Garrigue et al., 2004).

In summary, cardiovascular changes seen in the transition from wakefulness to NREM and to REM sleep is mainly mediated by a change in autonomic nervous system activity. With the initiation of sleep, sympathetic reduction and vagal dominance result in slowing of the

heart rate, a drop in cardiac output and peripheral vascular resistance. Blood flow to various tissues including the central nervous system decreases with NREM sleep. During phasic REM sleep, cerebral blood flow to the brainstem, and coronary blood flow increase, indicating a coupling between metabolic need and blood flow.

1.6.4. Overview of alterations associated with sleep disorders

In contrast to normal sleep, in sleep-related breathing disorders, respiratory events with resulting hypoxia may cause significant bradycardia (Miller, 1982). Furthermore, hypoxia and arousals lead to fluctuations of arterial pressure and heart rate due to increased sympathetic activity (Coccagna et al., 1971; Tilkian et al., 1976). This combination of events can lead to cyclical episodes of bradycardia in the early phase of respiratory events followed by tachycardia during the later stages of respiratory events and at post-event stages. In addition to this cyclical fluctuation in heart rate, various cardiac arrhythmias are also seen. These include prolonged sinus arrest (up to 13 seconds in duration), Mobitz type II second-degree AV nodal block, ventricular ectopy, bigemini, and rarely more severe ventricular arrhythmias (Harbison et al., 2000). In addition to changes in cardiac rhythm, several studies report a reduction in cardiac output caused by decreased stroke volume and heart rate with respiratory events during sleep (Tolle et al., 1983; Guilleminault et al., 1986; Stoohs and Guilleminault, 1992; Garpestad et al., 1992).

1.7. The gut during sleep

1.7.1. Overview

Gastrointestinal tract activity is controlled by both the autonomic and enteric nervous systems. The enteric nervous system (ENS) consists of complex neural networks in the walls of hollow visceral GI organs. The ENS regulates movement of the GI tract. In addition to the ANS and ENS, higher CNS centers interact with these two systems and affect GI tract activity. With the initiation of sleep this cortical influence is lost and the GI tract activity is regulated by the ENS and ANS.

1.7.2. Esophageal functions

Esophageal function changes with sleep. Frequency of primary (post swallowing) and secondary (sponta-

neous) peristaltic movements of esophagus is reduced with sleep and is stage dependent (Castiglione et al., 1993). Upper esophageal sphincteric function is maintained during sleep (Kahrilas et al., 1987). In contrast, lower esophageal sphincteric function may change with sleep. Gastroesophageal reflux (GER) consists of episodes of acid regurgitation into the esophagus. During normal sleep GER is infrequent (Orr et al., 1984). However, acid clearance from the esophagus is slower during sleep compared to wakefulness. This slowing is due to reduced swallowing and salivary flow with sleep (Orr, 2000). The majority of GER episodes during sleep occurs because of a fall in the lower esophageal sphincter tone (Dent et al., 1980). However, some of the GER episodes occur due to increased intra-abdominal pressure resulting from arousal caused by cough, change in position or swallowing.

1.7.3. Gastric function

Basal acid secretion follows a circadian oscillation and is highest between 10:00 p.m. and 2:00 a.m. (Moore and Englert, 1970). Sleep effect, if any, on basal acid secretion is not clear (Orr, 2000). Multiple studies showed that acid secretion is variable from night to night and person to person. Interestingly, acid secretion during sleep is much higher in subjects with duodenal ulcer and improves with vagotomy (Dragstedt, 1956).

Studies on gastric motility during sleep have produced inconsistent results (Chokroverty, 1999; Orr, 2000). It appears that gastric motor function diminishes during sleep. However, it is not clear if this is due to sleep or a circadian variation.

1.7.4. Small intestinal motility

Studies on small intestinal motility like the ones on gastric motility have produced controversial and often conflicting results (Chokroverty, 1999). The motor activity of the intestine produces a special pattern named migrating motor complex (MMC). MMC has a 90-minute cycle, similar to, but independent from, REM sleep. The speed with which MMC propagates through the intestinal tract follows a circadian rhythm with its slowest velocity in sleep (Orr, 2000).

Interestingly, contraction of the gastrointestinal tract lumen induces sleepiness. Orr and colleagues showed that sleep latency is significantly shorter after a solid meal than an equal volume of water (Orr et al., 1997).

1.7.5. Colonic and anorectal activity

Colonic contractile and myoelectric activity diminish during sleep (Naducci et al., 1987). With awakening these activities increase. This may explain the urge for defecation upon awakening in mornings (Orr, 2000). However, sudden awakening may induce a pattern of segmental rather than propagating colonic contraction.

Rectal motor activity is increased with sleep. In addition, the majority of cyclical rectal motor activity is retrograde during sleep. This pattern of activity during sleep prevents stool leakage during sleep (Rao and Welcher, 1996; Orr, 2000).

1.8. The genitourinary system during sleep

All healthy, sexually potent men have a cycle of penile erections that occur during sleep (Hirshkowitz et al., 1991; Ware and Hirshkowitz, 1992). Sometimes called nocturnal penile tumescence (NPT), the currently preferred term in sleep medicine is sleep-related erections (SREs). SREs are naturally occurring and involuntary. SRE episodes are closely coupled temporally to rapid eye movement (REM) sleep. An SRE episode begins near the transition from NREM to REM sleep, quickly increases to full tumescence, persist throughout the REM sleep episode, and rapidly shrinks to the flaccid state when NREM sleep recommences.

Karacan and associates studied SREs in young boys, young adults, middle-aged men and the elderly. SREs are very consistent. Normative studies find SREs in all subjects in all age groups (Karacan et al., 1975). Results have been replicated and confirmed (Reynolds et al., 1989; Ware and Hirshkowitz, 1992). Little or no age-related decline occurs in maximum circumference increase and number of erection episodes. Overall, small age-related decline is sometimes found for total tumescence time.

An analogous phenomenon occurs in women. Clitoral and nipple erections, increased vaginal blood flow, and increased uterine contractility all occur during REM sleep, however, recording techniques are not as well developed for overnight monitoring and consequently much less is known.

1.9. When things go awry: abnormal sleep

Understanding what constitutes normal sleep is essential to recognize and assess the severity of abnormal sleep. Better normative data are sorely needed. Sleep

disturbances can be evaluated objectively and quantitatively. Pathophysiology leading to disturbed sleep (for example, periodic leg movements provoking awakenings) are one way disorders adversely affect sleep. Other sleep disorders are characterized by defective or impaired mechanisms regulating sleep. For example, a weak homeostatic drive for alertness would likely produce chronic hypersomnia; whereas, the intrusion of REM sleep phenomena into the waking state underlies narcolepsy; the displacement of circadian rhythms by rapid travel across time zones produces jet-lag. Hundreds of sleep laboratories studying abnormal sleep make recordings every night. The polysomnograms being recorded digitally can easily be preserved in their entirety. If every major sleep laboratory contributed one polysomnogram, recorded according to standard protocol, for a healthy adult (male or female) we would not only be able to better gauge normal sleep. We would also have improved understand of abnormal sleep. In the meanwhile, we can use available actuarial information and our basic understanding of the sleep process.

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CHAPTER 2

NREM–REM sleep

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2.1. Introduction

Sleep is comprised of two distinct states known as non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is subdivided into four stages: stage 1, stage 2, stage 3 and stage 4. Stages 3 and 4 are collectively referred to as slow-wave sleep. REM sleep may be subdivided into two stages: phasic and tonic. NREM and REM sleep are associated with dynamic changes in the autonomic nervous system and immune system. The purpose of this chapter is to provide the reader with an overview of the salient features of NREM sleep and REM sleep.

2.2. Sleep architecture

2.2.1. NREM sleep

NREM sleep accounts for 75–80% of sleep time. Stage 1 NREM sleep comprises 3–8% of sleep time. Stage 1 sleep occurs most frequently in the transition from wakefulness to the other sleep stages or following arousals during sleep. In stage 1 NREM sleep, alpha activity, which is characteristic of wakefulness, diminishes and a low-voltage, mixed-frequency pattern emerges. The highest amplitude electroencephalography (EEG) activity is generally in the theta range. Electromyography (EMG) activity decreases and electro-oculography (EOG) demonstrates slow rolling eye movements. Vertex sharp waves are noted towards the end of stage 1 NREM sleep.

Stage 2 NREM sleep begins after approximately 10–12 minutes of stage 1 NREM sleep and comprises

45–55% of total sleep time. The characteristic EEG findings of stage 2 NREM sleep include sleep spindles and K complexes. Delta waves in the EEG may first appear in stage 2 NREM sleep but are present in small amounts. The EMG activity is diminished compared to wakefulness.

Stage 3 and 4 NREM sleep occupy 15–20% of total sleep time and constitute slow-wave sleep. Stage 3 sleep is characterized by moderate amounts of high-amplitude, slow-wave activity; whereas, stage 4 sleep is characterized by large amounts of high-amplitude, slow-wave activity. EOG does not register eye movements in stages 2–4 NREM sleep. Muscle tone is decreased compared to wakefulness or stage 1 sleep (Rechtschaffen and Kales, 1968).

2.2.2. REM sleep

REM sleep accounts for 20–25% of sleep time. The first REM sleep episode occurs 60–90 minutes after the onset of NREM sleep. EEG tracings during REM sleep are characterized by a low-voltage, mixed-frequency activity with slow alpha (defined as 1–2 Hz slower than wake alpha) and theta waves.

Based on EEG, EMG and EOG characteristics, REM sleep can be divided into two stages, tonic and phasic. Characteristics of the tonic stage include a desynchronized EEG, atonia of skeletal muscle groups and suppression of monosynaptic and polysynaptic reflexes. Phasic REM sleep is characterized by rapid eye movements in all directions as well as by phasic swings in blood pressure, heart rate, irregular respiration, tongue movements and myoclonic twitching of chin and limb muscles (Baust et al., 1972; Chokroverty, 1980; Orem, 1980; Oksenberg et al., 2001). Sawtooth waves, which have a frequency in the theta range, often occur in conjunction with rapid eye movements. A few periods of apnea or hypopnea may occur during REM sleep.

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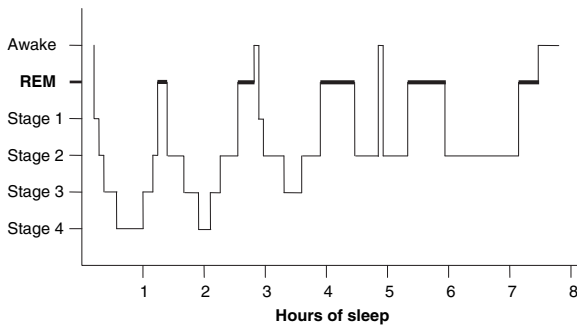


Fig. 2.1. Young adult hypnogram.

2.2.3. NREM-REM cycle

The NREM-REM sleep cycle occurs every 90 minutes and approximately 4–6 cycles occur per major sleep episode. The ratio of NREM sleep to REM sleep in each cycle varies during the course of the night. The early cycles are dominated by slow-wave sleep and the later cycles are dominated by REM sleep. The first episode of REM sleep may last only a few minutes and subsequent REM episodes progressively lengthen in duration during the course of the major sleep period. In summary, slow-wave sleep is prominent in the first third of the night and REM sleep is prominent in the last third of the night. The temporal arrangement of sleep type is described graphically by a hypnogram (Figure 2.1).

2.3. Neurophysiology

2.3.1. NREM sleep

The transition from wakefulness to NREM sleep is associated with altered neurotransmission at the level of the thalamus whereby incoming messages are inhibited and the cerebral cortex is deprived of signals from the outside world. NREM sleep is characterized by three major oscillations (Figure 2.2). Spindles (7–14 Hz) are generated within thalamic reticular neurons that impose rhythmic inhibitory sequences onto thalamocortical neurons. However, the widespread synchronization of this rhythm is governed by corticothalamic projections. There are two types of delta activity (Steriade et al., 1993a,b). The first type is clock-like waves (1–4 Hz) generated in thalamocortical neurons and the second type is cortical waves (1–4 Hz) that persist despite extensive thalamectomy. However, the hallmark of NREM sleep is the slow oscillation (<1 Hz), which is generated intracortically

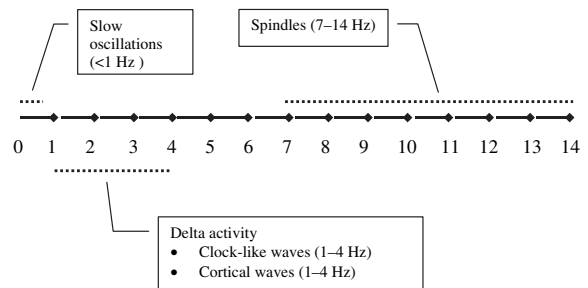


Fig. 2.2. NREM sleep oscillations.

and has the ability to group the thalamically generated spindles as well as thalamically and cortically generated delta oscillations, leading to a coalescence of the different rhythms (Amzica and Steriade, 1998; Steriade and Amzica, 1998). NREM sleep oscillations, particularly spindles, produce synaptic plasticity in target cortical neurons and resonant activity in corticothalamic loops (Steriade and Timofeev, 2003).

Upon arousal from NREM sleep, the spindles are blocked by inhibition of thalamic reticular neurons, the clock-like delta rhythm is abolished by depolarization of thalamocortical neurons; and the cortically generated slow oscillation is eliminated by selective erasure of its hyperpolarizing components (Steriade, 1994). Fast beta and gamma oscillations are suppressed by the depolarizing effects of mesopontine cholinergic neurons acting on thalamocortical neurons and nucleus basalis neurons acting on cortical neurons (Steriade, 2003).

2.3.2. REM sleep

Transection studies demonstrate that the pontomesencephalic region is critical for REM sleep generation (Siegel, 2000). When the mesopontine region is connected to rostral structures, REM sleep phenomena such as a desynchronized EEG and ponto-geniculo-occipital (PGO) spikes are seen in the forebrain. When the mesopontine region is continuous with the medulla and spinal cord, REM sleep phenomena such as skeletal muscle atonia can be seen.

The pontomesencephalic area contains the so-called cholinergic 'REM-on' nuclei, specifically the pedunculopontine tegmental (PPT) and laterodorsal tegmental (LDT) nuclei. The LDT and PPT nuclei project through the thalamus to the cortex, which produces the desynchronization of REM sleep. PGO spikes are a precursor to the rapid eye movements seen in REM sleep and are formed in the cholinergic

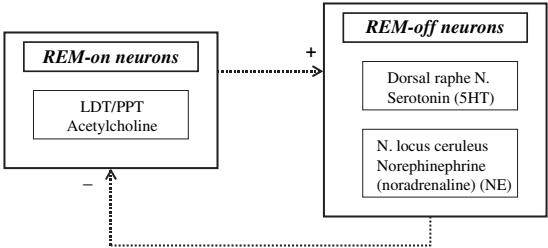


Fig. 2.3. NREM-REM reciprocal interaction model.

mesopontine nuclei and propagate rostrally through the lateral geniculate and other thalamic nuclei to the occipital cortex (Steriade et al., 1990). The LDT and PPT nuclei project caudally via the ventral medulla to alpha motor neurons in the spinal cord where skeletal muscle tone is inhibited during REM sleep by the release of glycine (Holmes and Jones, 1994). In addition, as NREM sleep transitions to REM sleep, tonic inhibition of REM-generating cholinergic pontomesencephalic nuclei by brainstem serotonergic and adrenergic nuclei decreases, thereby allowing the development of PGO spikes and muscle atonia (Aston-Jones and Bloom, 1981). Thus, the cholinergic ‘REM-on’ nuclei of the PPT and LDT slowly activate the monoaminergic ‘REM-off’ nuclei of the dorsal raphe and locus ceruleus which in turn inhibit ‘REM on’ nuclei (Figure 2.3).

Hypocretin has an important role in the modulation of wakefulness and REM sleep (Bourgin et al., 2000). Hypocretin neurons are located in the lateral hypothalamus and widely project to brainstem and forebrain areas, densely innervating monoaminergic and cholinergic cells. Hypocretin neurons promote wakefulness and inhibit REM sleep (Estabrooke et al., 2001). Elevated levels of hypocretin during active waking and in REM sleep compared to quiet waking and slow-wave sleep suggest a role for hypocretin in the central programming of motor activity (Kiyashchenko et al., 2002). Hypocretin projections to the nucleus pontis oralis may play a role in the generation of active sleep and muscle atonia (Xi et al., 2002).

2.4. Autonomic nervous system

The autonomic nervous system (ANS) regulates the vital functions of internal homeostasis. The ANS is comprised of the sympathetic nervous system and parasympathetic nervous system. The essential autonomic feature of NREM sleep is increased parasympathetic activity and decreased sympathetic activity.

Table 2.1

Autonomic nervous system fluctuations during sleep.

	Parasympathetic nervous system	Sympathetic nervous system
NREM Sleep	Increase	Decrease
REM Sleep		
Tonic	Increases further	Decreases further
Phasic		Intermittent increases

The essential autonomic feature of REM sleep is an additional increase in parasympathetic activity and an additional decrease in sympathetic activity, with intermittent increases in sympathetic activity occurring during phasic REM (Table 2.1). For example, pupilloconstriction is seen during NREM sleep and is maintained during REM sleep with phasic dilatations noted during phasic REM sleep.

2.5. Cardiac physiology

NREM sleep is characterized by an increase in parasympathetic discharge associated with heightened baroreceptor sensitivity (Conway et al., 1983). There is a concurrent decrease in sympathetic discharge resulting in a reduction in heart rate, blood pressure, cardiac output, and systemic vascular resistance. REM sleep is characterized by an increase in sympathetic tone that results in bursts in heart rate and coronary blood flow but a reduction in the overall blood flow to the peripheral circulation. During the transition from NREM sleep to REM sleep, there are surges in vagus nerve activity that result in sinus pauses and arrhythmias followed by an increase in coronary blood flow (Dickerson et al., 1993a).

2.6. Cerebral physiology

Positron emission tomography studies have demonstrated that the cerebral metabolism of glucose is reduced during NREM sleep and increased to comparable levels of waking during REM sleep (Buchsbaum et al., 1989; Nofzinger et al, 2002).

2.7. Respiratory physiology

NREM sleep is characterized by a breathing pattern that is regular in amplitude and frequency. REM sleep

is characterized by an irregular, shallow breathing pattern with irregularities in amplitude and frequency most prominent during phasic REM (Wiegand et al., 1991). NREM sleep and particularly REM sleep is associated with alveolar hypoventilation, which results in a 2–8 mmHg increase in PCO_2 and 3–11 mmHg reduction in PaO_2 , which decreases the mean arterial oxyhemoglobin saturation by less than 2% (Shepard, 1985). This hypoventilation may be due to changes in ventilatory drive and upper airway resistance during sleep.

Ventilatory drive is important for maintenance of ventilation during sleep. The ventilatory response to hypoxia is reduced during sleep. The hypoxic ventilatory response is reduced during NREM sleep compared to wakefulness in men, but the responses were similar during NREM sleep compared to wakefulness in women. The hypoxic ventilatory response is reduced further during REM sleep in men and women (Douglas et al., 1982a; White et al., 1982). The ventilatory response to hypercapnia is reduced during NREM sleep, with a further reduction observed during REM sleep (Douglas et al., 1982b).

Upper airway resistance increases during the transition from wakefulness to sleep (Weigand et al., 1989). Retroglossal cross-sectional area is decreased during NREM sleep and decreased further in phasic REM (Rowley et al., 2001). The upper airway resistance is expected to be highest during REM sleep due to the muscular atonia associated with this sleep stage.

2.8. Vascular physiology

2.8.1. Muscle circulation

Muscle sympathetic activity is significantly reduced during the deeper stages of NREM sleep but increases to levels above waking values during REM sleep (Somers et al., 1993). The increased sympathetic tone during REM sleep results in vasoconstriction and subsequent reduced muscle blood flow in skeletal muscle vessels.

2.8.2. Cutaneous circulation

The onset of NREM sleep results in a drop in the set point temperature which results in a vasodilatation in skin vasculature. During REM sleep, a cold environment results in an increase in skin blood flow due to a decrease in neurogenic vasoconstriction. In a warm environment, a decrease in skin blood flow may result

from either a decrease in blood pressure or neurogenic vasodilation (Parmeggiani et al., 1977; Franzini et al., 1982; Alfoldi et al., 1990; Noll et al., 1994).

2.8.3. Splanchnic circulation

No significant regional splanchnic blood flow changes occur in relation to the different states of the sleep–wake cycle (Cianci et al., 1990).

2.8.4. Renal circulation

There are no significant changes in renal vascular resistance to blood flow during sleep. However, a significant decrease was found in urine production during NREM sleep versus REM sleep (Oosterhof et al., 1993).

2.8.5. Coronary circulation

During NREM sleep, there is a reduction in coronary blood flow and heart rate and an increase in coronary vascular resistance. During REM sleep, the coronary blood flow returns to awake levels with surges in heart rate and coronary blood flow noted during phasic REM (Kirby and Verrier, 1989). Approximately 90% of the surges in heart rate and coronary blood flow are concentrated during periods of phasic REM sleep and only ten percent in tonic REM sleep (Dickerson et al., 1993b).

2.8.6. Cerebral circulation

Cerebral blood flow typically decreases during NREM sleep and increases during REM sleep (Kuboyama et al., 1997). However, there is an overall reduction of cerebral blood flow during the course of the night (Fischer et al., 1991).

2.9. Endocrine physiology

The secretory activity of the endocrine system displays a specific regulation during NREM sleep and REM sleep.

2.9.1. Growth hormone

Growth hormone secretory pulses occur shortly after sleep onset, in temporal association with the first slow-wave sleep period (Van Cauter and Plat, 1996). In men, approximately 70% of the daily growth output occurs during sleep. In women, the nocturnal secretion of

growth hormone is lower and more variable (Van Cauter and Copinschi, 2000). There is a linear relationship between the amount of slow-wave sleep and the amount of growth hormone secretion (Van Cauter et al., 1998). Nocturnal awakenings inhibit growth hormone secretion (Spath-Schwalbe et al., 1995).

2.9.2. *Prolactin*

Prolactin is secreted in a sleep-dependent pattern, with the highest levels occurring during sleep and the lowest levels occurring whilst awake (Spiegel et al., 1994). Like growth hormone, pulses of prolactin are linked to increases in delta wave activity and reduced by alpha and beta activity (Spiegel et al., 1995).

2.9.3. *Cortisol*

Corticotropic activity demonstrates an endogenous circadian and ultradian rhythm that is modulated by sleep (Weitzman et al., 1983; Fehm and Born, 1991). Concentrations are maximal during early morning hours and levels decline throughout the day (Chihara et al., 1976). Sleep onset inhibits cortisol secretion and awakenings stimulate cortisol secretion (Weibel et al., 1995). Unlike growth hormone and prolactin, which are linked to increases in delta wave activity, pulses of cortisol and thyroid-stimulating hormone (see below) are related to superficial phases of sleep (Luboshitzky, 2000).

2.9.4. *Thyroid-stimulating hormone*

Thyroid-stimulating hormone (TSH) levels are low during the day, increase during the evening, and reach a maximum just prior to sleep onset (van Coevorden, 1991). TSH is inhibited by sleep, with the greatest inhibition during slow-wave sleep. Awakenings interrupting sleep were associated with an increased TSH secretion (Gronfier et al., 1995).

2.9.5. *Renin*

Plasma renin activity oscillations are closely related to the NREM-REM cycle (Brandenberger et al., 1987). Plasma renin activity increases during NREM sleep and decreases during REM sleep (Brandenberger et al., 1985; Charloux et al., 2002). Specifically, slow-wave sleep results in an increase in plasma renin levels and alpha, beta and theta waves are inversely proportional to plasma renin activity (Luthringer

et al., 1995). A common mechanism within the central nervous system may control both plasma renin activity and the NREM-REM sleep cycle (Brandenberger et al., 1988).

2.9.6. *Insulin*

During wakefulness, there is a morning-to-evening increase in glucose levels and insulin secretion. During early sleep, plasma glucose and insulin secretion rates markedly increase when slow-wave sleep predominates. However, during late sleep, plasma glucose and insulin secretion rates decrease to pre-sleep levels when REM sleep predominates (Van Cauter et al., 1991; Scheen et al., 1996).

2.10. Thermoregulatory physiology

Thermoregulatory processes have been implicated in sleep onset and waking. Specifically, there is a tendency for sleep onset to occur in the descending phase of the temperature rhythm and for awakening to occur in the ascending phase of the temperature rhythm (Nakao et al., 1995; van den Heuvel et al., 1998). It has also been proposed that heat loss as opposed to core body temperature or its rate of change is the best predictor for sleep-onset latency (Krauchi et al., 2000). Furthermore, it has also been suggested that thermoregulatory processes initiate sleep but do not play a major role in its maintenance (Krauchi and Wirz-Justice, 2001). The circadian modulation of sleep is likely due to a myriad of factors (Van Someren, 2000).

During NREM sleep, thermoregulatory mechanisms such as shivering and sweating are intact but body temperature is regulated at a lower level than during wakefulness (Parmeggiani, 2003). However, in REM sleep, thermoregulation is severely inhibited and thermal homeostasis is disrupted (Glotzbach and Heller, 1984; Kobayashi et al., 2003).

2.11. Enteric physiology

The gastrointestinal system is regulated by both the autonomic nervous system and the enteric nervous system, a complex network of neurons located within the lumen of the gastrointestinal tract.

During sleep, the function of the gastrointestinal system is reduced most of the time. Salivation, swallowing rate, upper esophageal sphincter pressure, number of primary esophageal contractions, velocity of migrating motor complex propagation in the

proximal small bowel, and colonic tone and contractions have all been shown to be reduced during sleep. In addition, anal canal pressure is lower and rectum activity is higher during sleep, but the anal pressure is still higher than the rectum pressure and the rectum contractions are most frequently retrograde (Dantas and Aben-Athar, 2002).

Gastric emptying is slow during sleep but increased during REM sleep. Basal gastric acid secretion exhibits a circadian rhythm that is modified by buffering meals and nocturnal duodenogastric reflux (van Herwaarden et al., 1999). Gastric acid secretion generally peaks in early sleep (Moore and Englert, 1970). Intra-gastric pH monitoring has demonstrated some differences between NREM and REM sleep. The pH values of wakefulness were lower than those of sleep stages 1 and 4, and REM sleep. The pH values of REM sleep were higher than those of sleep stage 1 and 2 (Watanabe et al., 1995). Although results of pH monitoring are highly reproducible within individuals, there is considerable interindividual variation (Bumm et al., 1987).

2.12. Procreative physiology

Sleep-related erections occur in close temporal association with REM sleep in healthy men (Karacan et al., 1987). They are present throughout the life span with only a slight decline in frequency and duration of erections in older individuals (Schiavi and Schreiner-Engel, 1988).

The mechanism of penile erections appears to involve a vascular phase and a muscular phase (Karacan et al., 1983; Lavoisier et al., 1988). Penile blood flow peaks during maximal tumescence and bursts of phasic musculovascular activity are more frequent during ascending and maximal tumescence than during de-tumescence and baseline (Karacan et al., 1987).

An analogous phenomenon is present in women (Hirschkowitz and Moore, 1996).

2.13. Immune physiology

Sleep is altered during the course of an infection (Opp and Toth, 2003). The general pattern of sleep after an infectious challenge is an initial increase in NREM followed by a period of NREM inhibition. REM sleep is inhibited after infectious challenge (Krueger and Majde, 1994). For example, exposure to influenza results in increased NREM sleep and decreased REM sleep (Fang et al., 1996).

The cytokine network in the brain is involved in the physiological regulation of sleep and in the regulation of sleep responses to infection (Krueger et al., 1995). There is a diurnal rhythm of cytokines interleukin-1 beta (IL-1 β) and tumor necrosis factor alpha (TNF- α) in the brain with the highest levels occurring during sleep periods (Krueger et al., 1998). IL-1 and TNF promote slow wave sleep (Shoham et al., 1987).

The pro-inflammatory cytokines IL-1 and TNF are part of a complex biochemical cascade regulating sleep during infection. IL-1 and TNF are up-regulated in the initial response to an infectious challenge and enhance NREM sleep (Krueger et al., 1999; Opp and Imeri, 1999). Downstream events include complex interactions with nitric oxide, growth hormone releasing hormone, nerve growth factor, nuclear factor kappa B, and possibly adenosine and prostaglandins (Kapas et al., 1994; Krueger and Majde, 1994; Krueger et al., 1994; Takahashi et al., 1999). Endogenous substances, including IL-4, IL-10, and IL-13, moderate the effects of IL-1 and TNF (Kubota et al., 2000; Krueger et al., 2001). Bacterial cell wall products such as lipopolysaccharide and peptidoglycan and viral double-stranded RNA also enhance cytokine production and induce sleep responses (Krueger and Majde, 1995).

2.14. Conclusion

Considerable research has been directed towards elucidating the basic mechanisms of sleep physiology. NREM and REM sleep are associated with dynamic changes in the cardiac, cerebral, respiratory, vascular, endocrine, thermoregulatory, enteric, procreative and immune systems. A firm understanding of these physiologic changes is critical to understanding the pathophysiology of medical disorders affecting sleep. The future of sleep physiology research lies in the application of the fundamental principles learned in the laboratory to the clinical setting.

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CHAPTER 3

An overview of polysomnography

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3.1. Introduction

The term 'polysomnography' (PSG) was proposed by Holland, Dement, and Raynal in 1974 to describe the recording, analysis and interpretation of multiple, simultaneous, physiological parameters. As a tool, PSG is essential in the formulation of diagnoses for sleep disorder patients and in the enhancement of our understanding of both normal sleep and its disorders (Dement and Kleitman, 1957; Dement and Rechtschaffen, 1968; Dement et al., 1973; Raynal, 1976; McGregor et al., 1978; Weitzman et al., 1980; Broughton, 1987; Guilleminault, 1987; Keenan, 1992, 1999; Guilleminault et al., 1993, 1995; Springer et al., 1996; Butkov, 2002; Carskadon and Rechtschaffen, 2000). It is a complex procedure that should be performed by a trained technologist (ASDA, 1998). Today's sleep laboratory continues to undergo technologic evolution, particularly in terms of the increased reliance on digital systems (Wong, 1996; Hirshkowitz and Moore, 2000; Penzel and Conradt, 2000) and the collection of data outside of the traditional sleep laboratory setting (ASDA, 1994; Fry et al., 1998). This evolution requires sophisticated knowledge of equipment and procedures.

This chapter is a review of the technical and clinical aspects of PSG. The reader is directed to the references (Block et al., 1985; Martin et al., 1985; ATS,

1989, 1996; AEEGS, 1994; ASDA, 1994, 1995, 1997, 1998; AARC-APT, 1995; Reite et al., 1995; AASM, 1999, 2003; IOSET, 1999; AASM, 2000; Terzano et al., 2001; AAP, 2002) for current indications and standards of practice original sources.

3.2. Indications for polysomnography

Polysomnography is used to investigate the relationship between changes in physiology, impact on sleep, and consequences of waking function, performance and behavior. Issues such as shift work, time zone change, or suspected advanced or delayed sleep phase syndrome should be taken into consideration when scheduling the study. The PSG should be conducted during the patient's usual major sleep period, to avoid confounding circadian rhythm factors.

Questionnaires regarding sleep-wake history and a sleep diary that solicits information about major sleep periods and naps are useful adjuncts to PSG (Douglas et al., 1990; Johns, 1991). Questionnaires can be used to identify and triage patients prior to laboratory testing (Hoffstein and Szalai, 1993; Flemons et al., 1994; Maislin et al., 1995; Alexander et al., 1996; Chervin et al., 2000).

A full medical and psychiatric history should be completed and made available to the technologist performing the study. Without this information, the technologist is at a loss to understand how aspects of the medical or psychiatric history may affect the study or to anticipate difficulties. Technologists must also understand what questions the study seeks to answer. This enhances the ability to make protocol adjustments when necessary, and guarantees that the most pertinent data are collected.

3.3. Prestudy questionnaire

It is not uncommon for patients, particularly those with excessive sleepiness, to have a diminished capac-

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ity to evaluate their level of alertness (Thorpy, 1992). In addition, many patients with difficulty initiating and maintaining sleep often report a subjective evaluation of their total sleep time and quality that is at odds with the objective data collected in the laboratory referred to as sleep state misperception, an ICSD diagnosis classification (ASDA, 1997a or b). For these reasons it is recommended that subjective data be collected systematically, as part of the sleep laboratory evaluation.

The Stanford Sleepiness Scale (SSS) (Appendix 2) (Hoddes et al., 1972, 1973) is an instrument used to assess a patient's subjective evaluation of sleepiness prior to the PSG. The SSS is presented to the patient immediately before the beginning of the study. It offers a series of phrases, from which to choose the one that best describes their state of arousal or sleepiness. Patients respond by selecting the set of adjectives that most closely corresponds to their current state of sleepiness or alertness. The scale is used extensively in both clinical and research environments; however, it has two noteworthy limitations. It is not suitable for children who have a limited vocabulary or for adults whose primary language is not English. In these situations a linear analog scale is recommended. One end of the scale represents extreme sleepiness and the other end alertness. Patients mark the scale to describe their state just prior to testing (see Appendix 2).

Another instrument, the Epworth Sleepiness Scale (Johns, 1991) lends information about chronic sleepiness. Patients are asked to report the likelihood of falling asleep in situations such as riding as a passenger in a car, watching TV, etc.

Patients are also asked about their medication history, smoking history, any unusual events during the course of the day, their last meal prior to study, alcohol intake, and a sleep history for the last 24 hours, including naps. Involvement of the patient in providing this information usually translates into increased cooperation for the study. A technologist's complete awareness of specific patient idiosyncrasies, in the context of the questions to be addressed by the study, ensures a good foundation for the collection of high-quality data.

3.4. Nap studies

A proposed alternative to PSG has been the nap study (to be distinguished from the Multiple Sleep Latency Test (MSLT)) (Carskadon et al., 1986; Carskadon,

1989; Thorpy, 1992). The rationale is that if a patient has a sleep disorder it will be expressed during an afternoon nap as well as during a more extensive PSG. The nap study approach has been used most frequently for the diagnosis of sleep-related breathing disorders and was proposed in an effort to reduce the cost of the sleep laboratory evaluation. The short study in the afternoon avoids the necessity of having a technologist present for an overnight study. There are serious limitations to the use of nap studies, however, including the possibility of false-negative results or the misinterpretation of the severity of sleep-related breathing disorders if the patient is sedated or sleep deprived prior to the study. When a nap study is performed it should follow the guidelines as published by the American Thoracic Society (1989):

Although minimal systematic data exist on the value of nap recordings, nap studies of 2 to 4 hours' duration may be used to confirm the diagnosis of sleep apnea, provided that all routine polysomnographic variables are recorded, that both non-REM and REM sleep are sampled, and that the patient spends at least part of the time in the supine posture. Sleep deprivation or the use of drugs to induce a nap are contraindicated. Nap studies are inadequate to definitively exclude a diagnosis of sleep apnea.

3.5. Data collection

Data are collected using a combination of alternating current (AC) channels and direct current (DC) channels.

Equipment for recording polysomnograms is produced by a number of manufacturers. Each may have a distinctive appearance and some idiosyncratic features, but there is a remarkable similarity when the basic functioning of the instrument is examined.

Equipment preparation includes an understanding of how the filters and sensitivity of the amplifiers affect the data collected.

The amplifiers used to record physiologic data are very sensitive, so it is essential to eliminate unwanted signals from the recording. By using a combination of high- and low-frequency filters, and appropriate sensitivity settings, we maximize the likelihood of recording and displaying the signals of interest and decrease the possibility of recording extraneous signals. Care must be taken when using the high- and

low-frequency filters however, to ensure that an appropriate window for recording specific frequencies is established and that the filters do not eliminate important data.

3.6. Alternating current amplifiers

Differential AC amplifiers are used to record physiologic parameters of high frequency, such as the electroencephalogram (EEG), the electro-oculogram (EOG), the electromyogram (EMG) and the electrocardiogram (ECG). The AC amplifier has both high- and low-frequency filters. The presence of the low-frequency filter makes it possible to attenuate slow potentials not associated with the physiology of interest; these include galvanic skin response, DC electrode imbalance, and breathing reflected in an EMG, EEG or EOG channel. Combinations of specific settings of the high- and low-frequency filters make it possible to focus on specific band widths associated with the signal of interest. For example, breathing is a very slow signal (roughly 12–18 breaths per minute) in comparison with the EMG signal, which has a much higher frequency (approximately 20–200 Hz or cycles per second).

3.7. Direct current amplifiers

In contrast to the AC amplifier, the DC amplifier does not have a low-frequency filter. DC amplifiers are typically used to record slower-moving potentials, such as output from the oximeter or pH meter, changes in pressure in positive airway pressure treatment, or output from transducers that record endoesophageal pressure changes or body temperature. Airflow and effort of breathing can be successfully recorded with either AC or DC amplifiers.

An understanding of the appropriate use of filters in clinical PSG is essential to proper recording technique (Cooper et al., 1974; Tyner et al., 1983; Wong, 1996; Penzel and Conradt, 2000). Table 3.1 provides recommendations for filter settings for various physiologic parameters.

3.8. Calibration of the equipment

The PSG recording instrument must be calibrated to ensure adequate functioning of amplifiers and appropriate settings for the specific protocol. The first calibration is an all-channel calibration. During this calibration all amplifiers are set to the same sensitiv-

Table 3.1

Recommendations for filter and sensitivity settings for various physiologic parameters.

Channel ^a	Low-frequency filter (Hz)	Time constant (s)	High-frequency filter (Hz)	Sensitivity
EEG	0.3	0.4	35	50 (μV/cm)
EOG	0.3	0.4	35	50 (μV/cm)
EMG	5 ^b	0.03	90–120	20–50 (μV/cm)
ECG	1.0	0.12	15	1 MV/cm
Index of airflow	0.15 ^c	5 ^b	15	†
Index of effort	0.15 ^c	5 ^b	15	†

Source: Modified from SA Keenan. Polysomnography: technical aspects in adolescents and adults. *J Clin Neurophysiol* 1992; 9:21.

EOG = electro-oculography; EMG = electromyography; ECG = electrocardiography.

^a EEG includes C3/A2, C4/A1, O1/A2, and O2/A1. EOG includes right outer canthus and left outer canthus referred to opposite reference.

^b If shorter time constant or higher low-frequency filter is available, it should be used. This includes settings for all EMG channels including mentalis, submentalis, masseter, anterior tibialis, intercostal, extensor digitorum.

^c Because breathing has such a slow frequency (as compared to the other physiologic parameters) the longest time constant available, or the lowest setting on the low-frequency filter options, would provide the best signal. It is also possible to use a DC amplifier (with no low-frequency filter, time constant = infinity) to record these signals.

† It is common in clinical practice to index changes in airflow and effort to breathe by displaying qualitative changes in oral/nasal pressure, temperature, and chest and abdominal movement. It is well recognized that quantitative methods (such as endoesophageal pressure changes) provide a more sensitive and accurate measure of work of breathing. Ideally, a multi-method approach is used to increase confidence in detecting events of sleep-related breathing anomalies.

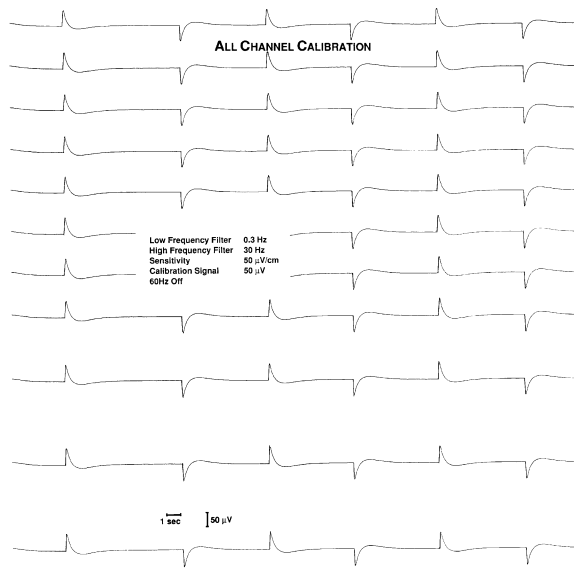


Fig. 3.1A. All channel calibration is shown. All amplifiers have the same sensitivity and high- and low-frequency filter settings.

ity, high-frequency filter and low-frequency filter settings and a known signal is sent through all amplifiers simultaneously. The proper functioning of all amplifiers is thus demonstrated, ensuring that all are functioning in an identical fashion (see Figure 3.1A).

A second calibration is performed for the specific study protocol. During this calibration amplifiers are set with the high-frequency filter, low-frequency filter and sensitivity settings appropriate for each channel; the settings are dictated by the requirements of the specific physiologic parameter recorded on each channel (see Table 3.1, Figure 3.1B). The protocol calibration ensures that all amplifiers are set to ideal conditions for recording the parameter of interest. Filter and sensitivity settings should be clearly documented for each channel.

3.9. Data display and analysis

The process of sleep stage scoring and analysis of abnormalities is accomplished by an epoch-by-epoch review of the data.

Historically, a common paper speed for analog polysomnography was 10 mm s^{-1} , providing a 30-s epoch (another widely accepted paper speed was 15 mm s^{-1} , which gave a 20-s epoch length). An expanded time base may be necessary to visualize EEG data, specifically the spike activity associated

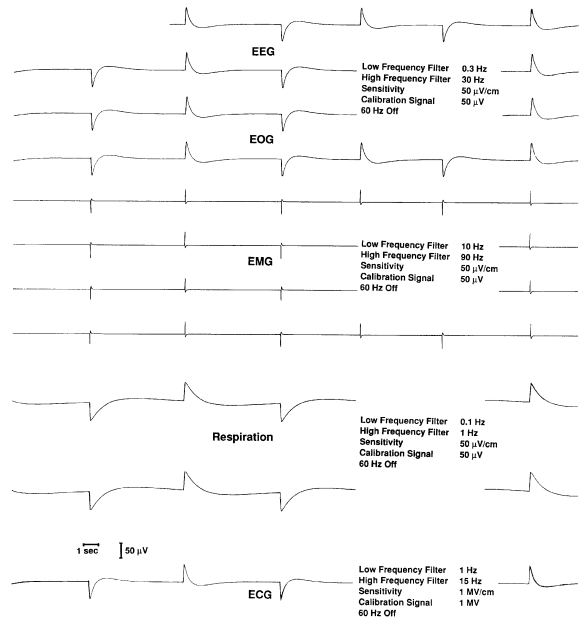


Fig. 3.1B. The montage calibration show changes in high- and low-frequency filter settings from the all-channel calibration to display a variety of physiologic signals for the polysomnograph. (EOG = electro-oculogram; EMG = electromyogram; ECG = electrocardiogram).

with epileptic discharges. Compressed displays of greater than 30-s screen for EEG should be avoided because they compromise an adequate display of EEG data. Data such as oxygen saturation, respiratory signals, or changes in penile circumference, however, can be more easily visualized when display time is compressed to 2–5 minutes per screen. A major advantage of the digital systems lies in the ability to manipulate the display after data collection. A brief discussion of digital systems appears later in this chapter.

3.10. The study: electrode/monitor application process

The quality of the tracing generated depends on the quality of the electrode application (Tyner et al., 1983; IOSET, 1999). Before any electrode or monitor is applied the patient should be instructed about the procedure and given an opportunity to ask questions. The first step in the electrode application process involves measurement of the patient's head. The International Ten–Twenty System (Jasper, 1958) of electrode placement is used to localize specific electrode sites (Figure 3.2). The following sections address the application process for EEG, EOG, EMG and ECG electrodes.

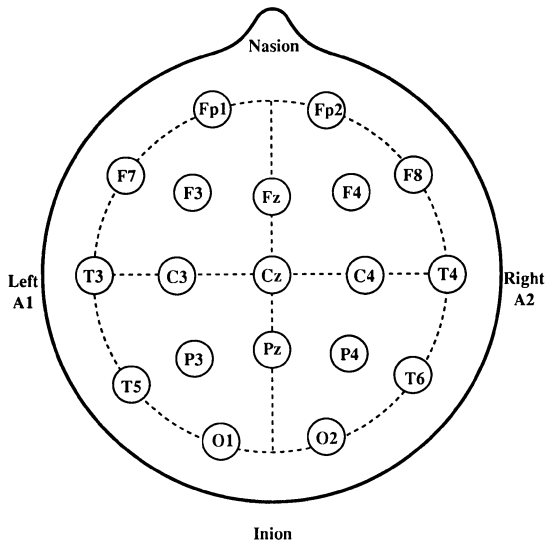


Fig. 3.2. The complete 10–20 system of electrode placement.

3.11. Electroencephalography

The EEG probably reflects local potential changes that occur on pyramidal cell soma and large apical dendrites of pyramidal cell neurons. The EEG is not likely the reflection of action potentials of the neurons (Walczak and Chokroverty, 1999).

To record EEG, the standard electrode derivations for monitoring EEG activity during sleep are C3/A2 or C4/A1, and O1/A2 or O2/A1, but in many situations there may be a need for additional electrodes. For example, to rule out the possibility of epileptic seizures during sleep, or the presence of any other sleep-related EEG abnormality, it may be necessary to apply the full complement of EEG electrodes according to the International 10–20 System (Appendix 3).

For recording EEG, a gold cup electrode with a hole in the center is commonly used. Silver–silver chloride electrodes are also useful to record EEG, though they may have limitations such as increased maintenance (evidenced by the need for repeated chloriding) and the inability to attach these electrodes to the scalp.

The placement of C3, C4, O1 and O2 are determined by the International 10–20 System of Electrode Placement. Reference electrodes are placed on the bony surface of the mastoid process. A description of the measurement procedure appears in Appendix 4.

There are a variety of methods used to attach electrodes. The collodion technique (Tyner et al., 1983;

Cross, 1992) has long been an accepted and preferred method of application for EEG scalp and reference electrodes. This technique ensures a long-term placement and allows for correction of high (over 5000ohms) impedances, after application. Other methods using electrode paste and conductive medium are acceptable and sometimes necessary in certain conditions.

3.12. Electro-oculography

The EOG is a reflection of the movement of the corneo–retinal potential difference within the eye. The retina is negative with respect to the cornea. Thus, the eye exists as the potential field within the head, which serves as the volume conductor for that field. It is important to recognize that EOG as described here is not measuring eye muscle potentials changes (Walczak and Chokroverty, 1999).

An electrode is typically applied at the outer canthus of the right eye (ROC) and is offset 1 cm above the horizontal. Another electrode is applied to the outer canthus of the left eye (LOC) and is offset by 1 cm below the horizontal. The previously mentioned A1 and A2 reference electrodes are used as follows: ROC/A1 and LOC/A2. Additional electrodes can be applied infraorbitally and supraorbitally for either the right or left eye. The infraorbital and supra-orbital electrodes enhance the ability to detect eye movements that occur in the vertical plane and can be particularly useful in the MSLT (Raynal, 1976; Keenan, 1999; Mitler et al., 2000) (Figure 3.3).

EOG electrodes are typically applied to the surface of the skin with an adhesive collar.

3.13. Electromyography

The EMG recording represents the summation of activity taking place on many individual motor end plates (Walczak and Chokroverty, 1999).

A gold cup or a silver–silver chloride electrode attached with an adhesive collar is used to record EMG activity from the mentalis and submental muscles. At least three EMG electrodes are applied to allow for an alternative electrode, in the event that artifact develops in one of the others. The additional electrode can be placed over the masseter muscle to allow for detection of bursts of EMG activity associated with bruxism (Figure 3.4).

Additional bipolar EMG electrodes are placed on the surface of the anterior tibialis muscles to record periodic limb movements in sleep (Coleman et al.,

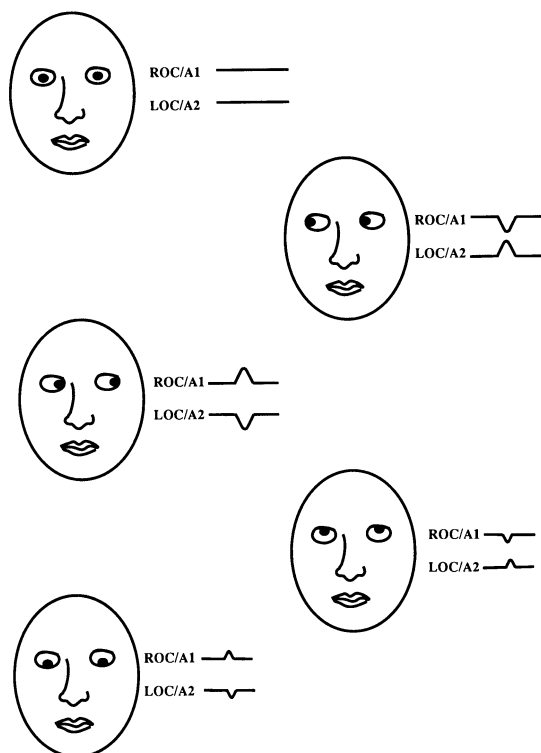


Fig. 3.3. The recording montage for a two-channel EOG demonstrates out-of-phase signal deflection in association with conjugate eye movements. Schematic diagram shows placement of the electromyography (EMG) electrodes to record activity from the mental, submental, and masseter muscles. (ROC, LOC = outer canthus of the right and left eye, respectively; GND = ground (earth).)

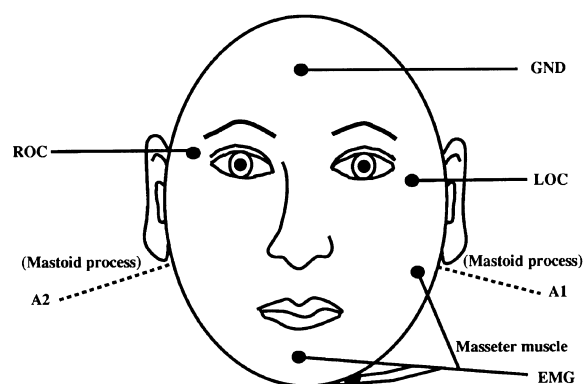


Fig. 3.4. Schematic diagram shows placement of the electromyography (EMG) electrodes to record activity from the mental, submental and masseter muscles. (ROC, LOC = outer canthus of the right and left eye, respectively; GND = ground (earth).)

1980) and on the surface of the extensor digitorum muscles if REM sleep behavior disorder (Schenk et al., 1986) is suspected.

3.14. Electrocardiography

There are a variety of approaches for recording the ECG during PSG. The simplest approach involves use of standard gold cup electrodes. However, disposable electrodes are also available.

ECG electrodes are applied with an adhesive collar to the surface of the skin just beneath the right clavicle and on the left side at the level of the seventh rib. A stress loop is incorporated into the lead wire to ensure long-term placement.

3.15. Monitoring breathing during sleep

It is necessary to record airflow and effort to breathe, and it is with these two measures that breathing irregularities can be detected. There are many sophisticated technical advances on the horizon, but the following describes common clinical practice.

It is well recognized that the pneumotachograph is the gold standard for measuring airflow. However, it is customary for many clinical studies to rely on qualitative methods to index airflow during sleep. Historically, thermistors or thermocouples were used, while presently a more accepted practice is to record change in pressure to indicate airflow (AASM, 1999).

Respiratory inductive plethysmography (RIP) is often thought of as a reliable, non-invasive measure of work of breathing. If calibrated, it can give a measure of changes in tidal volume. There have been reports of difficulty maintaining calibration for the duration of the study. Piezo crystals embedded into adjustable belts worn around the chest and abdomen reflect changes in association with effort to breathe, and are commonly used. There are numerous ways to index work of breathing, including but not limited to: intercostal and/or diaphragmatic EMG and impedance pneumography.

A quantitative measure of work of breathing is endoesophageal manometry (German and Vaughn, 1996). For greater reliability and validity, multiple methods of monitoring airflow and effort of breathing should be used.

Commercially available devices also allow for non-invasive blood gas monitoring during sleep. These measures are essential in assessment of the severity of the sleep-related breathing disorder.

3.16. Gastroesophageal reflux studies

It is common for PSG to include monitoring of endoesophageal pH when patients complain of reflux or waking with a choking sensation (Orr et al., 1982). Commercially available devices allow for the recording of changes in pH at the level of the distal esophagus during sleep. Events of reflux and the 'clearing time' or time necessary to return to normal acid levels can be demonstrated and correlated with other physiologic events or EEG arousals.

3.17. Quality control

Before recording, electrodes should be visually inspected to check the security of their placement and an impedance check should be obtained and documented. Adjustment should be made to any EEG, EOG, ECG or chin EMG electrode with an impedance greater than 5000 ohms. Impedances of 20000 ohms are acceptable for limb EMG recordings (Bonnet et al., 1993).

3.18. Physiologic calibrations

Physiologic calibrations are performed after the electrode and monitor application is complete. This calibration allows for documentation of proper functioning of the electrodes and other monitoring devices, and provides baseline data for review and comparison when scoring the PSG. The specific instructions given to the patient for this calibration include:

- Eyes open, look straight ahead for 30 seconds.
- Eyes closed, look straight ahead for 30 seconds.
- Hold head still, look to left and right, up and down. Repeat.
- Hold head still, blink eyes slowly, five times.
- Grit teeth, clench jaw, or smile.
- Inhale and exhale.
- Hold breath for 10 seconds.
- Flex right foot, flex left foot.
- Flex right hand, flex left hand.

As these instructions are given to the patient, the technologist examines the tracing and documents the patient's responses. When the patient stares straight ahead for 30 seconds with eyes open, the background EEG activity is examined. As the patient looks right and left the tracing is examined for out-of-phase deflections of the signals associated with recording the

EOG. Out-of-phase deflection occurs if the inputs to consecutive channels of the polygraph are ROC/A1 for the first EOG channel and LOC/A2 for the second. It is also important, when the patient closes the eyes, to observe the reactivity of the alpha rhythm seen most prominently in the occipital EEG (O1/A2 or O2/A1); usually alpha is best visualized when the patient's eyes are closed. The patient is also asked to blink five times.

The mentalis/submentalis EMG signal is checked by asking the patient to grit the teeth, clench jaws or yawn. The technologist documents proper functioning of the electrodes and amplifiers used to monitor anterior tibialis EMG activity by asking the patient to flex the right foot and the left foot in turn. If REM sleep behavior disorder is suspected, additional electrodes should be applied to the surface of the skin above the extensor digitorum muscles of each arm. Patients are asked to flex their wrists while the technologist examines the recording for the corresponding increase in amplitude of the EMG channel amplitude.

Inhalation and exhalation allow for examination of channels monitoring airflow and effort of breathing. A suggested convention is that inhalation causes an upward deflection of the signal and exhalation a downward deflection. It is most important that the signals on all the channels monitoring breathing are in phase with each other to avoid confusion with paradoxical breathing. The technologist should observe a flattening of the trace for the duration of a voluntary apnea.

If the 60- or 50-Hz notch filter is in use, a brief examination (2–4 seconds) of portions of the tracing with the filter in the 'off' position is essential. This allows for identification of any 60- or 50-Hz interference that may be masked by the filter. Care should be taken to eliminate any source of interference and to ensure that the 60- or 50-Hz notch filter is used only as a last resort. This is most important when recording patients suspected of having seizure activity, because the notch filter attenuates the amplitude of the spike activity seen in association with epileptogenic activity. If other monitors are used, the technologist should incorporate the necessary calibrations.

The physiologic calibrations enable the technologist to determine the quality of data before the PSG begins. If artifact is noted during the physiologic calibrations, it is imperative that every effort be made to correct the problem; the condition is likely to get worse through the remaining portions of the recording. The functioning of alternative (spare) electrodes should also be examined during this calibration.

When a satisfactory calibration procedure is completed and all other aspects of patient and equipment preparation are completed, data collection can begin. This is referred to as 'lights-out' and time should be clearly noted.

3.19. Monitoring recording: documentation

Complete documentation for the PSG is essential. This includes patient identification (patient's full name and medical record number), date of recording and a full description of the study. The names of the technologist performing the recording should be noted and any technologists involved in preparation of patient and equipment. The specific instrument used to generate the recording should be identified. This is particularly useful in the event that artifact is noted during the analysis portion (scoring) of the sleep study.

Specific parameters recorded on each channel should be clearly noted, as should a full description of sensitivity, filter and calibration settings for each channel. The time of the beginning and end of the recording must be noted, as well as specific events that occur during the night. Usually a predetermined montage is available as a simple software selection. Any changes made to filter and for sensitivity settings should be clearly noted.

The technologist is also responsible for providing a clinical description of unusual events. For example, if a patient experiences an epileptic seizure during the study, the clinical manifestations of the seizure must be detailed: deviation of eyes or head to one side or the other, movement of extremities, presence of vomiting or incontinence, duration of the seizure and postictal status. Similar information should be reported on any clinical event observed in the laboratory, such as somnambulism or clinical features of REM sleep behavior disorder. Physical complaints reported by the patient are also noted.

3.20. Trouble shooting/artifact recognition

In general, when difficulties arise during recording, the troubleshooting inquiry begins at the patient and follows the path of the signal to the recording device. More often than not, the problem can be identified as a difficulty with an electrode or other monitoring device. It is less likely that artifact is the result of a problem with an amplifier. If the artifact is generalized (i.e., on most channels) then the integrity of the ground electrode and the instrument cable should be checked. If the artifact is localized, i.e., on a limited

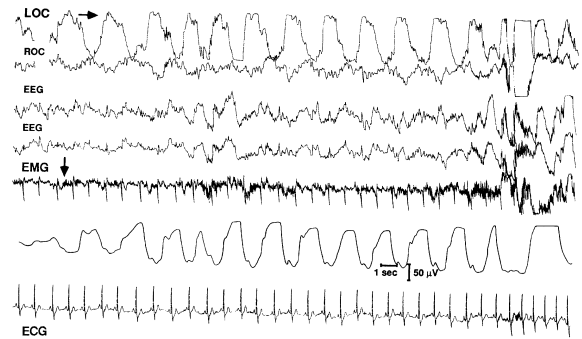


Fig. 3.5. Artifact in LOC channel (LOC/A1) can be localized to the left outer canthus electrode. The EEG channels in the trace are C3/A2 and O2/A1. Since the artifact does not appear in the O2/A1 channel the artifact is localized to the LOC electrode. The electrode placement may be insecure or the patient may be lying on the electrode and producing movement of the LOC electrode in association with breathing. Additional artifact is noted in the EMG channel. This signal is contaminated with ECG artifact and the intermittent slower activity as well as the wandering baseline are most likely due to a loose lead. The ECG channel also shows a pattern consistent with a loose electrode wire.

number of channels, then the question should be, which channels have this artifact in common and what is common to the channels involved? The artifact is probably the result of a problem located in an electrode or monitoring device that is common to both channels. If the artifact is isolated to a single channel, the source of artifact is limited to the inputs to the specific amplifier, the amplifier itself, or to the ink-writing system for the channel.

Figures 3.5–3.13 depict some frequently encountered artifacts seen during PSG.

3.21. Ending the study

Clinical circumstances and laboratory protocol dictate whether the patient is awakened at a specific time or allowed to awaken spontaneously. After awakening, to end the study the patient should be asked to perform the physiologic calibrations to ensure that the electrodes and other monitoring devices are still functioning properly. The equipment should be calibrated at the settings used for the study, and finally, the amplifiers should be set to identical settings for high- and low-frequency filters and sensitivity and an all-channel calibration should be performed. This is essentially the reverse of the calibration procedures mentioned for the beginning of the study.

A subjective evaluation is made by the patient. The patient is asked to estimate how long it took to fall

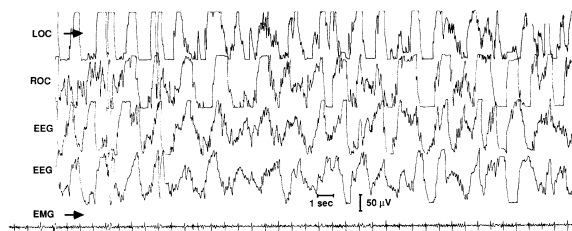


Fig. 3.6. This figure illustrates the blocking artifact seen with inappropriate sensitivity settings. This can be alleviated by decreasing sensitivity. If adjustments to sensitivity are made they should be clearly noted and should be made on all channels displaying EEG data. It is common procedure to calibrate the equipment with decreased sensitivities (i.e., $100\mu\text{v cm}^{-1}$) for children's studies or increasing sensitivity (i.e., $30\mu\text{v cm}^{-1}$) for older patients. Typically, sensitivity settings are not changed frequently during the recording (as they may be in routine EEG). As a result it is not uncommon to see this artifact when the patient enters slow-wave sleep. This is not a common problem with digital systems because of the user's ability to manipulate sensitivity after collection.

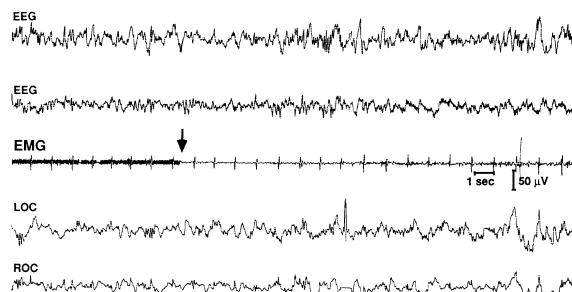


Fig. 3.7. A 60-Hz artifact exists in the EMG channel in this tracing. At the arrow the 60-Hz filter is turned on. However, there is continued evidence of difficulty with electrodes on this channel, as evidenced by the ECG artifact and occasional spike-like activity. Turning on the 60-Hz filter is not the correct response to eliminate the artifact. If possible, the technologist should switch to an alternative electrode or fix the one involved.

asleep, the amount of time spent asleep, and if there were any disruptions during the sleep period. Patients should report on quality of sleep and the level of alertness upon arousal.

It is also worthwhile for the sleep laboratory staff to know how patients intend to leave the laboratory. A patient who has a severe sleep disorder should avoid driving. An arranged ride or public transportation should be used, particularly if the patient has withdrawn from stimulant medications for the purpose of the study.

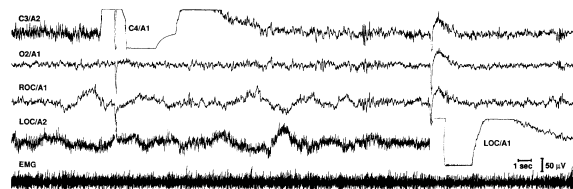


Fig. 3.8. The high-frequency (probably EMG) artifact noted in the C3/A2 and LOC/A2 channels can be localized to the A2 electrode. This problem can be solved by switching to the alternative reference (A1) electrode. A high-amplitude discharge is noted during the switch from C3/A2 to C4/A1 and LOC/A2 to LOC/A1. This can be avoided by placing the amplifier in standby mode while making the change.

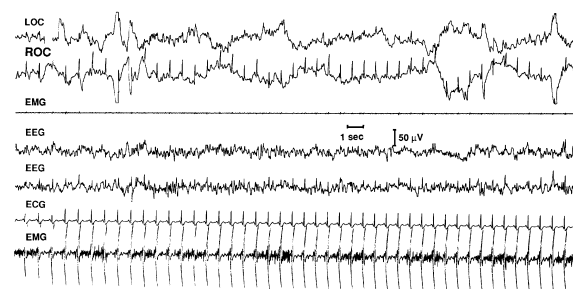


Fig. 3.9. The ROC channel (ROC/A1) and the second EEG (O2/A1) channels are contaminated with ECG artifact. The artifact can be identified by aligning the spike-like activity noted in channels with the R wave on the ECG channel. It is localized to the A1 electrode because it is seen in both ROC/A1 and O2/A1 channels and A1 is common to both channels. It should be noted that the high-amplitude ECG artifact, seen in the EMG channel below the ECG channel, is unavoidable. This artifact is due to the proximity of EMG electrodes to the heart, which creates a robust signal superimposed on the intercostal EMG signal.

3.22. The final report

The interpretation of the PSG is a process involving review of clinical presentation, history, as well as parametric analysis of the polysomnogram. The variables listed in Table 3.2 are ones most commonly used to inform the interpretation and create the final report.

3.23. Digital systems

Within the past two decades digital systems have made it possible to manipulate data after recording and to permit extraction of otherwise inaccessible information. Digital systems provide flexibility in the manipulation of filter settings, sensitivities, and change in the display of montages after collection. The first digital EEG systems

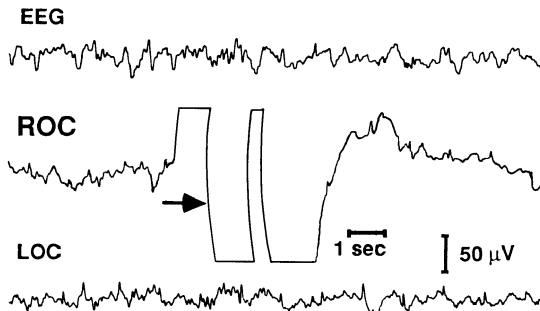


Fig. 3.10. The high-amplitude deflection in the ROC (ROC/A1) channel is associated with an electrode artifact commonly referred to as an 'electrode pop'. This can be the result of a compromised electrode placement or insufficient electroconductive gel under the electrode. When this artifact is observed the electrode involved should not be trusted to give reliable data.

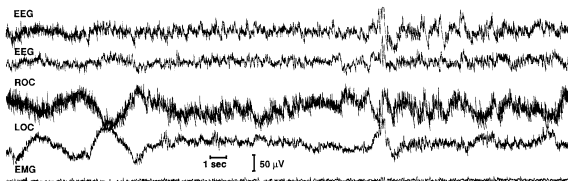


Fig. 3.11. There is a generalized, high-frequency activity superimposed upon the EEG and EOG channels. This is most likely secondary to muscle activity. The EMG channel shows only artifact.

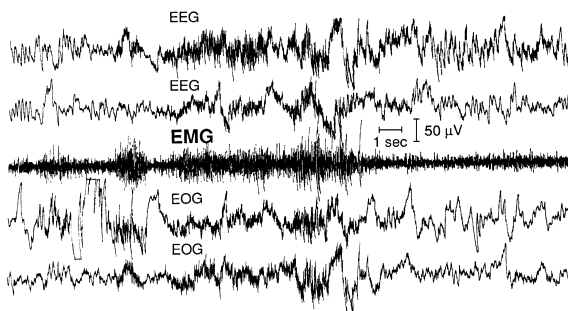


Fig. 3.12. This burst of high-frequency artifact, superimposed on the EEG and EOG channels, is due to a brief movement on the part of the subject. As in Figure 3.10, this is a superimposition of EMG activity on the EEG and EOG channels. It should also be noted that in the first EOG channel there is an electrode pop. The EMG channel in this tracing is of good quality and should be compared to Figure 3.10.

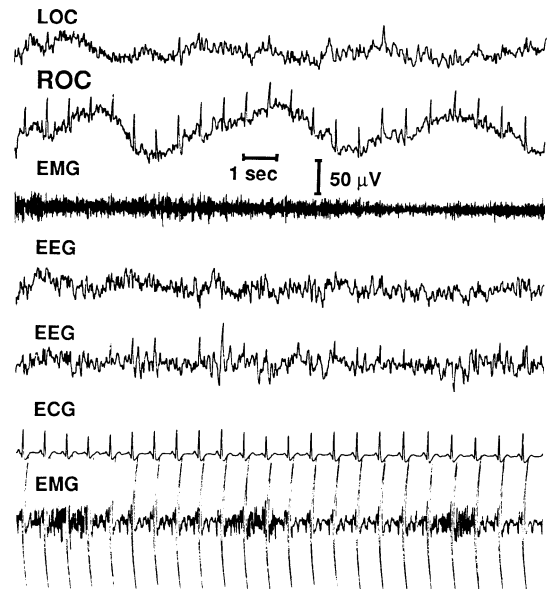


Fig. 3.13. A high-amplitude, slow artifact is noted in the ROC (ROC/A1) channel. This is most likely associated with the patient's breathing and is secondary to a loose electrode or the patient lying on the right side and disturbing the electrode in synchrony with breathing. A relatively high-amplitude ECG artifact is also seen. The artifact can be localized to the ROC electrode. The EMG tracing noted at the bottom of this example is an intercostal EMG. The high-amplitude ECG spike in this channel is impossible to eliminate, however, the brief bursts of EMG activity can be noted in association with the artifact seen in the ROC/A1 channel. This lends further evidence that the artifact noted in the ROC electrode is probably associated with breathing inasmuch as the bursts of intercostal EMG activity are seen in association with the effort of breathing.

became available in the late 1980s and caused a revolution in electroencephalography and polysomnography (Wong, 1996; IOSET, 1999; Penzel and Conradt, 2000). This revolution has been primarily in making the static format of analog system data more flexible.

Significant advantages of digital systems include: auto-correction of amplifier gains, self-diagnostic tests of amplifier functions, and the software controlled in-line impedance testing. The use of the computer has facilitated storage of data, manipulation of data after collection, and the presentation of different views of the data. Both analog and digital systems require electrodes and other sensors be applied with the greatest of care. Ideally, calibration procedures should be performed to document and ensure the collection of high-quality data

*Table 3.2***Definitions of PSG variables.**

Lights out	Time	Clock time when the technologist turns the lights out for the patient to go to sleep
Lights on	Time	Clock time when the technologist turns the lights on to end the study
SO	Time and/or epoch #	Sleep onset. Operational definitions vary, but commonly used definition for sleep onset is first of 3 consecutive epochs of stage 1 or the first epoch of any other stage of sleep
Latency to SO	Min	Time from lights out to the first of 3 continuous epochs of stage 1 or any other stage of sleep in minutes
Latency to S1	Min	Time from lights out to the first epoch of Stage 1 sleep in minutes
Latency to S2	Min	Time from lights out to the first epoch of Stage 2 sleep in minutes
Latency to SWS	Min	Time from lights out to the first epoch of Stage Slow Wave Sleep in minutes (Stages 3 or 4)
Latency to REM	Min	Time from sleep onset to the first epoch of Stage REM sleep in minutes
Stage 1	%	The percentage of time spent in stage 1. Calculated by taking the entire total sleep time (TST) and dividing it into the time spent in Stage 1 sleep
Stage 2	%	The percentage of time spent in stage 2. Calculated by taking the entire total sleep time (TST) and dividing it into the time spent in Stage 2 sleep
Stage SWS	%	The percentage of time spent in SWS. Calculated by taking the entire total sleep time (TST) and dividing it into the time spent in SWS
Stage REM	%	The percentage of time spent in stage REM. Calculated by taking the entire total sleep time (TST) and dividing it into the time spent in REM sleep
Stage MT	%	The percentage of time spent in Movement Time. Calculated by taking the entire total sleep time (TST) and dividing it into the time spent in stage Movement Time
Average O2 sat	%	The average oxygen saturation for the entire night
Low O2 sat	%	The lowest oxygen saturation for the entire night
TS1	Min	Total number of minutes spent in stage 1
TS2	Min	Total number of minutes spent in stage 2
TREM	Min	Total number of minutes spent in stage REM
TMT	Min	Total number of minutes spent in stage Movement Time
TRT (TIB)	Min	Total Recording Time (Time in Bed). Calculated by determining the amount of time from lights out to lights on
TST mins:	Min	Total Sleep Time. The amount of time spent sleeping in minutes
TWT mins:	Min	Total Wake Time. The amount of time spent awake in minutes
SE	%	Sleep Efficiency. The amount of time spent sleeping divided by the total time in bed (TIB)
WASO	Min	Wake After Sleep Onset. The amount of time spent awake after sleep onset in minutes
OSA	#	The total number of obstructive sleep apnea events during the night
CSA	#	The total number of central sleep apnea events during the night
HYP	#	The total number of hypopneas during the night
AHI	#	Apnea Hypopnea Index. Calculated by adding the apneas and hypopneas during the night and dividing it by total sleep time (events per hour)
RDI	#	Respiratory Disturbance Index. Calculated by adding all respiratory events during the night and dividing it by total sleep time (events per hour)
AI	#	Apnea Index. Calculated by taking the number of apnea events during the night and dividing it by total sleep time (events per hour)

at the beginning and end of the recording. Knowledge of the specifics of the equipment and of the physiology of interest is important to ensure accurate signal processing.

In digital systems it is rare to encounter breakdown of any mechanical component – most frequently encountered problems have to do with the disk drives or cables. The most important things to avoid for trouble-free operation are mechanical shock, dust or static electricity.

An important factor for understanding digital PSG systems is the concept of sampling rate. Sampling rate can be understood as the frequency with which the signal is reviewed (sampled) for conversion to a digital signal. The minimum acceptable sampling rate for EEG, EOG and EMG in PSG is 100 Hz when using a 35-Hz filter. A 200-Hz sampling rate is required for a 70-Hz high filter setting (AEEGS, 1991).

Another issue unique to digital systems is the accuracy or precision of recordings. The resolution of the signal is a function of the number of binary bits used to represent the digital values. Readers will recall that a bit is a value of 1 or 0. Eight bits is 2 to the 8th power or 256. For example, if we assume an EEG voltage over 256 microvolts, from negative 128 microvolts to positive 128 microvolts this would result in a resolution using an 8-bit system of 1 microvolt difference being represented in 1 bit of change. The 8-bit system is a system which represents the least amount of precision. A 12-bit system is the accepted minimum for sleep recording (Hirshkowitz and Moore, 2000). This provides a range of values between –2048 and +2047. The 12-bit successive digital values represent a 0.0625 microvolt change. The 12-bit representation is far more precise and reflects a smaller change in the signal. (It is interesting to note that the equivalent precision of paper-tracings is approximately 6 bits. The decreased precision for analog systems is a function of the limitation in the amount of paper available for one channel and pen thickness.)

Also to be considered is the display resolution, which is determined by the resolution of the monitor. The screen used for reviewing the data must be at least 20 inches in size, and display a resolution of 1280 × 1024 pixels (flicker free, i.e., 75-Hz monitor scan rate) (Hirshkowitz and Moore, 2000).

3.24. Digital recording samples

The following figures (Figs. 3.14–3.17) are examples of digital data used with permission of the author and publisher (Butkov, 1996).

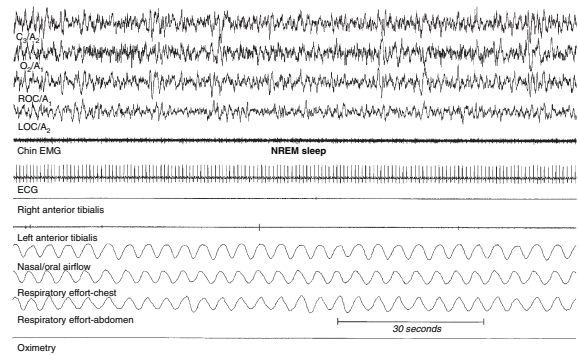


Fig. 3.14. Digital record sample. Digital record sample of NREM sleep using time-scale compression. Digital data can be further compressed to display several epochs on a screen simultaneously. The sample above, and the recordings shown in Figures 3.15–3.17 have been compressed to accommodate four epochs of data (2 min) to a page. This type of display offers the scorer or interpreter a general overview of the sleep recording, as well as a practical method of counting any prominent sleep-related events such as obstructive apneas, hypopneas or body movements. The resolution of the data is inadequate, however, for precise EEG evaluation or sleep-stage scoring. This sample shows a normal respiratory pattern during NREM sleep, without any apparent evidence of arousal, movement, or other form of sleep disturbance. (ROC, LOC = outer canthus of the right and left eye, respectively; EMG = electromyography; ECG = electrocardiography.) (Reproduced with permission from Butkov, 1996.)

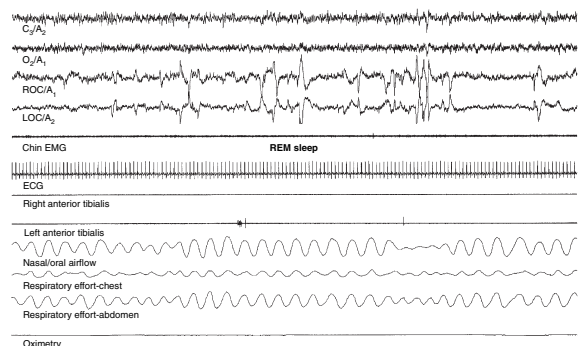


Fig. 3.15. Digital record sample of REM sleep. Although altered by time-scale compression, the sleep-stage pattern seen in the above sample can readily be identified as REM. Note the mild respiratory irregularity, which is a normal variant of REM sleep physiology. (ROC, LOC = outer canthus of the right and left eye, respectively; EMG = electromyography.) (Reproduced with permission from Butkov, 1996.)

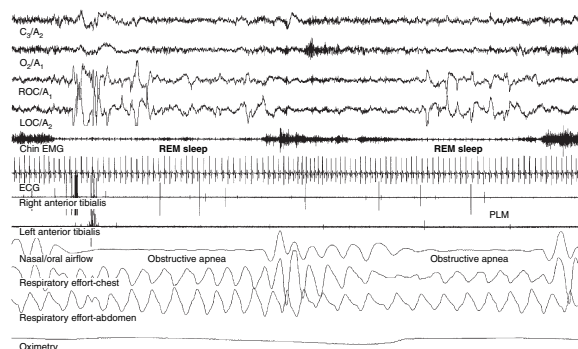


Fig. 3.16. Digital record sample of obstructive apneas. This sample shows a compressed display of repetitive obstructive apneas, occurring during REM sleep. As noted before, these represent the extreme end of the sleep-disordered breathing continuum. In the example above, all the features of classic obstructive sleep apnea are present, including distinct paradoxical (out-of-phase) respiratory effort, instances of complete cessation of airflow, subsequent EEG arousals and cyclic O_2 desaturations. (ROC, LOC = outer canthus of the right and left eye, respectively; EMG = electromyography; ECG = electrocardiography.) (Reproduced with permission from Butkov, 1996.)

3.25. Summary

Throughout its evolution PSG has proven a robust tool for enhancing understanding of sleep and its disorders. It is an essential diagnostic procedure.

PSG is complex and labor-intensive. It requires specialized technical skills and knowledge of normal sleep and sleep disorders. Technologists need to be experts with equipment, competent in dealing with medically ill patients, and capable of dealing with emergencies that may be encountered in the sleep laboratory. They must also be skilled enough to work in many

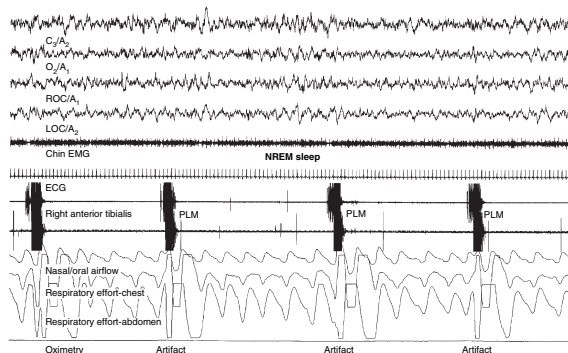


Fig. 3.17. Digital record sample of periodic limb movements. As described previously, periodic limb movements often generate artifacts in the respiratory channels that appear similar to cyclic hypopneas. This sample shows a compressed version of the characteristic pattern of periodic limb movement (PLM), recorded by the right and left anterior tibialis electromyography (EMG). Note that the respiratory channel artifact appears almost identical to the cyclic hypopneas seen in the preceding sample. (ROC, LOC = outer canthus of the right and left eye, respectively; EMG = electromyography; ECG = electrocardiography.) (Reproduced with permission from Butkov, 1996.)

circumstances outside of the traditional laboratory setting.

Our field faces many challenges. Evaluation of sleep disorders must be made readily available to millions of sleep-disorder patients lacking diagnosis and treatment (Phillipson, 1993; Young et al., 1993, 1997). Cost-effectiveness in sleep health care and maintenance of high-quality evaluation and treatment remain important challenges. Digital systems can facilitate data storage, manipulation and analysis provided the user is knowledgeable of both instrumentation and the physiology of interest.

Appendix 1 Template for 24-hour sleep/wake log

This log should be completed by the patient for a period of 2 weeks prior to the study.

Date			Date			Date		
Time	Awake	Asleep	Time	Awake	Asleep	Time	Awake	Asleep
12:00			12:00			12:00		
13:00			13:00			13:00		
14:00			14:00			14:00		
15:00			15:00			15:00		
16:00			16:00			16:00		
17:00			17:00			17:00		
18:00			18:00			18:00		
19:00			19:00			19:00		
20:00			20:00			20:00		
21:00			21:00			21:00		
22:00			22:00			22:00		
23:00			23:00			23:00		
24:00			24:00			24:00		
01:00			01:00			01:00		
02:00			02:00			02:00		
03:00			03:00			03:00		
04:00			04:00			04:00		
05:00			05:00			05:00		
06:00			06:00			06:00		
07:00			07:00			07:00		
08:00			08:00			08:00		
09:00			09:00			09:00		
10:00			10:00			10:00		
11:00			11:00			11:00		
Exercise			Exercise			Exercise		
Treatment			Treatment			Treatment		
Sleep quality			Sleep quality			Sleep quality		
Medications			Medications			Medications		
Comments			Comments			Comments		

For each hour of the day:

- indicate sleep or wake time with an (X)
- indicate naps with an (N)
- indicate periods of extreme sleepiness with an (S)

Appendix 2

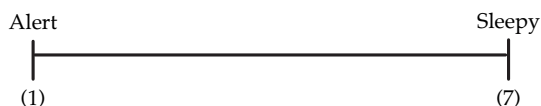
Subjective evaluation of sleepiness

Stanford Sleepiness Scale (Hoddes et al., 1972, 1973)

- (1) Feeling active and vital; alert; wide awake.
- (2) Functioning at a high level, but not at peak; able to concentrate.
- (3) Relaxed; awake; not at full alertness; responsive.
- (4) A little foggy; not at peak; let down.
- (5) Fogginess; beginning to lose interest in remaining awake; slowed down.
- (6) Sleepiness; prefer to be lying down; fighting sleep; woozy.
- (7) Almost in reverie; sleep onset soon; lost struggle to remain awake.

Linear Analog Scale

Ask patient to make a mark on the scale that corresponds to state prior to testing.



Appendix 3

Suggested montage for recording sleep-related seizure activity for a 12-channel study

- (1) Fp1 – C3
- (2) C3 – O1
- (3) Fp1 – T3
- (4) T3 – O1
- (5) Fp2 – C4
- (6) C4 – O2
- (7) Fp2 – T4
- (8) T4 – O2
- (9) EMG – submental–mentalis
- (10) Right outer canthus – left outer canthus
- (11) Nasal/oral airflow
- (12) ECG.

Suggested montage for recording sleep-related seizure activity for a 21-channel study

- (1) Fp1 – F3
- (2) F3 – C3
- (3) C3 – P3

- (4) P3 – O1
- (5) Fp2 – F4
- (6) F4 – C4
- (7) C4 – P4
- (8) P4 – O2
- (9) Fp1 – F7
- (10) F7 – T3
- (11) T3 – T5
- (12) T5 – O1
- (13) Fp2 – F8
- (14) F8 – T4
- (15) T4 – T6
- (16) T6 – O2
- (17) EMG mentalis–submental
- (18) Right outer canthus/A1
- (19) Left outer canthus/A2
- (20) Nasal/oral airflow
- (21) ECG.

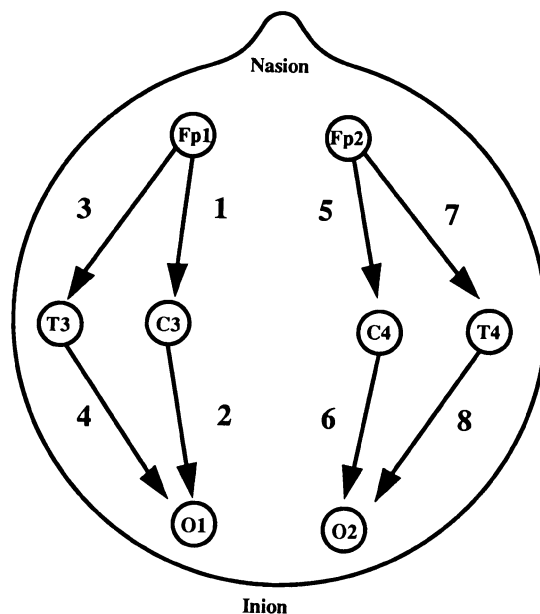


Fig. 3.A2. Suggested montage to be used to screen for possible seizure activity during sleep. Use of wide inter-electrode distance affords for a global view of EEG activity and conserves the channels. To more adequately localize epileptogenic activity a full complement of electrodes should be used. For a more comprehensive review of montages the reader is referred to *Standard EEG Montages* as proposed by American EEG Society Guidelines 1980 No. 7, Grass Instruments.

Appendix 4

Measuring the head for C3, C4, O1 and O2

Before measuring the head, it is helpful to make an initial mark at the inion, the nasion, and the two preauricular points.

- (1) Measure the distance from the nasion to inion along the midline through the vertex. Make a preliminary mark at the midpoint (Cz). An electrode will not be placed on this spot, but it will be used as a landmark.
- (2) Center this point in the transverse plane by marking the halfway point between the left and right preauricular points. The intersection of marks from steps 1 and 2 give the precise location of Cz.
- (3) Reposition the measuring tape at the midline through Cz and mark the points 10% up from the inion (Oz) and nasion (Fpz).
- (4) Reposition the measuring tape in the transverse plane, through Cz, and mark 10% (T3) and 30% (C3) up from the left pre-auricular point and 10% (T4) and 30% (C4) up from the right preauricular point.
- (5) Position the tape around the head through Fpz, T3, Oz, and T4. Ten percent of this circumference distance is the distance between Fp1 and Fp2 and between O1 and O2. Mark these four locations on either side of the midline.
- (6) The second marks for O1 and O2 are made by continuing the horizontal mark for Oz. Do this by

holding the tape at T3 and T4 through Oz, and extend the horizontal mark to intersect the previous O1 and O2 marks.

- (7) To establish the final mark for C3, place the tape from O1 to Fp1 and make a mark at the midpoint of this line. When extended, this mark will intersect the previous C3 mark. Repeat on the right side for C4.

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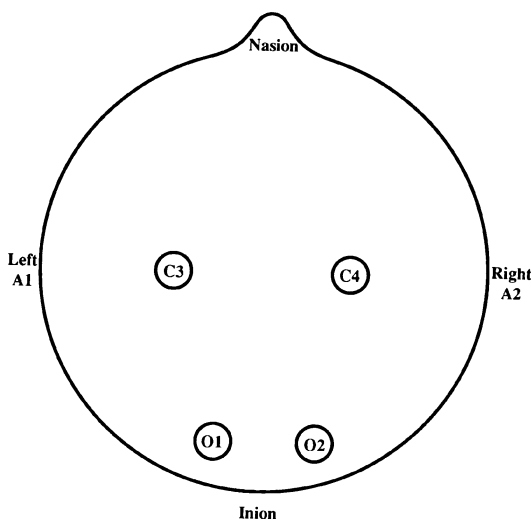


Fig. 3.A3. The international 10–20 EEG electrode placement for sleep recordings are shown.

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CHAPTER 4

Multiple sleep latency test

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4.1. Introduction

The Multiple Sleep Latency Test (MSLT) is the most commonly used method for objective evaluation of daytime sleepiness. This test measures speed of falling asleep on a series of naps, which directly correlates with levels of sleepiness. Thus excessive daytime sleepiness (EDS) is indicated by more rapid sleep onsets than normal control levels. The MSLT has achieved widespread acceptance because of its simple, intuitive approach to sleepiness. Furthermore, the MSLT provides several opportunities to test for sleep-onset REM episodes, the primary diagnostic sign of narcolepsy.

Quantification of EDS is an important procedure as it is a major cause of accidents and other catastrophes (Carskadon and Dement, 1987). EDS also leads to impaired performance, diminished intellectual capacity during everyday activity. Thus, finding a reliable method of assessment of EDS has been the target of much research in the past.

In the 1960s, pupillometry was proposed as a method of assessing EDS. It depends on the fact that the level of arousal of a subject affects the size of his pupil. Yet this method proved to be a difficult technique with several factors affecting the results such as autonomic lesions and the level of patient cooperation (Yoss et al., 1969). Performance tasks were also used to assess EDS. Tasks that are long, repetitious, self-paced and simple, were once thought best to assess the effect of sleepiness, yet more recent work with brief high signal-load tasks, such as the psychomotor vigilance task (PVT) of Dinges and colleagues, show a

significant sensitivity to sleepiness resulting from sleep deprivation or sleep restriction (Dinges, 1992).

Brief questionnaires and self-rating scales were also used. One of the first to be designed and validated specifically to measure sleepiness was the Stanford Sleepiness Scale (SSS), developed by Hoddes and colleagues (1972). The SSS was carefully constructed as a seven-point rating scale of equal-appearing intervals from wide awake to devastatingly sleepy, and validated against sleep deprivation. Though a well-validated measure for assessing sleepiness in controls, patients with chronic sleepiness appear to lose the ability to assess their internal level of sleepiness accurately (Herscovitch and Broughton, 1981). Another approach to measuring sleepiness is exemplified by the Epworth Sleepiness Scale, introduced by Johns (1991). This scale is commonly used by sleep specialists and evaluates behavior not internal state. Thus, the patient is asked to rate the likelihood of falling asleep in eight specific real-life situations. The score ranges from 0 to 24, and a score of 10 or more usually warrants further investigation (Benbadis, 1998).

In the mid-1970s, a new approach was developed which is the 90-minute day, in which a 30-minute 'night' was provided every 90 minutes. It was shown that during the 90-minute day study, the amount of the 30-minute night filled with sleep, which was nearly 100%, correlated to the speed of falling asleep, varied across the 24 hours, and was associated with the temporal distribution of sleep and feelings of sleepiness (Carskadon and Dement, 1975).

The MSLT arose directly from the results of the 90-minute day experiments. This technique was developed by Mary A Carskadon and William C Dement (1977) in the Stanford University laboratory during the early 1970s. There was a great demand for a method that could objectively assess EDS in both clinical and experimental settings. Thus multiple naps during the day, separated by 2 hours and each lasting 20 minutes constitute the MSLT. The 2-hour interval

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was chosen to allow for other measures or experimental assessment tests to be carried between the naps and to avoid overshadowing by the 90-minute ultradian sleep rhythm. The 20-minute nap duration was chosen to avoid excessively long and boring tests.

Lastly, the physiological sleepiness measured by the MSLT cannot be reliably assessed by most subjects (Zorick et al., 1983). For example, recent evidence found no correlation between the subjective Epworth Sleepiness Scale and the objective MSLT, suggesting subjective and objective methods may assess different aspects of sleepiness (Benbadis et al., 1999). This discrepancy may also relate to the ways in which such measures detect state versus trait characteristics. On the other hand, a number of groups have shown that with chronic partial sleep loss, for example, introspective sleep assessments show a far different pattern from the MSLT (Carskadon and Dement, 1981) or performance (Dorrian et al., 2003).

4.2. MSLT procedure

The MSLT procedure is well-standardized according to the guidelines set out by the American Academy of Sleep Medicine (Carskadon et al., 1986). An overnight polysomnogram is carried out the night before the MSLT to examine both the quality and quantity of the night's sleep, which influence the MSLT results. It is ideal that subjects complete sleep diary forms or otherwise have their sleep assessed (e.g., actigraphy) for 1–2 weeks before the MSLT as it was shown that the MSLT may be influenced by sleep for up to 7 nights before the test (Carskadon and Dement, 1981). A sleep diary generally includes information on bedtime, wakeup time, napping and the use of drugs. Subjects should stop any medication that might affect sleep latency (e.g., sedatives, hypnotics, antihistamines) or REM latency (e.g., tricyclic antidepressants) 2 weeks before the study. A urine drug screen on the morning of the MSLT is helpful in identifying patients in whom drug usage is suspected. Subjects should be prohibited from taking caffeine and alcohol the day of the study; however, acute withdrawal from high doses of caffeine may affect test results.

The MSLT is routinely performed at 2-hour intervals, beginning 1.5–3 hours after awakening from nocturnal sleep, and consists of 4–6 naps. Subjects should be in bed 5 minutes before the scheduled nap, to allow for calibrations of the recorded parameters and to establish a standard lead-in into the test. This is an important step as different levels of activity

before the nap affect the sleep latency (Bonnet and Arand, 1998). Between the naps, subjects should remain out of bed and technicians should check that the subject is not sleeping. The naps should be carried out in a sleep-inducing environment; thus, the rooms must be dark and quiet and the temperature adjusted to a comfortable level. The subject is instructed to try to sleep and bedroom lights are turned off, signaling the start of the test, from which sleep latency is calculated. The test is ended after 20 minutes if there has been no sleep, or after 15 minutes from the beginning of sleep (Carskadon et al., 1986). However in some experimental studies, the nap can be terminated at unequivocal sleep onset.

The recording montage includes the standard Rechtschaffen and Kales (1968) technique; central EEG (electroencephalogram), horizontal EOG (electro-oculogram) and chin EMG (electromyogram) electrodes. Strongly recommended additions to this montage are occipital EEG, vertical EOG and ECG (electrocardiogram) electrodes. In clinical studies of patients known to snore, measures of respiratory flow and respiratory sounds may be helpful to identify occasions when snoring affects the sleep onset (Van den Hoed et al., 1981).

4.3. Interpretation and results of the MSLT

Sleep-onset latency and sleep stages are recorded according to standard criteria (Rechtschaffen and Kales, 1968). The criteria used for sleep onset are somewhat variable, with some preferring to score sleep onset by the first 30-second epoch of sleep, while others require three 30-second epochs to determine sleep onset (Benbadis et al., 1996). Standard guidelines recommend defining sleep latency as the first single 30-second epoch of sleep (Carskadon et al., 1986). In experimental settings, the sleep-onset latency is the most commonly required measure, rather than SOREM episodes. Indeed, some studies have utilized a 'modified' MSLT, in which naps were ended directly after sleep onset (Glovinsky et al., 1990).

The MSLT can sometimes be difficult to interpret, and different raters may vary in their findings of whether a patient has sleep-onset REM periods, but less so for the sleep-onset latency (Benbadis et al., 1995). Generally the mean of the sleep-onset latencies is used rather than the median latency.

The MSLT guidelines state that a daily average score of less than 5 minutes indicates a pathological level of daytime sleepiness. This level is associated

with impaired performance in patients and in sleep-deprived normal subjects (Carskadon and Dement, 1985). Adult normal controls usually range from 10–20 minutes (Richardson et al., 1982). Scores between 5–10 minutes lie in the gray zone. They indicate moderate sleepiness, and may or may not be associated with pathologic conditions (Van den Hoed et al., 1981).

Abnormal SOREM periods, which occur within 15 minutes of sleep onset, are of major importance in the diagnosis of narcolepsy. However, other causes of SOREM periods, such as sleep deprivation or other sleep disorders (e.g., obstructive sleep apnea), must be excluded (Mitler et al., 1979).

4.4. Applications of the MSLT

4.4.1. Narcolepsy

One of the most common indications of the MSLT is evaluation of a suspected case of narcolepsy. EDS is usually the main symptom of narcolepsy, often preceding the onset of the other well-known symptoms of the disease, namely cataplexy, sleep paralysis and hypnagogic hallucinations (Dement et al., 1976). Evaluation of the MSLT of narcoleptic patients has demonstrated a short sleep latency (<5 minutes) and more than one SOREM period. The more specific finding in the MSLT of narcoleptic patients is two or more SOREM periods, shown to reach a specificity of 99% by Amira et al. (1985), which further increased to 99.2% if three SOREM periods were recorded (Aldrich et al., 1997). On the other hand, more than one SOREM period can occur in non-narcoleptic patients, such as those with sleep apnea, sleep deprivation, depression, periodic limb movements, circadian rhythm disruption or withdrawal from REM-suppressing medications (Benbadis, 1998; Kader, 1998). Thus, the findings of the MSLT must be interpreted in view of the clinical history and nocturnal PSG.

4.4.2. Other disorders of EDS

The differential diagnosis of EDS includes narcolepsy, obstructive sleep apnea, sleep deprivation, periodic limb movement disorder, idiopathic CNS hypersomnia, psychiatric diseases and use of sedating medications (Parkes, 1993). Attempts to reach a differential diagnosis using the MSLT have been made by Reynolds et al. (1982) and Zorick et al. (1982), who

carried out the MSLT for groups of patients with various disorders of EDS. They found that the patients with narcolepsy or sleep apnea had the shortest sleep latency (<5 minutes), while patients with psychiatric disorders showed the longest latency (>10 minutes), reaching values similar to normals. Patients with idiopathic CNS hypersomnia, periodic limb movement disorder, or insufficient sleep occupied a middle position (5–10 minutes). REM latency was significantly shorter in narcolepsy than in apnea, and more than 70% of the naps were SOREM positive in narcolepsy and less than 20% in the other disorders. A non-standard MSLT measure, sleep percentage, increased and sleep latencies decreased during the day in patients with narcolepsy or sleep apnea. In contrast, sleep percentage was gradually reduced from a mean of 52.5% to a mean of 39.8% during the day in depressives, paralleling improvement in mood and energy levels.

In a study by Van den Hoed et al. (1981), 100 patients with EDS due to disorders other than sleep apnea underwent the MSLT and nocturnal PSG. When the results were compared to the established diagnosis in an attempt to verify the MSLT's ability to classify patients, mean sleep latency on the MSLT alone correctly classified 82% of narcoleptics. The MSLT mean sleep latency value and the sleep latency on the nocturnal PSG were able to objectively differentiate between different groups with EDS.

In a more selective study, Kayumov et al. (2000) studied 22 patients with depression/anxiety and 47 non-depressed patients with sleep apnea using the PSG, MSLT and maintenance of wakefulness test (MWT). They found that depressed patients with more disturbed nocturnal sleep paradoxically showed greater daytime alertness. These findings may indicate an underlying factor that inhibits sleep at night and in the daytime. In contrast, more disturbed nocturnal sleep in the sleep apnea patients was associated with lower sleep latency scores on the MSLT.

Although the above studies point to a potential value of the MSLT as a tool in the differential diagnosis for complaints of EDS, it cannot be used alone without a PSG in evaluation of sleep-disorder patients, but rather it serves as a complementary test.

4.4.3. Insomnia

It is expected that, as in the sleep-deprived individuals, patients with insomnia would have a short sleep latency on the MSLT. However, in a study by Seidel and Dement (1982), only 7% of insomniacs were in

the pathological range on MSLT (<5 minutes), while 17% were in the 'gray area' (5–10 minutes), and 41% had scores >15 minutes. These data point to the heterogeneity of patients with insomnia.

Bonnet and Arand (1996) performed a study in which sleep recordings from ten insomniacs were used as a template for disrupting similar sleep in a group of matched normal sleepers for seven nights. The aim was to determine if specific electroencephalographic sleep patterns were responsible for the secondary insomnia symptoms reported by the insomniacs. Although both groups complained of decreased vigor, insomniacs had increased sleep latencies on the MSLT, while normal subjects showed decreased latencies following the sleep manipulation. These investigators concluded that the secondary symptoms reported by patients with primary insomnia are probably not related to their poor sleep per se, but occur secondary to central nervous system hyperarousal.

The previous studies led to the hypothesis that the insomnia patients may be suffering from a state of chronic activation that disturbs night sleep but protects against or prevents EDS from occurring in the morning. Conversely, such patients may be naturally 'short sleepers' whose sleep need may be fulfilled with relatively short sleep at night.

4.4.4. *Evaluation of medications*

Hypnotic drug efficacy depends not only on improving the quality of nocturnal sleep, but also on the diurnal effects of the drug. The ideal sleeping pill would increase the amount and consolidation of nocturnal sleep, which should improve waking alertness or at least should not further compromise it. Carskadon and colleagues (1982) compared two hypnotics; a short-acting (e.g., triazolam) and a long-acting (e.g., flurazepam) benzodiazepine in insomnia. They found that the insomniacs treated with flurazepam had a shorter sleep latency on the MSLT using the drug than on baseline, while the triazolam group had a longer sleep latency with treatment. These findings were attributed to a carry-over of sedating effects of the long-acting compounds, and improvement of daytime alertness with short-acting compounds due to improved nocturnal sleep.

In another study, two groups of subjects underwent sleep deprivation combined with either bedtime midazolam or a placebo drug. It was found that both groups had similar latencies on the MSLT with partial sleep deprivation, while the placebo group had a shorter

latency with complete sleep deprivation. They interpreted these findings as showing that bedtime midazolam does not affect alertness the following day (Borbely et al., 1985).

The MSLT has also been used for assessment of other types of compounds that may affect diurnal somnolence. Roehrs et al. (1984) showed that certain types of antihistamines increase sleepiness, with the MSLT used as the objective measure, while other types do not. On the other hand, the alerting effect of caffeine has been proven by its ability to increase the sleep latency on the MSLT of normal sleep-deprived subjects (Lumley et al., 1987).

Objective assessment of different lines of treatment for obstructive sleep apnea syndrome, such as continuous positive airway pressure or airway surgery, is offered by the MSLT. It was shown that in comparing pre- and post-treatment symptoms, a subject may perceive an improvement of awareness as very substantial, whereas the MSLT may reveal that the vulnerability remains (Zorick et al., 1983; Wittig et al., 1986).

The assessment of various drug regimens using a sensitive measure of diurnal somnolence may aid in the determination of appropriate treatment strategies while minimizing sleepiness-inducing side effects. These studies underscore the potential of the MSLT as a valuable tool for assessing many types of compounds, not only for those in which the primary action is sleep-inducing (Carskadon and Dement, 1987).

4.4.5. *Studies of effects of sleep deprivation, fragmentation or extension*

Chronic partial sleep restriction is a topic of current interest and one that was examined two decades ago by Carskadon and Dement (1981). During a week of restriction to 5 hours of sleep a night, ten college-aged adults manifested an accumulating decrease of sleep latency scores that did not plateau. A more recent chronic sleep restriction study (Dinges et al., 1997) showed a 0.95 correlation of performance measures with the Carskadon et al. (1981) MSLT scores. These studies provided important support for the concept of sleep deficits that continue to grow as sleep reduction is prolonged. A more recent interpretation implicates 'excess wakefulness' as the primary factor rather than sleep deficit (Van Dongen et al., 2003).

Another interesting question that was examined using MSLT was the effect of deprivation of specific sleep stages. Walsh et al. (1994) found that selective deprivation of SWS does not appear to produce

greater decrements in alertness than deprivation of non-SWS sleep. Another study by Glovinsky et al. (1990) found that REM sleep and stage 2 awakenings produced comparable increased levels of sleepiness during subsequent daytime MSLTs compared to baseline non-disturbed sleep. However, Nykamp and colleagues (1998) reported a contradictory finding from a study of sleeping subjects who were awakened each time they entered REM stage. They did not demonstrate any changes in MSLT scores compared to baseline non-disturbed nights. These investigators concluded that the REM-deprivation procedure antagonized the effects of sleep loss on daytime sleepiness. The mechanism by which REM deprivation would exert such an alerting effect is unknown.

As regards total sleep deprivation, Carskadon and Dement (1979) performed the first MSLT study to test the effects of two nights of sleep loss in six young subjects. The scores fell to about 1 minute at 06.00 on the first night of sleep loss and remained at similarly low values throughout the sleep loss period. After one night of recovery sleep the scores remained significantly below baseline levels, which were not achieved until after the second recovery night.

Direct comparison of sleep deprivation in healthy 80-year-olds and 20-year-olds showed that young subjects had shorter daytime sleep latencies than the old subjects after sleep deprivation, suggesting a greater unmet sleep need in the former group. This finding suggests that acute total sleep loss is a more disruptive procedure for the young than for the old (Brendel et al., 1990).

Howard and colleagues (2002) suggested a reform of residents' work and duty hours based on a study that assessed the levels of physiologic and subjective sleepiness in 11 anesthesia residents in three conditions: (1) during a normal (baseline) work schedule, (2) after an in-hospital 24-hour on-call period, and (3) following a period of extended sleep. MSLT scores were shorter in the baseline (6.7 min) and post-call (4.9 min) conditions, compared with the extended-sleep condition (12 min), and there was no significant difference between the baseline and post-call conditions. Residents' daytime sleepiness on the MSLT in both baseline and post-call conditions was near or below levels associated with clinical sleep disorders, and residents were subjectively inaccurate determining EEG-defined sleep onset.

Roehrs et al. (1994) carried out a sleep fragmentation study without sleep deprivation. Sleep was disrupted on two nights by presenting tones that produced

brief electroencephalographic (EEG) arousals (without shortening sleep time). Daytime function was assessed the following day with the MSLT and a divided attention performance test. These investigators found that sleep fragmentation produced significant disruption of nocturnal sleep and reduced daytime alertness.

On the other hand, studies of adults extending sleep beyond an average of 7.5 hours of sleep at night have produced contradictory findings. While Roehrs and colleagues (1996) found that sleep extension produced significantly longer sleep-onset latency MSLT scores, Harrison and Horne (1996) found that extended sleep produced no improvements in self-rated mood or subjective sleepiness. In fact, MSLT scores during extended sleep in the latter study showed small (about 1 min) reductions. These investigators suggested that their findings provided little support to the view of chronic sleep deprivation in the average 7.5-h sleeper. However, Carskadon and colleagues have shown substantial differences in daily MSLT scores in several age groups as a function of sleep times that are shorter or longer than thought to be 'usual' sleep need (Carskadon and Dement, 1987).

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CHAPTER 5

The maintenance of wakefulness test

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5.1. Introduction

In clinical, industrial and research settings, the complaint of sleepiness can represent a serious, potentially life-threatening condition that affects the individual, his family, co-workers and society in general. The maintenance of wakefulness test (MWT) is a physiological test of this complaint. It assesses, via polysomnography, an individual's ability to successfully resist the urge to fall asleep (i.e., the ability to remain awake) during soporific circumstances and provides, therefore, an objective measure of wake tendency.

5.2. Historical overview

Daytime nap studies have been utilized extensively as a way of assessing the extent of daytime somnolence (Tepas, 1967; Weitzman et al., 1974; Moses et al., 1975; Webb and Agnew, 1975; Carskadon and Dement, 1979). The first such procedure to be utilized for clinical purposes was the MSLT introduced by Richardson et al. (1978). Initially, its primary application had been the confirmation of the diagnosis of narcolepsy. It was soon applied, however, to assess the extent of daytime somnolence in narcolepsy and other disorders, most notably obstructive sleep apnea syndrome (Roth et al., 1980), both at baseline and following treatment. Questions were soon raised, however, whether MSLT accurately measures the clinical function of greatest interest in some sleepy patients. The MSLT assesses how easily patients succumb to sleep,

i.e., sleep tendency. However, the function of greater relevance in some situations is how successful they are in resisting this urge, inasmuch as the latter more closely reflects the challenge that they face in the soporific situations of everyday life such as driving and reading. Hartse et al. (1982) investigated sleep and wake tendency in a multiple nap study in normal subjects and noted that sleep latency increased by changing instructions from 'try to sleep' to 'try to stay awake'. They then developed the repeated test of sustained wakefulness (RTSW), which involves instruction to remain awake while lying in bed. Mitler et al. (1982a,b) then developed the MWT which is similar in its instructions to the RTSW, yet patients are positioned in a comfortable, partially reclining, chair or propped-up in bed. In this study, they reported both the methodology and results in ten narcoleptics and eight controls. Mean sleep latency differed significantly between narcoleptics and controls (9.9 min vs 17.9 min, respectively). Narcoleptics also exhibited an average of 3.2 sleep-onset REM episodes over the five sessions vs none for the controls. Sleep latency increased by 300% when instructions were changed from 'try to sleep' to 'try to remain awake'. Nevertheless, eight narcoleptics who were re-tested following treatment did not exhibit a significant increase in MWT sleep latency.

In the intervening years, the MWT has been utilized clinically to quantify the extent of daytime somnolence, to assess the effects of treatment in sleepy patients, and to determine patients' suitability for performing tasks at home and in the workplace. Despite diversity in methodology, the core aspects of the test have remained constant. Following a night of polysomnography, and while being monitored polysomnographically, patients are given four to five opportunities, at 2-hour intervals, to remain awake while comfortably reclining in a bed or armchair. The first trial begins at 10:00. Patients are instructed to

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remain awake as long as possible. Depending on the application, trials are terminated either at sleep onset or following a constant period of sleep. Sleep latency is calculated for each wakefulness opportunity and an average sleep latency score is reported, which is regarded as being inversely proportional to the extent of daytime somnolence.

Methodological diversity has existed in various areas. These include polysomnographic montage, illuminance level, seating position, room temperature, meal timing and patient instructions. The effect of many of these factors on sleep latency in nap test protocols has been demonstrated (Doghramji et al., 1994; Bonnet and Arand, 2001). Methodological uniformity is clearly desirable for those who wish to compare results of various trials and assess clinical results in the context of normative data. The two areas of greatest variability have been the definition of sleep onset and duration of each wakefulness opportunity. The initial studies of Mitler et al. (1982a,b) utilized a stringent definition of sleep onset, i.e., three 30-s epochs of stage 1 or one epoch of any other sleep stage. On the other hand, later studies with obstructive sleep apnea patients (Sangal et al., 1992a; Sangal and Sangal, 1997) under treatment utilized a more lenient definition of sleep onset, i.e., one 30-s epoch of any sleep stage. The former, stricter, definition of sleep onset would be anticipated to yield longer sleep latency scores than the latter. Similarly, wakefulness opportunity durations have varied between 20 minutes and 40 minutes. Scores for the 40-minute trial would be anticipated to be longer. To a certain extent, methodological variations have resulted from attempts to adapt the MWT to a variety of situations depending on the degree of sleepiness and motivational characteristics of the population to be studied. As examples, with extremely somnolent subjects such as patients with narcolepsy, a shorter trial duration, say 20 minutes, can be used with minimal ceiling effects. In individuals who are only moderately sleepy (say, MSLT sleep latencies in the 6–10 minute range), as opposed to extremely sleepy (say MSLT sleep latencies in the 0–5 minute range), MWT trial durations of 30 or 40 minutes are needed to reduce problems with ceiling effects (Timms et al., 1985; Poceta et al., 1992; Ionescu et al., 2001).

5.3. Normative data

Normative data for the MWT under standardized conditions were recently provided (Doghramji et al.,

1997) in a multi-center study of 64 healthy subjects (27 males and 37 females) whose ages ranged between 30 and 70 years. Test conditions were kept uniform across sites and subjects, including polysomnographic montage, illuminance level, seating position, room temperature, meal timing and subject instructions. Subjects were given four 40-minute MWT trials at 2-hour intervals with the first trial beginning at 10:00. Bedrooms were dimly lit and illuminance was measured at 0.10–0.13 lux at the corneal level. Subjects sat up in bed with their backs and heads supported by a bed-rest cushion. Ambient temperature was kept at 72°F. Meal timing was set at 1 hour prior to the first MWT trial, and immediately after the termination of the noon trial. Instructions to the subjects were 'Please sit still and remain awake for as long as possible. Look ahead of you, and do not look directly at the light.' Subjects were not allowed to maintain wakefulness by using extraordinary measures such as slapping the face or singing. Each wakefulness trial was terminated either at the first onset of sleep or, if sleep onset was not achieved, after a maximum in-bed duration of 40 minutes. Sleep onset was defined as the first occurrence of sustained sleep defined as three consecutive 30-second epochs of stage 1 or any single 30-second epoch of another sleep stage (II, III, IV or REM). However, in an effort to understand the effects of variations in trial duration and definition of sleep onset, sleep latency scores were also calculated on the basis of a sleep onset defined as the first epoch of any sleep stage. Similarly, although the study was conducted with a maximum wakefulness trial duration of 40 minutes, sleep latency scores were also calculated on the basis of 20-minute trial durations. Therefore, the trial not only yielded normative data, but also allowed for comparison of these data to those of prior trials utilizing various methods. In summary, results were calculated utilizing the following four protocols:

- (1) **SUSMWT40:** 40-minute MWT trials with sleep onset defined as three continuous epochs of stage 1 sleep or any single epoch of another sleep stage.
- (2) **MWT40:** 40-minute MWT trials with sleep onset defined as the first epoch of any sleep stage.
- (3) **SUSMWT20:** 20-minute MWT trials with sleep onset defined as three continuous epochs of stage 1 sleep or any single epoch of another sleep stage.
- (4) **MWT20:** 20-minute MWT trials with sleep onset defined as the first appearance of any sleep stage.

Normative data obtained from this trial are summarized in Tables 5.1 and 5.2. As anticipated, longer maximum trial durations yielded longer sleep latency scores. However, average scores were not affected by the definition of sleep onset.

5.4. Clinical applications

5.4.1. Assessment of the 'normality' of an individual

The problem of defining normal and abnormal performance on tests such as the MWT has no universal solution. Some have advocated the use of standard deviation criteria; threshold values for normality are often considered to be two standard deviations (SDs) from the mean (American Electroencephalographic Society, 1994). Applying this definition to normative

Table 5.1

Individual and average MWT sleep latency scores for the SUSMWT40 protocol. Sleep latency scores are in minutes. SD – standard deviation; pertl – percentile. See text for additional details (Doghramji et al., 1997).

	Trial 1	Trial 2	Trial 3	Trial 4	Mean
Mean	36.3	34.0	34.2	36.5	35.2
SD	9.2	12.0	11.5	8.8	7.9
Minimum	3.0	4.5	3.5	1.2	7.1
Maximum	40.0	40.0	40.0	40.0	40.0
10th percentile	18.2	9.6	11.5	25.4	21.7
25th percentile	40.0	40.0	40.0	40.0	32.8
50th percentile	40.0	40.0	40.0	40.0	40.0
75th percentile	40.0	40.0	40.0	40.0	40.0
90th percentile	40.0	40.0	40.0	40.0	40.0

Table 5.2

Comparison of MWT normative with clinical data.

Study	Sample	N	Sleep Onset Criteria	Trial Duration	Protocol	Mean Sleep Latency	p ^a
Doghramji et al., 1997	Normals	64	A	40	SUSMWT40	35.2 ± 7.9	
‘			A	20	SUSMWT20	18.7 ± 2.6	
‘			B ^b	40	MWT40	32.6 ± 9.9	
‘			B ^b	20	MWT20	18.1 ± 3.6	
Poceta et al., 1992	OSA	322	A	40	SUSMWT40	25.9 ± 11.8	<0.0001
Sangal et al., 1992a	Excessive daytime sleepiness	258	B	20 ^c	MWT20 ^c	15.9 ± 5.0	<0.001
‘	Excessive daytime sleepiness	258	B	40	MWT40	26.5 ± 12.4	<0.001
Browman et al., 1986	Narcolepsy	11	A	20	SUSMWT20	10.7 ± 5.3	<0.001
‘	Normal Controls	11	A	20	SUSMWT20	19.0 ± 1.5	≥0.05
Browman et al., 1983	Narcolepsy	12	A	20	SUSMWT20	11.0 ± 5.6	<0.001
‘	OSA	12	A	20	SUSMWT20	11.0 ± 4.8	<0.001
‘	Normal Controls	10	A	20	SUSMWT20	18.3 ± 4.0	≥0.05
Mitler et al., 1982b	Narcolepsy	10	A	20	SUSMWT20	9.9 ± 6.1	<0.001
‘	Normal Controls	8	A	20	SUSMWT20	17.9 ± 4.4	≥0.05

A: Three 30-sec epochs of stage 1 or one epoch of any other sleep stage

B: One 30-sec epoch of any sleep stage

^a Compared with corresponding measure of sleep latency in Doghramji et al, 1996

^b Or 10 seconds of μ sleep

^c Data based on a 40-minute protocol were recalculated for the 20-minute protocol
Trial durations are in minutes and mean sleep latency scores in minutes ± SD.

Table 5.3

Lower limits for normality as assessed by two standard deviations lower than the mean for various MWT protocols. Abbreviations: SD – standard deviation. (Doghramji et al., 1997).

Protocol	Lower limit (mean minus 2 SD in minutes)	% Subjects scoring less than lower limit
SUSMWT40	19.4	8
MWT40	12.9	9
SUSMWT20	13.5	6
MWT20	10.9	8

data yields low limits for normality, which appear in Table 5.3. Depending on the protocol utilized, therefore, individuals scoring below these cutoff points would be considered to be ‘too sleepy’. An example of the application of these threshold values is their comparison to the MWT results of 258 patients with complaints of sleepiness reported by Sangal and colleagues (1992a). A total of 19% had mean sleep latency scores less than 10.9 min on the MWT20, and the same number had scores less than 12.9 min on the MWT40. Thus, 19% of these patients can be considered to be ‘too sleepy’ by these criteria.

The use of standard deviation criteria is, however, problematic since normative MWT sleep latencies form a skewed distribution that is truncated at 40 minutes (Figure 5.1) with most subjects able to maintain wakefulness on each trial, but with a few subjects failing to maintain wakefulness after as little as 10 minutes. Some investigators have, therefore, suggested using a percentile cut-off. If abnormal were regarded as average MWT scores below, say, the 10th percentile, the cutoff value for the 40-minute protocol would be 21.7 minutes (Table 5.1), and for the 20-minute protocol would be 14.0 minutes. Others have suggested that the number of trials in which a subject fails to maintain wakefulness should define pathology. The normative data indicate that, on average, for both the 40-minute and 20-minute trials, that number is less than 1 (0.81 ± 1.25 and 0.56 ± 1.02 , respectively).

5.4.2. Assessment of safety

Occupations in which the assessment of safety can be important include airline pilots and truck drivers. The

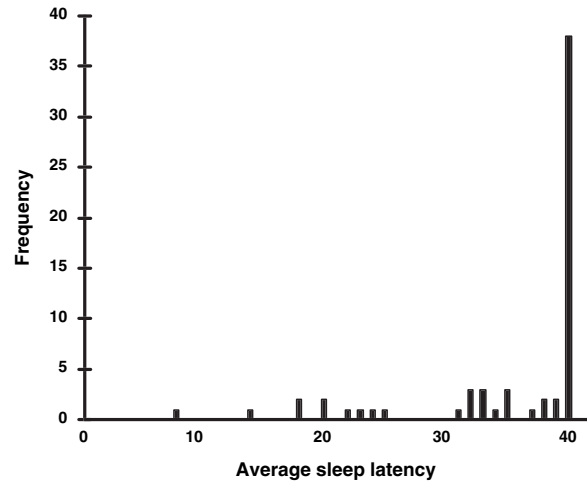


Fig. 5.1. Normative MWT data. Average sleep latencies over four 40-minute long MWT trials were calculated for each of 64 healthy volunteers and plotted in frequency histogram format. See text for details (Doghramji et al., 1997).

assessment of safety in driving is also of great importance for most patients with disorders of daytime somnolence. Unfortunately, no physiologically based test, including the MWT, has been shown to be a valid predictor of operator errors on the highway or in the workplace. Therefore, the use of the MWT as a stand-alone tool in determining fitness for duty cannot be fully supported. That having been said, ignoring poor performance on the MWT also seems inappropriate. No cut-off points with respect to average sleep latency or number of failed MWT trials are suggested here. However, it is wise to consider several MWT parameters (e.g., average sleep latency, number of failed trials, etc.) as part of a comprehensive evaluation. It may also be useful to establish, with the participation of relevant stakeholders, guidelines for pass/fail ranges.

5.4.3. Providing a profile of sleepiness for groups with certain disorders

It is useful to describe the characteristic degree of impairment in alertness for disorders of excessive somnolence. The MWT has been utilized in this capacity for narcolepsy and sleep apnea syndrome, as summarized in Table 5.2 (Browman et al., 1983, 1986; Poceta et al., 1992; Sangal et al., 1992a; Sangal and Sangal, 1997). All studies also include a comparison with healthy controls.

5.4.4. Detecting the effect of therapeutic interventions

The MWT has also proven to be sensitive in assessing treatment efficacy of continuous positive airway pressure in obstructive sleep apnea syndrome (Sangal et al., 1992b) and of various pharmacological agents in narcolepsy (Fry et al., 1986; Mitler et al., 1986, 1990). The MWT and the RSW have been shown to be sensitive to pharmacological interventions aimed at reducing sleepiness (Sugerman and Walsh, 1989; Mitler et al., 1990; U.S. Modafinil in Narcolepsy Multicenter Study Group, 2000). Data on the ability to sustain wakefulness during the night and the remedial effects of napping and caffeine on functioning during simulated shiftwork are also available (Sugerman and Walsh, 1989; Walsh et al., 1990a,b; Walsh et al., 1991a,b).

5.5. MWT vs MSLT

The MWT can be conceptualized as an outgrowth of the MSLT with altered instructions and body position. Some studies have shown that the MSLT and MWT produce similar data when detecting remedial interventions (U.S. Modafinil in Narcolepsy Multicenter Study Group, 2000). However, other studies have failed to show a consistent relationship between the two when applied to the same patient groups (Timms et al., 1985; Sangal et al., 1992a; Doghramji et al., 1993, 1997). Such data suggest that the MSLT and the MWT assess fundamentally separate functions, i.e., waking ability and sleeping ability. Discordance between the MSLT and the MWT may also be partially understood, as Bonnet and Arand (2001) suggest, in terms of the additive effects of instruction and posture. Another potential explanation is that the MWT, because of its instructions to remain awake, adds a non-linear motivational factor that is not present with the MSLT. The MWT often reveals improvement in treated patients who continue to be physiologically sleepy on MSLT. Thus, the MWT is sometimes considered to be a way of extending the sensitivity range of the MSLT (Mitler and Miller, 1996). Such reasoning is complicated, however, by the possibility that the MSLT may also incorporate non-linear motivational factors.

The MSLT and the MWT may have a unique set of clinical applications. Various studies have indicated that, whereas the MSLT is not particularly sensitive in

detecting treatment effects in patient groups (Browman et al., 1986; Gaddy and Doghramji, 1991), the MWT is. The MWT is also sensitive in detecting the effects of the manipulation of the prior night's sleep quality and quantity (Sugerman and Walsh, 1989) on daytime alertness. It also stands to reason that the MWT may be more accurate in assessing the risk of falling asleep unintentionally during soporific activities where individuals are attempting to stay awake, such as driving, reading and other activities of daily life. However, no such comparisons between the two tests have been yet performed. Clearly greater studies are needed to explore the reasons for the discordance between the two tests and the relative utility of each.

5.6. Protocol recommendations

As noted above, various definitions of sleep onset and trial duration have been utilized for the MWT since its introduction. Regardless of definition, however, the MWT appears to be capable of separating sleepy from healthy individuals. Therefore, the determination of which of these protocols should be utilized in each individual case can be based on the specific clinical need and the nature of practical constraints. For example, if the sample being tested is likely to have subjects with a low level of sleepiness, maximizing the test's sensitivity in detecting sleep onset and maximizing the duration of each trial may minimize the potential for a ceiling effect and, in turn, allow for more meaningful comparison among subjects tested. In this case, therefore, utilizing the 40-minute trial duration and the first appearance of any epoch of sleep as the definition of sleep onset may be optimal. The same protocol may be best suited for assessing treatment response. If the population under investigation is highly sleepy, or if accuracy is critical, the more stringent definition of sleep onset (three epochs of stage 1 or one epoch of any other sleep stage) may be preferred. Practical, economic, limitations may favor the use of the 20-minute duration.

For routine, clinical, applications, authors of the normative trial (Doghramji et al., 1997) recommended the use of the 20-minute protocol with sleep latency measured to the onset on any sleep stage. They noted that the 20-minute protocols are more cost-effective, and, unlike the 40-minute protocol, are not affected by age. Below are their recommendations, noted in a consensus statement:

- (1) Lighting: The room should be maximally insulated from external light. The light source should be positioned slightly behind the subject's head such that it is just out of his field of vision, and should deliver an illuminance of 0.10–0.13 lux at the corneal level (in our study a 7.5 watt night light was utilized, 1 ft. off the floor, and 3 ft. laterally removed from the subject's head).
- (2) Seating position: Sitting in bed, back and head supported by a bedrest such that neck is not uncomfortably flexed/extended during sleep.
- (3) Room temperature as close to 22°C (72°F) as possible. Temperature should be recorded at the beginning of each trial.
- (4) Meals: A light breakfast at least 1 hour prior to the first nap, and a light lunch immediately after the termination of the noon nap.
- (5) Instructions to patients: 'Please sit still and remain awake for as long as possible. Look directly ahead of you, and do not look directly at the light.' Patients should be disallowed from using extraordinary measures such as slapping the face or singing.
- (6) Monitoring montage: C3/A2, O1/A2, EMG, EOG.
- (7) Sleep onset: The first occurrence of one epoch of any stage of sleep.
- (8) Trials should be performed at 2-hour intervals, the first beginning at 10:00.
- (9) Trial termination: (a) At sleep onset or (b) after 20 minutes in bed if sleep onset not achieved.
- (10) Scoring: Sleep latency is defined as the time from trial onset to the first epoch of any sleep stage.
- (11) Data to be recorded: Sleep latency, total sleep time, total wake time, stages of sleep achieved for each trial.
- (12) Interpretation: Impairment in wake tendency exists if the mean sleep latency is less than 11 minutes.

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CHAPTER 6

Actigraphy

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6.1. Introduction

Over the last few decades, actigraphy has gained popularity and credibility in the fields of sleep medicine and sleep research. Reviews commissioned by the Standards of Practice Committee of the American Sleep Disorders Association (now the American Academy of Sleep Medicine) accompanied by specific professional guidelines have established actigraphy as an important instrument for the assessment of sleep–wake patterns and specific sleep disorders (American Sleep Disorders Association, 1995; Sadeh et al., 1995; Ancoli-Israel et al., 2003; Littner et al., 2003).

6.2. What is actigraphy?

Actigraphy (or actimetry) refers to activity monitoring for extended periods. Activity monitoring has been extensively used for different applications in biomedical research (Tryon, 1991). In the sleep field monitoring of crib movements has already been used to document infant sleep in the early 1950s (Kleitman and Engelmann, 1953). With the advance of technology, the modern use of actigraphy for sleep research was accelerated in the 1980s.

Modern actigraphy is based on wristwatch-like devices attached to the wrist or the ankle in young subjects or for other special purposes (see Figure 6.1). A typical device has a piezoelectric movement sensor that translates movements in two or three dimensions to an analog signal. This signal is filtered using different filter settings and then digitized and stored in the internal solid-state memory. The filter settings,

sampling rate, storage capacity and other technical features vary from one device to another and some devices are programmable and permit different modes of operation. The most common mode of operation is with 1-minute epochs, which allow continuous monitoring of at least 1 week. The data from the actigraph are downloaded to a computer using a special interface or other form of communication.

The raw activity data (see Figure 6.2) could be viewed and analyzed on a computer using tailored programs. Some of these programs have sleep–wake scoring algorithms that have been validated with polysomnography or other scoring methods. The scoring algorithms determine the status of each minute (e.g., sleep versus wake), and then provide summary measures that are comparable to familiar sleep measures (e.g., sleep onset time, sleep efficiency, sleep latency).

Different devices and associated software programs have been produced and distributed by different commercial companies. Although this chapter does not discuss distinct features of specific commercial units, it is important to emphasize that different devices have different features including the status of their validation and reliability studies. Therefore, the following information on reliability and validity of actigraphy is only relevant to the specific tested devices.

Analyzing actigraphy data requires familiarity with artifacts that are an integral feature of this methodology. Actigraphy measures movements of the device and externally induced movements are registered regardless of their source. Therefore, sleeping in a moving vehicle or in a crib rocked by an automatic rocking device would be registered as a high-activity period although the individual might be fully asleep (Sadeh et al., 1994). Additional common artifacts include removal of the device during the monitoring period, sensitivity problems related to technical failures, or inappropriate attachment of the device.

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Fig. 6.1. A child sleeping with an actigraph attached to her left wrist.

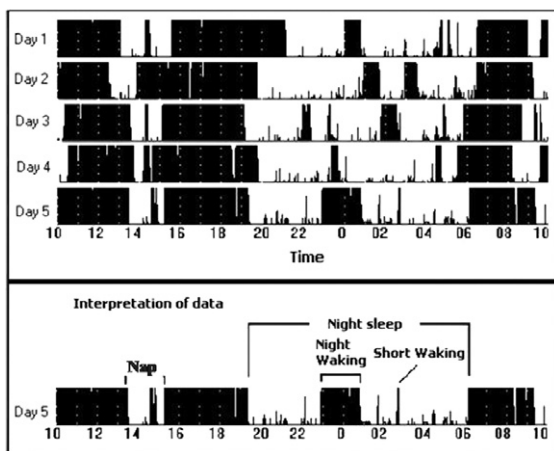


Fig. 6.2. Raw data obtained from actigraphy. This figure describes 5 days of continuous monitoring in a 1-year-old infant. The lower frame represents the interpretation of the last day of monitoring. The data reflect the activity level of each minute of monitoring. 'Black' areas are periods of increased activity, usually associated with wakefulness. 'Quiet' areas with low levels of activity are usually identified as quiet or active sleep. Reprinted with permission from: Sadeh, A (2001) 'Sleeping like a Baby', New Haven: Yale University Press.

Another important methodological issue is related to actigraph placement. The common practice has been the non-dominant wrist in adults and the ankle in young children. Studies assessing the issue of placement found systematic differences in activity level recorded from different body sites (van Hilten et al., 1993c; Sadeh et al., 1994; Middelkoop et al., 1997; Violani et al., 1998). Studies suggested that sleep-wake algorithms may be robust to these differences in activity level (Jean-Louis et al., 1997; Sadeh et al., 1994). However, it is important to maintain

standard placement to minimize variability associated with actigraph location and to enable comparisons between individuals and between studies.

6.3. Reliability and validity of actigraphy

A growing number of studies have demonstrated the reliability of actigraphy for documenting sleep-wake patterns (Sadeh et al., 1995; Acebo et al., 1999; Sadeh and Acebo, 2002; Ancoli-Israel et al., 2003). A substantial number of studies focused on developing and validating sleep-wake scoring algorithms against polysomnography (e.g., Webster et al., 1982; Sadeh et al., 1989, 1994; Cole et al., 1992; Horne et al., 1994; Jean-Louis et al., 1996). In normal subjects, these algorithms have generally provided high (above 80%) agreement rates for minute-by-minute sleep-wake scoring and reasonable correlations for most of the summary sleep measure (e.g. sleep onset, sleep efficiency). However, studies have also shown that actigraphy may significantly overestimate sleep in insomnia patients because these patients often spend a significant portion of their time in bed in motionless wakefulness which the algorithms score as sleep (Sadeh et al., 1989; Hauri and Wisbey, 1992; Chambers, 1994; Jean-Louis et al., 1999). Furthermore, actigraphic sleep-wake scoring accuracy drops in other clinical groups where activity patterns may be affected by other factors such as breathing efforts in sleep apnea patients (Sadeh et al., 1989) and psychopathology (Jean-Louis et al., 2000c).

Additional studies have demonstrated high reliability and stability of the measures on the basis of night-to-night variability (Acebo et al., 1999; Sadeh et al., 2000; Tikotzky and Sadeh, 2001). It has been suggested that 5 days of monitoring provide sleep measures with acceptable night-to-night reliability indices (Acebo et al., 1999).

6.4. Actigraphic sleep measures across development

A growing number of studies have demonstrated developmental features and trends that correspond well to the existing knowledge on the maturational aspects of sleep in infants, children and adolescents (Acebo et al., 2000; Aronen et al., 2000; Carskadon et al., 1998; Sadeh et al., 1996, 2000; Tikotzky and Sadeh, 2001).

In an actigraphic study of 220 full-term infants during their first 48 hours in the hospital nursery, Sadeh et al. (1996) documented a daily average of 16 hours of sleep, similarly to what had been reported more than 40 years earlier by Kleitman and

Engelmann (1953). The study also demonstrated very large individual variability in sleep patterns existing at this early phase of development. In a study of older children, 1–5 years of age, it has been demonstrated that most dramatic changes in sleep are related to daytime sleep and that nocturnal sleep remains quite stable (Acebo et al., 2000).

Actigraphic sleep studies of older children provided information on the relative high prevalence of night-wakings and sleep fragmentation phenomena (Sadeh et al., 2000; Tikotzky and Sadeh, 2001). In school-age children, actigraphic sleep measures were associated with neurobehavioral functioning, behavior problems and family stress (Aronen et al., 2000; Sadeh et al., 2002).

Surprisingly, there is limited information on normative actigraphic sleep measures in adults and older populations. Most of the information on actigraphic sleep patterns in adults and elderly people comes from studies in which ‘normal’ control participants were included (Sadeh et al., 1989; Cohen-Mansfield et al., 1990; van Hilten et al., 1993a, 1993b; Evans and Rogers, 1994; Sakurai and Sasaki, 1998; Kramer et al., 1999; Jean-Louis et al., 2000a, 2000b). Overall, these studies have demonstrated the phenomena of sleep fragmentation and compromised circadian rhythm that have been associated with aging.

6.5. Actigraphy in the assessment of sleep disorders

A large number of studies have shown that actigraphic measures can be used to assess specific sleep disorders and that these measures differentiate between sleep-disordered individuals and normal controls. However, the use of actigraphy for diagnostic purposes is still very limited and should be cautiously considered (American Sleep Disorders Association, 1995; Sadeh et al., 1995; Ancoli-Israel et al., 2003; Littner et al., 2003).

The most extensive evaluation of actigraphy for assessment of sleep disorders has been focused on insomnia (Sadeh et al., 1989, 1995; Hauri and Wisbey, 1992; Chambers, 1994; Jean-Louis et al., 1999; Ancoli-Israel et al., 2003). It has been demonstrated that sleep–wake algorithms often misclassify quiet wakefulness as sleep and that this state of motionless wakefulness is typical in insomnia patients while they are trying to fall asleep. This could lead to significant errors in sleep onset latency and sleep efficiency estimates. In some patients, these errors could lead to an overestimation of sleep by an hour or more. Chambers,

in his analysis of published data showed that actigraphy was not superior to daily logs when compared to PSG (Chambers, 1994). More recently the opposite results vis-à-vis actigraphy and daily log comparisons to PSG have been reported (Vallieres and Morin, 2003). Furthermore, the high night-to-night reliability of sleep estimates found in insomnia patients suggests that actigraphy might be a valid instrument to monitor intra-individual changes such as those estimated in intervention studies. Indeed, actigraphy has been successfully used in intervention studies with insomnia patients (Brooks et al., 1993; Lack and Wright, 1993; Haimov et al., 1995; Garfinkel et al., 1997; Pat-Horenczyk et al., 1998; Friedman et al., 2000; Usui et al., 2000; Vallieres and Morin, 2003).

In infants and young children actigraphic sleep measures significantly distinguished between sleep-disturbed and control infants (Sadeh et al., 1991). Furthermore, significant discrepancies have been observed between actigraphic sleep measures and parental daily reports on infant sleep (Sadeh, 1994, 1996). These discrepancies resulted mainly from the fact that parents are mostly aware of their infant’s night-wakings when the infant signals and requires their intervention.

Actigraphy has been shown to be sensitive to sleep variations associated with breathing disorders (Aubert-Tulkens et al., 1987; Sadeh et al., 1989, 1998; Middelkoop et al., 1995). Actigraphy measures enabled differentiation between sleep apnea patients and other patients and controls and to estimate the severity of the disorder (Aubert-Tulkens et al., 1987; Sadeh et al., 1989; Middelkoop et al., 1995). Actigraphic measures also reflected treatment response in SAS patients (Aubert-Tulkens et al., 1987). However, because of the complex requirements for appropriate diagnosis of breathing disorders, actigraphy alone is not an appropriate method for assessing sleep-related breathing disorders (American Sleep Disorders Association, 1995; Sadeh et al., 1995; Ancoli-Israel et al., 2003; Littner et al., 2003).

Recent studies suggested that actigraphy provides valuable data pertaining to periodic leg movements during sleep (Kazenwadel et al., 1995; Sforza et al., 1999). Although, the accuracy of the method is still debated, it has been suggested that it could be a valuable tool to assess treatment response in patients with periodic leg movement disorder (Trenkwalder et al., 1995; Collado-Seidel et al., 1999).

Actigraphy is particularly useful in disorders where multi-day information is required for diagnosis or treatment follow-up. This is particularly relevant for sleep-schedule disorders where assessment of the

instability or the daily changes in sleep–wake schedule (circadian rhythms) is essential (Teicher, 1995; Gruber et al., 2000; Pollak et al., 2001; Ancoli-Israel et al., 2003). In addition, actigraphy provides an alternative to subjective reports where the ability to report or the reliability of such reports is questionable as in the case of severe psychiatric and medical conditions or in young children (Littner et al., 2003).

6.6. Actigraphy in the assessment of clinical interventions

The usefulness of actigraphy in the assessment of clinical interventions has been demonstrated in many studies. Most studies have focused on the assessment of drug and behavioral treatments for insomnia and circadian rhythm disorders in infants, children, adults and elderly patients (Borbely et al., 1983, 1984; Balderer and Borbely, 1985; Drennan et al., 1991; Tobler et al., 1991; Brooks et al., 1993; Sadeh, 1994; Dawson et al., 1995; Guilleminault et al., 1995; Haimov et al., 1995; Garfinkel et al., 1997; Middleton et al., 1997; van Someren et al., 1997, 1999; Nagtegaal et al., 1998; Okawa et al., 1998; Pat-Horenczyk et al., 1998; Alessi et al., 1999; Shamir et al., 2000; Shilo et al., 2000; Smits et al., 2001; Paavonen et al., 2003; Vallieres and Morin, 2003). In these studies, actigraphic measures have shown therapeutic benefits of a wide range of clinical approaches including medication, bright light therapy, and behavioral interventions.

6.7. Summary and conclusions

The use of actigraphy as a valid cost-effective method to assess sleep in naturalistic settings for extended periods has been established and guidelines for appropriate clinical use have been outlined (American Sleep Disorders Association, 1995; Littner et al., 2003). The main advantages of actigraphy are its simplicity and unobtrusiveness and the fact that it provides continuous objective data. However, the main limitation of the method is the simple fact that it only measures activity levels and although activity does reflect rest–activity and sleep–wake patterns it is also influenced by other internal and external factors that may produce artifacts or false interpretation of the data. Furthermore, when actigraphy data suggest that sleep is indeed disrupted, the actual causes or nature of the disruption cannot be directly deduced from actigraphy alone and additional diagnostic information and examinations are needed.

In summary, actigraphy is an excellent instrument for research and screening purposes and as an adjunct method to other diagnostic procedures. Sleep–wake scoring algorithms should only be applied under appropriate circumstances (those used for validation, including similar populations and settings) and after potential artifacts have been addressed. The relative lightness of using actigraphy should not undermine its limitations and the need for cautious evaluation and interpretation of the derived data.

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CHAPTER 7

The Oxford sleep resistance test

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7.1. Introduction

Excessive daytime somnolence sleepiness (EDS) has been increasingly recognized as an important public health problem, estimated to affect as much as 9% of the general adult population (Young et al., 1993) and contributing to both motor-vehicle and work-related accidents, impaired cognitive and social functioning and reduced quality of life (Leger, 1994; Briones et al., 1996; Roth and Roehrs, 1996).

Commonly, EDS refers to the subjective feeling of having difficulties remaining awake and fully alert and an increased tendency to fall asleep. However, complaints do not always coincide with the objective impairment of vigilance.

Thus, several tests have been developed to objectively measure the propensity to actually fall asleep in favorable conditions (multiple sleep latency test, MSLT (Richardson et al., 1978)), or the capacity to remain awake under soporific conditions (maintenance of wakefulness test, MWT (Mitler et al., 1982)).

However, these tests are labor intensive as they require continual inspection of the electroencephalogram (EEG) trace during each test in order to determine the exact time of sleep onset. Hence, difficulties arise in using such tests in clinical practice and community studies.

7.2. Oxford sleep resistance test: standard test protocol

The Oxford sleep resistance test (OSleR test) (Stowood Scientific Instruments, Oxford, UK) has

been recently proposed as a behavioral test which simplifies the performance of the maintenance of wakefulness test (Bennett et al., 1997).

With this test, the occurrence of sleep is assessed behaviorally rather than by EEG monitoring. The test consists of a resistance challenge lasting 40 minutes. In order to minimize external disturbances and to allow vigilance degradation, the subject lies semi-recumbent in a dark room and isolated from external sound. A light-emitting diode (LED) device is placed at eye level, 2 meters away from the head of the subject. The LED flashes regularly for 1 second every 3 seconds (corresponding to 800 stimulations for the entire test). The subject is asked to respond by hitting a button each time the dim light flashes.

The switch used for the test is a proximity detector. For a response to be registered, the switch only needs to be touched, thus there is no 'click' which might provide an alerting feedback to the subject performing the test. The software of the device continuously monitors the switch. The LED and the response button device are connected to a personal computer located outside the room. The computer counts and records the responses and the failure to respond.

The instruction is to remain awake in this soporific situation for the duration of the test (undisclosed to the subject, maximum testing time of 40 minutes).

When the subject fails to respond for 21 seconds (i.e. seven consecutive illuminations), the computer beeps, the test is automatically terminated and it is assumed that the patient has fallen asleep. The subject is, then, immediately awakened by the technician monitoring the test. The computer stores the time to sleep onset (sleep latency) and the number of stimulations missed during the test.

The OSleR test is less laborious than the MWT because it only requires the technician to start and terminate the test. The technician needs to stay in the observance area for the duration of the test, but is free to perform other tasks.

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Thus, the OSleR test reproduces many of the MWT characteristics, with the advantage of being a simpler and less-expensive tool, which does not require the presence of a trained technician. Moreover, the test requires no particular capacity in electrophysiology. The simplicity of the test makes it easy to be used outside the sleep laboratory setting.

The OSleR test is performed on four occasions throughout the day (9:30, 11:30, 13:30 and 15:30). Video recording is sometimes useful to ensure that subjects follow the instructions and do not use extraordinary measures to achieve the test. In our experience, some hypersomnolent patients tried to perform the OSleR test standing up or using their cellular phone to avoid falling asleep.

The standard way to analyze the OSleR test is to determine the sleep latency, measured as the delay before the occurrence of seven consecutive flashes without response (21 seconds) (Bennett et al., 1999). A 21-second threshold was chosen because it corresponds to the minimal sleep duration generally used to score one epoch of sleep when using standard scoring rules for overnight polysomnography (Rechtschaffen and Kales, 1968).

7.3. Validation studies

Bennett et al. (1997) proposed the first validation of this test. This study shows that the OSleR test reproduces many of the characteristics of the EEG MWT and allowed to separate normal from sleepy subjects with obstructive sleep apnea syndromes (OSAS). In this study, comparing ten healthy subjects to ten symptomatic patients with sleep apnea, the authors demonstrated that the OSleR test not only shares the instructions and the protocol with the MWT but closely reproduces the results of this gold standard test of maintenance of wakefulness. The mean sleep latency in the normal group was 39.8 minutes with the OSleR compared to 10.5 minutes in the OSAS group. The mean sleep latencies for the traditional MWT were similar, 38.1 and 7.3 minutes in the control and OSAS groups, respectively. Moreover, the OSleR test was more consistent across the day in normal subjects and at 9:30, 11:30 and 15:30, all the normal subjects were able to stay awake for 40 minutes.

Retrospective analysis of the data revealed that in this study the test termination time could be shortened to 15 seconds (five stimulations missed) and still allowed the authors to discriminate between the two

groups, without over sensitivity leading to misclassification of normal subjects.

However, OSAS patients selected for this study were mostly from the severe end of the spectrum (O_2 saturation dip rate $32.7 h^{-1}$) and all had obvious symptoms of daytime sleepiness (Epworth Sleepiness Score median = 17/24). This selection bias may explain why other researchers (see below) failed to find such short latencies using the OSleR test in unselected OSAS patients.

Further studies showed that effective treatment patients normalized the OSleR test performances in OSAS. Jenkinson et al. showed that after 4 weeks of nasal continuous positive airway pressure (NCPAP) treatment ($>5.4 h$ night $^{-1}$), OSAS patients normalized their sleep latencies in the OSleR test. In this study, the median maintenance of wakefulness score was 38.3 min after therapeutic treatment, which is similar to healthy people performances and 12 min longer than after subtherapeutic controlled NCPAP. Furthermore, patients with lower compliance exhibited a mean test time of 32.9 min after effective NCPAP (Jenkinson et al., 1999). When compliant and non-compliant patients were pooled, the sleep latency of the OSleR test for the whole group was 6.75 min longer after treatment than at baseline.

In another report, Bennett et al., examining sleep fragmentation indices, demonstrated that OSleR sleep latency improved on NCPAP even in those patients who used it less than 4 h per night (Bennett et al., 1998).

These results support the fact that the OSleR test is an adequate tool to assess vigilance improvement on NCPAP treatment; moreover, this test is sensitive enough to evaluate the partial amelioration due to incomplete compliance to treatment.

However, all patients recruited in the Jenkinson et al. study had excessive daytime sleepiness (Epworth ≥ 10) and presented more than ten episodes of O_2 desaturation greater than 4% per hour of sleep (Jenkinson et al., 1999). It is quite possible that patients with SaO_2 dip rates lower than the strict inclusion criteria for this study would nonetheless show response to NCPAP through objective improvements in sleepiness. The population studied by Bennett et al. included subjects evenly distributed across the disease severity spectrum, from non-snorers to severe OSAS. The OSleR test demonstrated a vigilance improvement on NCPAP in this group: the OSleR test increased from 29.6 min to 39.5 min (Bennett et al., 1999).

7.4. Errors analysis

As previously explained, the standard way to analyze the OSleR test is to determine the sleep latency, measured as the delay before the appearance of seven consecutive flashes without response (21 seconds). A 21-second threshold was chosen because it corresponds to the minimal sleep duration generally used to score one epoch of sleep when using standard scoring rules for night polysomnography (Rechtschaffen and Kales, 1968). However, this threshold is inappropriate to detect fluctuations in vigilance occurring before the end of the test. Indeed, it is quite possible for a hypersomnolent subject to fall asleep several times during the test for less than 21s, without ever missing seven consecutive stimuli, and thus finish the 40-minute test (see example on Fig. 7.1). Alternatively, subjects with low motivation can miss occasional LED flashes without any significant sleepiness. In this case, errors are not expected to be consecutive.

Priest et al. (2001) recorded EEG during the OSleR test in order to examine the occurrence of sleep during the test in a group of normal subjects. In this study, the OSleR test was performed on the day following a full night polysomnography (Priest et al., 2001). Their results showed that latencies were significantly shorter after sleep deprivation than after a normal night ($25 \text{ min } 33 \text{ s} \pm 7 \text{ min } 29 \text{ s}$ and $38 \text{ min } 20 \text{ s} \pm 4 \text{ min } 10 \text{ s}$, respectively). There was a significant positive correlation between the individual total sleep time and the OSleR latency performed on the following day. Moreover, as the number of consecutive misses increased, the probability that the subject was asleep during the intervening period also increases. When three consecutive stimuli were missed, the probability of finding a microsleep (sleep episodes of at least 3 seconds dura-

tion) was 92%. This probability increased to 96% for four successive stimuli, 100% for six consecutive misses, and 94% for seven consecutive misses (corresponding to an interrupted session). The sensitivity of an OSleR session to detect sleep was 85% and its specificity was 94%.

Therefore, analyzing sleep latencies only during the OSleR test does not seem to give a thorough view of fluctuations in vigilance during the period preceding the end of the test. Consequently, we hypothesized that the analysis of all omissions and their distribution during the test could provide a more sensitive index in the assessment of daytime somnolence in OSA patients (Mazza et al., 2002). Indeed, the error profile obtained by the analysis of all missed stimuli could reflect different aspects of vigilance: one or two consecutive misses might represent lack of attention, three to six successive omissions might correspond to microsleep episodes and seven consecutive misses to sleep onset. Comparing 27 OSAS patients and 20 control subjects three times during the day (9:00, 11:00, 13:30), we found that OSAS patients not only fell asleep earlier but also demonstrated specific patterns of errors profiles, with a high prevalence of three to six consecutive errors. Patients not only exhibited reduced sleep latencies but also spent a greater percentage of time making errors than did control subjects during their awake period (before the end of the test). In the OSAS group, time spent making errors represented 5.4% of the test duration, whereas it represented 0.4% in the control group. This finding suggests that the OSleR test can not only identify OSAS patients with a difficulty to maintain wakefulness during a soporific task but also identify those with a difficulty to maintain a constant level of vigilance during the test. When an error profile analysis was added to the classical sleep latency assessment, a loss of vigilance could be suspected in up to 40% of patients who presented normal sleep latencies. By considering sleep latency as the only measurement of vigilance in the OSleR test, one risks neglecting interesting indicators, such as error analyses, as a useful means of identifying patients with hypersomnolence. For instance, in our study, using the sleep-onset criterion alone, a number of patients were categorized as 'not hypersomnolent' when they should have been diagnosed as 'hypersomnolent'.

In addition, in our study, the session test performed at 13:30 was the least specific in distinguishing patients from healthy subjects: when we excluded this

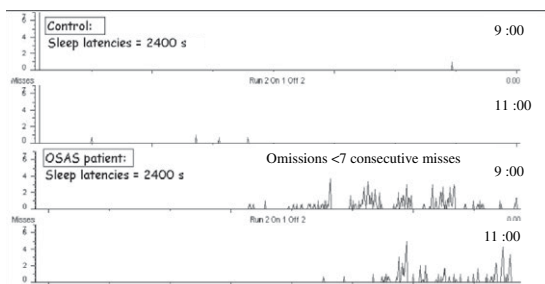


Fig. 7.1. OSleR test performances. Misses scale on y-axis (0–7), time scale on x-axis (2400 seconds). The red pattern represents errors committed.

session because of the loss of specificity, the 9:00 and the 11:00 sessions provided the same information in terms of percentage of patients classified as exhibiting daytime hypersomnolence (the 11:00 session classified only two additional patients with OSAS as hypersomnolent). It could therefore be possible to omit the 13:30 test without losing information.

7.5. New version of the OSleR test

Based on the reports mentioned above and considering the importance of error analysis, a new version of the OSleR test is now proposed by the supplier. In this new version, the test termination timing as well as the number of missed events is stored. This provides the opportunity to analyze attentional fluctuations occurring before the end of the test by interpreting the presence of errors.

The new OSleR test also allows testing without a connection to a computer. The wireless OSleR test device can be used in a similar way to the original OSleR test, which was connected to the serial port of a computer. It uses an integrated microcomputer to run the test and shows the results on a two-line LCD panel. This device consists of a central unit with the LED and LCD screen, and a separate event button box (subject unit) totally independent of the computer (see Fig. 7.2). The central unit with its LED is normally placed facing the patient on the wall at the end of the bed. The subject unit is placed at the patient's side.

The pre-test description by the technician is made in the room with the subject. A switch 'check' mode

option is available for patient acclimatization to proximity switch operation.

The test run is then initiated. The run mode has a 30-second delay to allow the technician to leave the room. The procedure is identical to the first version: an illumination of the LED for 1 second in three, to which the subject has to respond with the proximity switch.

If the subject fails to respond, a speaker in the observation room will buzz, with increasing amplitude until seven failures have occurred: at this point, an alarm will sound on the speaker, and the technician will re-enter the room and will awaken the subject.

We have recently conducted a pilot study in French elderly subjects examining 'Sleep, vigilance and driving ability'. Two hundred 60–80-year-old volunteers were assessed using the OSleR test in an outpatient clinic setting. Personnel without any specific qualification in sleep techniques were trained by us to use the OSleR test. Volunteer subjects were tested in three different centers, following the same protocol (dark and sound isolated room, semi-recumbent position . . .). All the patients completed the OSleR test. The OSleR test results showed that 76.5% of this elderly population sample completed the total test duration (without omitting seven consecutive stimulations) and 65% did not accumulate more than three consecutive errors during the entire test. This result shows that 25% of this elderly population sample could be considered as somnolent during this test.

Apart from these preliminary results regarding vigilance in elderly subjects, this preliminary study confirms that the OSleR test can be an adequate objective tool to assess vigilance outside the sleep laboratory and without specialized staff.

7.6. Summary

The OSleR test represents an adequate and objective tool to assess maintenance of wakefulness in a soporific situation. The simplicity of the protocol makes it easy to use in clinical practice and for large studies.

The OSleR test validation studies show that this test provides a strong indicator of daytime sleepiness and improvement under treatment in OSAS patients. Sleep latency associated with the analysis of the errors occurring during the test provides an interesting measure of maintenance of constant level of vigilance over the time.

However, further evaluations are needed in other sleep disorders to validate the specificity of this tool.



Fig. 7.2. OSleR test device: central unit, LED and LCD screen.

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CHAPTER 8

The cyclic alternating pattern (CAP) in human sleep

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8.1. Rhythms and periodic EEG patterns

Rhythms (delta, theta, alpha, beta, spindles) are continuous bioelectrical cerebral oscillations without intervals. Subdivided in frequency bands, they constitute the EEG background and vary on the basis of the ongoing condition: wakefulness, non-REM (NREM) sleep, REM sleep. Some rhythms are physiologic and some are pathological. Rhythms may be focal, widely scattered or generalized and synchronous. A spontaneous EEG pattern of relaxed wakefulness is the alpha rhythm that lies in the frequency range of 8–13 Hz, appears mainly at eye closure and can be recorded best from the posterior regions of the human scalp. With the onset of sleep, the alpha rhythm commonly seen in the waking state tends to vanish and is replaced by slower activities.

Normal rhythms may be also distorted by cerebral disturbance. If there is a focal slowing of physiological rhythms (for example, the alpha rhythm) by 1 Hz or more, this usually identifies the side of a focal abnormality. The unilateral loss of reactivity, such as the disappearance of the alpha rhythm to eye opening also reliably identifies the focal side of an abnormality.

Rhythms may be interrupted by periodic patterns. These are stereotyped EEG features, which recur at regular intervals, generally of 1 s to several seconds, and are clearly distinguishable from the background rhythm for their abrupt frequency shift or amplitude variation. Periodic activities are most commonly an important EEG feature of a severe ongoing CNS dis-

order. They may be disease-suggestive and sometimes are disease-specific.

Periodic activities are defined by three parameters (Figure 8.1):

- (1) The repetitive element (phase A of the period), represented by the recurring stereotyped EEG feature. This may be a simple sharp wave or compounded and polymorphic.
- (2) The intervening background (phase B of the period), identified by the interval that separates the repetitive elements.
- (3) The period or cycle (C), which is the sum of phase A and phase B duration.

8.1.1. Short periodic activities

Short periodic activities are characterized by a phase A with a duration <2 s and a phase B varying from 0.5–4 s. Subacute spongiform encephalopathy (Jones and Nevin, 1954), later referred to as Creutzfeldt–Jakob disease, hepatic encephalopathy (Bickford and Butt, 1955), and post-anoxic encephalopathy (Pampiglione, 1962; Nilsson et al., 1972) are all characterized by short periodic activities.

8.1.2. Long periodic activities

Long periodic activities are characterized by a phase A <2 s in duration and a phase B varying from 4–30 s. Long periodic activities are a typical EEG finding in subacute sclerosing panencephalitis (Rademacher, 1949).

8.1.3. Cyclic activities or cyclic alternating pattern (CAP)

The cyclic alternating pattern (CAP) is a specific type of periodic activity in which both phase A and phase B can range between 2–60 s. Phase A and the following phase B compose a CAP cycle (Gaches, 1971).

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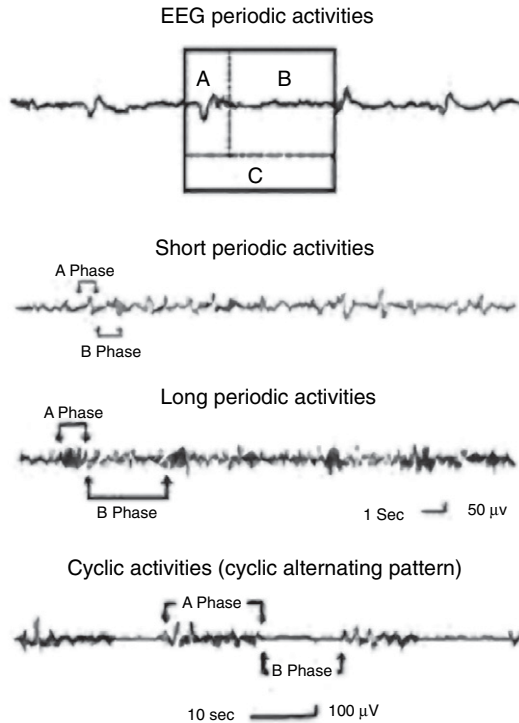


Fig. 8.1. Classification of periodic activities based on the duration of the repetitive EEG element (phase A) and of the interval (phase B). C (cycle) is the sum of A plus B. In short periodic activities, phase B oscillates between 0.5 s and 4 s, while phase A has a brief duration. In long periodic activities phase B ranges between 4 s and 30 s, while phase A has a brief duration. In cyclic activities, both phase A and phase B have a duration between 2 and 60 s.

8.2. CAP in states of reduced vigilance

In the history of EEG practice, CAP was initially considered as an EEG sign of cerebral disturbance. A prolonged cyclic alternation of high-voltage slow waves (phase A) and low-voltage irregular activity (phase B) can be recorded in comatose patients and correlates with the clinical outcome (Bergamasco et al., 1968; Mancía et al., 1975; Bricolo et al., 1979; Valente et al., 2002). In lighter stages of coma, the A phases are closely related to hyperventilation and increased pulse rate and can be associated with greater muscle activity, restlessness and pressure variations of the cerebrospinal fluid (Lundberg, 1960). In contrast, autonomic and muscle activities are attenuated during the B phases. This two-fold behavior indicates during CAP the comatose patient shifts repeatedly between more aroused (during phase A) and less aroused (during phase B) states that entrain also vegetative and

motor functions under a common oscillatory process (Evans, 1992).

As the clinical condition improves and a normal sleep structure is recovered, the cyclic EEG is progressively replaced by periodic sequences of K-complexes indicating that CAP is the expression of a basic arousal modulator, which survives in conditions of severely impaired vigilance, but that essentially belongs to physiological sleep. In effect, alternating periods of EEG high-amplitude slow waves and low-voltage activity are typical features of quiet sleep in preterm newborns (described as *tracé alternant*) and of NREM sleep in normal humans (Terzano et al., 1985). According to these findings CAP appears as a well-defined marker of cerebral activity occurring under conditions of reduced vigilance (sleep, coma), translating a state of instability and involving muscle, behavior and autonomic functions. The absence of CAP coincides with a condition of sustained arousal stability and is defined as non-CAP. CAP and non-CAP can be consistently manipulated by sensorial inputs.

8.3. Reactivity of CAP

The role of EEG reactivity in comatose patients is highly informative. In deep coma, no response even to repetitive and powerful stimulation can be observed. In light coma, parts of the arousal system are still functioning and every stimulus applied during the low-voltage period of CAP leads to high-voltage slow activity. This behavior is observed also during phase A and phase B in NREM sleep. Applying separately the same arousing stimulus during the two EEG components of CAP, phase B is the one that immediately assumes the morphology of the other component, whereas the inverse transformation never occurs when the stimulus is delivered during phase A. This stereotyped reactivity persists throughout the successive phases of CAP with a lack of habituation attitude. In contrast, when the same acoustic impulse, applied for the assessment of phase A and phase B reactivity, is presented during non-CAP, the EEG responses are generally brief, hypersynchronized and proceed toward a progressive habituation (Terzano and Parrino, 1991). However, a flexible boundary separates steadiness (non-CAP) from oscillation (CAP). A robust or sustained stimulus delivered during non-CAP induces the immediate appearance of repetitive CAP cycles displaying the same morphology and reactive behavior of spontaneous CAP sequences. The evoked CAP sequence may herald a lightening of sleep

depth or continue as a damping oscillation before the complete recovery of non-CAP (Terzano et al., 1990a).

8.4. The EEG features of CAP

Naturally, in sleep the EEG features of CAP are more complex and polymorphic compared to coma and vary in the different stages. In NREM sleep, CAP appears throughout stages 1, 2, 3 and 4 (Terzano et al., 2001), where phase A is identified by transient events which clearly stand out from the background rhythm (phase B). Compared to phase B, phase A can be composed of slower higher-voltage rhythms, faster lower-voltage rhythms, or by mixed patterns including both (Figure 8.2). Although EEG patterns of phase A are not strictly stereotyped, they generally include one of the phasic events (Terzano et al., 1997) which are described in Table 8.1.

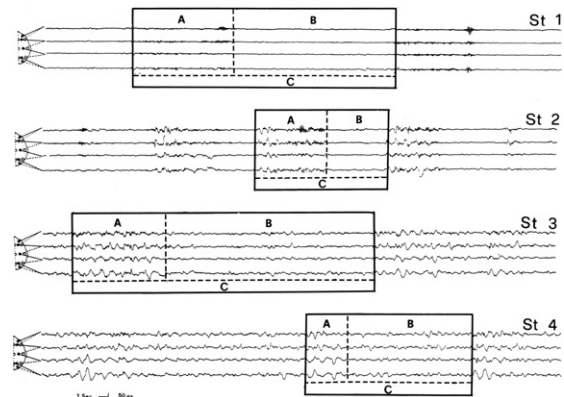


Fig. 8.2. Specimens of CAP cycles in the four NREM stages (stages 1–4). In stage 1, the phase A is identified by intermittent alpha rhythm. In stage 2, the phase A is identified by a mixture of k-complexes and rapid rhythms. In stages 3 and 4, the A phases of CAP are characterized by delta bursts separated by an interval of slow waves of lower amplitude.

Table 8.1

Phasic events, EEG characteristics and neurophysiological significance.

Phasic events	EEG characteristics and neurophysiological significance
Intermittent alpha rhythm	Typical pattern of alpha fragmentation during light stage 1 characterized by the intermittent replacement by low-voltage slow activity in the range of 2–7 Hz. Arousing stimulation applied during the intermittent stretches of alpha dropout leads to immediate return of the alpha rhythm.
Vertex sharp waves	EEG potential of cuspidate morphology, of 50–200 ms duration, of variable voltage (up to 250 μ V), with a maximum topographic expression on the central areas, particularly the median region (Cz). It occurs in isolation or repetitively, bilaterally and symmetrically, in stages 1 and 2. From the neurophysiological perspective, they are considered as evoked potentials, like K-complexes, and present similarities with evoked acoustic responses in waking which have their maximum expression on the vertex regions. It is thought that they have an excitatory significance and that they are related to a lowering of the threshold of cortical excitability. They can accompany myoclonic hypnic jerks and, according to some authors, are related to startle reactions.
K-complex	Widespread cortical phenomenon. Spontaneous or evoked arousal response associated with or followed by vasoconstriction, an increase of sympathetic activity and a rise in arterial pressure. A component of Stage 2 but also of Stages 3 and 4; not present (neither spontaneously nor elicited) in REM sleep.
K-alpha	Alpha activity 8–12 Hz, 0.5–5 s duration which follows a K-complex, a stronger arousal signal of a non-refreshing sleep.
Delta burst	Of cortical origin, with thalamic (reticular nucleus) influence and modulation. It can be elicited by sensory stimuli (acoustic, tactile, etc.). Arousal significance in synchronization during NREM sleep, prevalently in the slow-wave stages. Often heralds body movements, which emerge from deep sleep (stages 3 and 4). It corresponds to a weak variation of the arousal level (activation) often associated with modest polygraphic variations. It can precede signs of EEG desynchronization (see arousal).
Arousal	Frequency shift to theta, alpha or beta rhythms but not spindles. Longer than 3 s. High level of internal activation. Closely related to strong exogenous or endogenous stimulation. Spontaneous arousals are characterized by an age-related nocturnal increase and by an age-related stability in SWS and in REM sleep. Arousal with slow wave synchronization: EEG arousal preceded by K-complexes or delta bursts.

8.5.7. Movement artifacts

Body movements can trigger or interrupt a CAP sequence. Body movements linked to one or more phase As in the temporal range of 2–60s, can be included within the CAP sequence if other scoring criteria are met (Terzano et al., 1990b).

8.5.8. Recording techniques and montages

CAP is a global EEG phenomenon involving extensive cortical areas. Therefore, phase As should be visible on all EEG leads. Bipolar derivations such as Fp1–F3, F3–C3, C3–P3, P3–O1 or Fp2–F4, F4–C4, C4–P4, P4–O2 guarantee a favorable detection of the phenomenon. A calibration of $50\mu\text{V}/7\text{mm}$ with a time constant of 0.1s and a high-frequency filter in the 30Hz range is recommended for the EEG channels. Monopolar EEG derivations (C3–A2 or C4–A1 and O1–A2 or O2–A1), eye movement channels and submentalis EMG, currently used for the conventional sleep staging and arousal scoring, are also essential for scoring CAP. For clinical studies, airflow and respiratory effort, cardiac rhythm, oxygen saturation, and leg movements should be included as part of standard polysomnographic technique.

8.5.9. Amplitude limits

Changes in EEG amplitude are crucial for scoring CAP. Phasic activities initiating a phase A must be a third higher than the background voltage (calculated during the 2s before onset and 2s after offset of a phase A). However, in some cases, a phase A can present ambiguous limits due to inconsistent voltage changes. Onset and termination of a phase A are established on the basis of an amplitude/frequency concordance in the majority of EEG leads. The monopolar derivation is mostly indicated when scoring is carried out on a single derivation. All EEG events which do not meet clearly the phase A characteristics cannot be scored as part of phase A.

8.5.10. Temporal limits

The minimal duration of a phase A or a phase B is 2s. If two consecutive phase As are separated by an interval $<2\text{s}$, they are combined as a single phase A. If they are separated by a $\geq 2\text{s}$ interval, they are scored as independent events.

8.6. The A phases of CAP

Phase A activities can be classified into three subtypes. Subtype classification is based on the reciprocal proportion of high-voltage slow waves (EEG synchrony) and low-amplitude fast rhythms (EEG desynchrony) throughout the entire phase A duration. The three phase A subtypes are described below (Figure 8.4).

8.6.1. Subtype A1

EEG synchrony is the predominant activity. If present, EEG desynchrony occupies $<20\%$ of the entire phase A duration. Subtype A1 specimens include delta bursts, K-complex sequences, vertex sharp transients, polyphasic bursts with $<20\%$ of EEG desynchrony.

8.6.2. Subtype A2

The EEG activity is a mixture of slow and fast rhythms with 20–50% of phase A occupied by EEG desynchrony. Subtype A2 specimens include polyphasic bursts with more than 20% but less than 50% of EEG desynchrony.

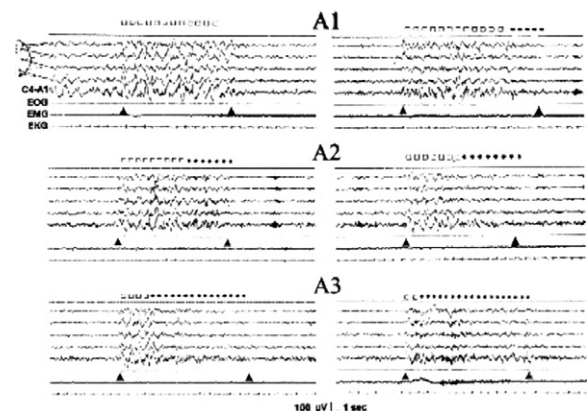


Fig. 8.4. Specimens of phase A subtypes in NREM sleep. Top, A1 subtypes mainly composed of K-complexes and delta bursts (white boxes) with an amplitude that exceeds the background EEG activities by at least 1/3. EEG low-voltage fast rhythms (black dots) occupy only a minor portion of the entire phase A length. Middle, A2 subtypes that start with a dominant EEG synchronization (white boxes) and continue with a prevailing desynchronized EEG pattern (black dots). The slow and fast EEG components are approximately equivalent in duration. Bottom, A3 subtypes introduced by a short EEG synchronization (white boxes) followed by a sustained desynchronized pattern (black dots) which occupies extensively the whole phase A. Notice the increase of muscle tone associated with the appearance of the rapid EEG activities (right-side specimen).

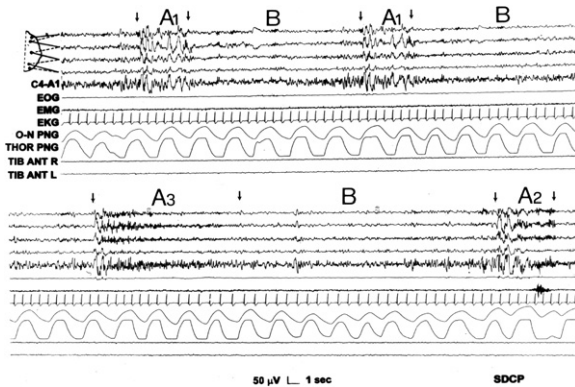


Fig. 8.5. Sequence of four A phases of CAP arising in stage 2 sleep. The boundaries of the A and B phases are marked by black arrows. The CAP phenomenon is not driven by any motor or respiratory disturbance. Bipolar parasagittal EEG derivation of the right side. C4-A1: C4 connects to left ear (A1). EOG: electro-oculogram. EMG: electromyogram. EKG: electrocardiogram. O-N PNG: oro-nasal flow. THOR PNG: thoracic effort. TIB ANT R: right tibialis anterior muscle. TIB ANT L: left tibialis anterior muscle.

8.6.3. Subtype A3

The EEG activity is predominantly rapid low-voltage rhythms with >50% of phase A occupied by EEG desynchrony. Subtype A3 specimens include K-alpha, EEG arousals and polyphasic bursts with >50% of EEG desynchrony. A movement artifact within a CAP sequence is also classified as subtype A3.

CAP sequences include different phase A subtypes (Figure 8.5). The majority of arousals occurring in NREM (87%) are inserted within the CAP sequences, and basically coincide with a phase A2 or A3. In particular, 95% of subtypes A3 and 62% of subtypes A2 meet the ASDA criteria for arousals (Parrino et al., 2001; Terzano et al., 2002). The broad overlap between arousals and subtypes A2 and A3 is further supported by their similar evolution in relation to age and to their positive correlation with the amount of light NREM sleep and negative correlation with the amount of deep NREM sleep (Terzano et al., 2002).

8.7. The concept of cortical, subcortical and autonomic arousal

The conventional definition of arousal includes a cluster of physiologic manifestations expressed by an activation of electrocorticographic rhythms, an increase of blood pressure and muscle tone and a vari-

ation of heart rate. Arousal has been considered as an essential element for restoration of homeostasis during respiratory and cardiovascular failure during sleep providing an excitation drive to vital processes. Arousal, by definition, means cortical activation. However, somatosensory and auditory stimulation during sleep may result in cardiac, respiratory and somatic modifications without overt EEG activation. This observation implies that there is a range of partial arousal responses with EEG manifestations different from conventional arousals and even without any EEG response. The different arousal responses rely on the different combinations of the central and peripheral components, on the intensity scale of their manifestation, and on the morphological variations of the cortical reactions (Halasz et al., 2004).

Different expressions of arousal can be identified:

- (1) Behavioral arousal: reported in the R&K manual (Rechtschaffen and Kales, 1968) as movement arousal described as any increase in electromyographic activity that is accompanied by a change in any other EEG channel.
- (2) Cortical arousal: defined by the ASDA committee (1992) as EEG arousal, it is characterized by transient desynchronized EEG patterns interrupting sleep. It reflects a brief awakening of the cerebral cortex regardless of any concomitant participation of the autonomic system or behavioral components.
- (3) Subcortical arousal: identified when vegetative activation is associated with a transient EEG pattern different from a conventional ASDA arousal (Rees et al., 1995; McNamara et al., 2002).
- (4) Autonomic arousal: expressed by spontaneous or evoked vegetative activation not accompanied by any EEG modification (Martin et al., 1997a; Pitson and Stradling, 1998).

Behavioral arousals and autonomic arousals represent the two extremes of a gradual scale of cerebral activation. However, they are not separated by rigid boundaries. Movement and behavioral arousals without either EEG or autonomic concomitants cannot exist, and in turn, an arousal from sleep can occur even without a concomitant body movement. The temporal overlap between cortical, somatomotor and vegetative events within the same arousal episode does not necessarily imply synchrony and the order of activation of the single compartments can vary in the different physiological or pathological circumstances. In arousal phenomena during sleep there is no manda-

tory chronological and etiologic subordination. The phenomenon takes place within interactive loops in which the cerebral cortex can be the starting or the ending point but anyway a source of control. The origin of arousal should be defined by the subsystem primarily activated or perturbed. The arousal can be generated directly by the cortex under the impulse of the physiologic evolution of sleep or in response to a sensorial perturbation, such as respiratory interruption, noisy environment, alteration of blood pressure or heart rate, or a movement disorder. In any case, it is the involvement of the brain that makes arousal a unitary phenomenon in which activation is modulated through a hierarchy of responses ranging from the generalized activation of all subsystems to the controlled attenuation of arousal-inducing activation.

8.8. CAP and the gating mechanisms of sleep

The link between phasic delta activities and enhancement of vegetative functions indicates the possibility of physiological activation without sleep disruption. In effect, non-visible sleep fragmentation induced by acoustic tones has been seen to be associated with increased daytime sleepiness, indicating that the processes of sleep consolidation may be impaired – in this case by sensorial stimulation – without evidence of sleep discontinuity (Martin et al., 1997b). In other words, slow EEG events (K-complexes and delta bursts) and conventional arousals (fast rhythms) share some functional properties, and, despite their EEG differences, they may be included within the comprehensive term of activating complexes. Such a variety of EEG manifestations relies on specific gates which control the flow of internal and external inputs. The thalamic-basal forebrain gate is an ultimate step of resistance against arousing impulses. Initially the cortex tries to preserve sleep continuity with reinforcement of its gates that are indicated by the occurrence of K-complexes and delta bursts in the sleep EEG. However, when the thalamic gate cannot control the afferent inputs a cortical change is seen translated by an alpha mixed or an alpha/beta frequency burst (Hirshkowitz, 2002). Anyway, the initial reaction of the cerebral cortex is a sleep-protective response as the majority of transient rapid activities are preceded by a slow high-amplitude EEG burst (Halasz, 1993). Power spectra analysis of CAP shows that the different phase A subtypes in NREM sleep are variants of a continuous two-fold process: an initial high-voltage slow-wave component, which predisposes the cere-

bral cortex to a greater readiness and opens the way to the more rapid activity, correlated with strong activating effects (De Carli et al., 2004; Ferri et al., 2005). What distinguishes the single arousal event is the build-up and reciprocal distribution of the EEG components. In the A1 phases of CAP, which host exclusively K-complexes and equivalent slow-wave activities (vertex potentials and delta bursts), the starting delta power increase is maintained and prevails throughout the entire arousal process. A balanced representation of slow and fast EEG frequency bands is the main characteristic of the A2 phases, while rapid EEG activities are the dominant feature of the A3 subtypes and of arousals.

This does not mean that all activating complexes exert equivalent effects on sleep structure and on vegetative functions. A hierarchical activation from the slower EEG patterns (moderate autonomic activation without sleep disruption) to the faster EEG patterns (robust vegetative activation associated with visible sleep fragmentation) has been described (Guilleminault and Stoohs, 1995; Halasz, 1998; Sforza et al., 2000).

8.9. CAP and the <1 Hz oscillation

Besides CAP, the other major EEG activity in the frequency range below 1 Hz (Table 8.2), characterizing states of reduced tonic arousal, is the so-called slow oscillation (Steriade et al., 1993). This 0.5–0.9-Hz EEG rhythm was outlined by deep EEG recordings performed during anesthesia and NREM sleep of cats and rats as well as by surface EEG and magnetoencephalography during NREM sleep of human subjects. The slow oscillation is generated in cortical neurons, and consists of phases of depolarization, characterized by intensive neural firing, followed by long-lasting hyperpolarization. Hence the two phases of the slow oscillation are characterized by opposite neural phenomena: cortical excitation made up of synaptic potentials and cortical inhibition mainly due to network dysfacilitation. The excitatory component of the slow oscillation is effective in grouping the K-complexes and delta waves, which do not occur in isolation but are grouped into complex wave sequences. The coalescence of slow rhythms is especially visible during NREM sleep. In the descending branch of the sleep cycle, EEG synchronization is a relatively delayed process, as at least 20 min generally separate sleep onset from the deepest slow-wave sleep (SWS) stage. According to the conventional coding, the

Table 8.2

Comparative characteristics of CAP and <1 Hz oscillation.

	CAP	<1 Hz oscillation
Rhythm	Collection of long-lasting (>2 s) EEG features in very slowly (0.047 Hz) recurring sequences present in all NREM stages	Collection of short-lasting (<2 s) EEG features in slowly (0.6–0.9 Hz) recurring sequences fully developed during slow wave sleep
EEG features	Clusters of K-complexes/delta bursts K-alpha complexes Arousals (preceded or not by slow wave synchronization)	Single rhythmic K-complexes (often accompanied by spindles during light sleep)
Cerebral networks	Cortical-brainstem interplay	Intracortical generators
Reactivity to stimulation	Increased by activating inputs	Absent during arousal
Polygraphic correlates (muscle and vegetative activities)	Phase A: enhancement Phase B: decrease	Quiescent
NREM stages	Lowest incidence in stage 4	Highest incidence in stage 4
Distribution within sleep	Falling asleep NREM stage shifts NREM to REM transition Nocturnal awakenings Body movements	Consolidated NREM sleep

percentage of high-voltage slow waves is <20% in stage 2, <50% in stage 3 and >50% in stage 4. Within a given epoch of SWS, high-voltage slow waves rarely appear as isolated features while in most cases they converge into collectives resulting in the phase A1 subtypes of CAP. As sleep progresses from stage 1 to stage 4, the differences in morphology and voltage between phase A (clusters of K-complexes and delta bursts) and the successive phase B (sleep stage background) become gradually less evident until the EEG is dominated by a uniform pattern (non-CAP) with the high-amplitude slow waves recurring in the frequency range of the <1 Hz oscillation. Neurophysiological investigation has ascertained that the slow cortical oscillation (<1 Hz) is absent at sleep onset but begins to organize in small territories, thereafter recruiting larger ones through coupling mechanisms as sleep deepens. A sustained <1 Hz oscillation characterizes the non-CAP condition of SWS, as well as short periods of oscillating EEG during natural sleep (Steriade, 2003). The mean interval between K-complexes and delta waves within A phases hosting large portions of EEG synchronization (A1 and partially A2 subtypes) actually ranges between 0.8 Hz and 0.9 Hz.

8.10. CAP and the structure of sleep

Sleep architecture is based on the cyclic alternation of two major neurophysiological states: NREM and REM sleep. NREM sleep is composed of four stages (stage 1, stage 2, stage 3 and stage 4) in which EEG synchrony grows with the increasing depth of sleep. In contrast, EEG desynchrony is the dominant feature of REM sleep. The alternation of NREM and REM sleep constitutes the sleep cycle and its recurrence during the night determines the classical sleep profile (macrostructure). The NREM portion of the sleep cycle starts with a slow descending branch sloping from the more superficial to the deeper NREM stages, continues with a central trough that represents the deepest stages of the sleep cycle, and ends with a rapid reverse ascending branch, expressed by the more superficial NREM stages that precede REM sleep. In the light of this, the classical NREM sleep architecture delineates a continuous pattern of build-up (descending branch), maintenance (trough) and resolution (ascending branch) of EEG synchrony. A detailed investigation has ascertained that the spontaneous EEG fluctuations centered on the 20–40 second

periodicity of CAP are implicated in the subtle mechanisms that regulate the production and attenuation of slow-wave activities during sleep. In particular, there is evidence that the different components of CAP have a sculpturing effect on the profile of the sleep cycle. Comparing spectral assessment and EEG visual scoring of NREM sleep in normal healthy subjects, the amount of slow rhythmic oscillations (spectral analysis) parallels the number of CAP cycles (visual detection), with a striking agreement between spectral power gatherings and visually scored A phases (Ferrillo et al., 1997). The regular EEG oscillations that accompany the transition from light sleep to deep stable sleep are basically expressed by the A1 subtypes. Within the sleep cycle, 90% of the A phases detected in the descending branches and 92% of the A phases detected in the troughs are subtypes A1, while 64% of the A phases identified in the ascending branches are subtypes A2 (45%) or A3 (19%). These findings indicate that both slow and rapid EEG activating complexes are involved in the structural organization of sleep (Terzano et al., 2000). In particular, the build-up and maintenance of deep sleep is achieved through a process of periodic EEG instability accompanied by mild neurovegetative swings. In contrast, the breakdown of SWS and the introduction of REM sleep are mostly associated with desynchronized EEG patterns and powerful activation of muscle and autonomic functions. The abundance of A1 subtypes in the descending branches and troughs can be the EEG expression of the cerebral mechanisms involved in the REM-off activity, while the predominance of subtypes A2 and A3 (and arousals) in the ascending branches reflects the REM-on drive (Figure 8.6). Therefore, besides their manifold EEG features, activating complexes are also characterized by a non-random distribution across the night, which assumes a clear-cut periodicity during NREM sleep within the framework of CAP (Terzano and Parrino, 2000).

8.11. The measures of CAP

CAP is the marker of sleep instability reflected by several parameters. We have already described the close relationship between the amount and distribution of phase A subtypes and the physiological structure of sleep. A number of CAP parameters have been measured both in clinical and experimental settings (Box 8.1).

In adult normal sleepers, the mean amount of CAP cycles ranges between 233 (20–39 years of age) and

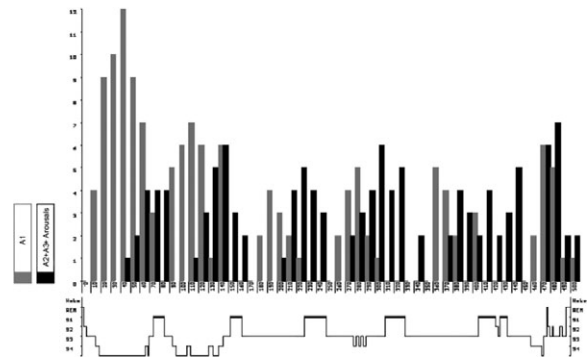


Fig. 8.6. Representation of the phase A subtypes (A1: gray bars; A2 + A3 + arousals: black bars) matched with the sleep histogram. Notice the consistent correspondence between the number of A1 subtypes and the amount of stages 3 and 4, as well as the close relation between the black bars and the preparation (stage 2), onset and consolidation of REM sleep.

Box 8.1

Main CAP parameters

- CAP cycle length
- Duration of phase A
- Duration of phase B
- Phase A rate $[(\text{phase A duration} / \text{CAP cycle duration}) \times 100]$
- Phase B rate $[(\text{phase B duration} / \text{CAP cycle duration}) \times 100]$
- CAP rate: percentage ratio of CAP time to NREM sleep time
- CAP index: the number of CAP cycles per minute of NREM sleep
- Number of CAP cycles per CAP sequence
- Number of CAP sequences per sleep

343 (>60 years of age). The mean duration of CAP cycles ranges between 25 s and 31 s, with a dominant phase B rate (about 65% of the CAP cycle length). In children aged 6–10 years (Bruni et al., 2002), the mean number of CAP cycles is even higher 363. The mean CAP cycle duration is 30.49 s, with a prominent phase B prevalence (81%).

Among the various CAP parameters, CAP rate is the one most extensively used for clinical purposes. Calculated as the percentage ratio of total CAP time to non-REM sleep time, CAP rate is the measure of arousal instability. From adolescence to old age CAP rate shows a U-shape evolution (teenagers: mean

43.4%; young adults: 31.9%; middle aged: 37.5%; elderly: 55.3%). The pre-adolescent period (Bruni et al., 2003) shows a gradual increase of CAP rate (25.9% in pre-school children aged 3–6 years and 33.4% in school children aged 6–10 years) which peaks at the pubertal age (which may reach levels of 60%) and then descends to the lower values of teenagers and young adults. These age-related changes of CAP rate could reflect the biological growth processes that accompany the preparation and onset of adolescence. The pubertal peak of CAP rate corresponds to higher amounts of subtypes A1, which are more numerous in school children (84.4% of all A phases) and in teenagers (71.3%). The percentages of subtypes A1 follow a plateau trend between 30 and 60 (mean: 61.6%) and then decline after the age of 60 (46.6%). In contrast, subtypes A2 and A3 undergo a linear increase from pre-school children to the old age, similar to the arousal evolution across the life span (Boselli et al., 1998; Parrino et al., 1998a).

At a given age, CAP parameters in normal sleepers tend to remain stable. In particular, CAP rate is characterized by a low intraindividual variability from night to night (Terzano et al., 1986). CAP rate is the marker of arousal instability and in a given subject it can be enhanced when sleep is disturbed by internal or external factors. The variation of CAP rate correlates with the subjective appreciation of sleep quality with higher values of CAP rate associated with poorer sleep quality. The pathological amounts of CAP rate are decreased by hypnotic medication (Parrino et al., 1997).

8.12. CAP and sleep disorders

These cyclic changes occur either spontaneously or in response to external stimuli of different sensorial modality (tactile, thermal, acoustic, painful, etc.). Accordingly, the amount of CAP increases when sleep is achieved under conditions of noise stimulation (Terzano et al., 1990a). CAP rate is increased also in situations of sleep disruption, such as organic and psychophysiological insomnia (Terzano and Parrino, 1992), while it is lowered by sleep-promoting conditions such as night-time recovery sleep after prolonged sleep deprivation (Parrino et al., 1993). During NREM sleep, the phase A of CAP triggers and modulates the distribution of epileptic events (Parrino et al., 2000a; Halasz et al., 2002) and myoclonic jerks (Parrino et al., 1996). In contrast, the phase B of CAP is closely related to the repetitive respiratory events of

sleep-disordered breathing, and only the powerful autonomic activation during the following CAP-A phase can restore post-apnea breathing (Terzano et al., 1996). These observations suggest that CAP-A is the activation phase, which alternates with a reduced neural excitability characterizing CAP-B phases. According to these data we can postulate that there is a periodic window in NREM sleep which allows, like an alternatively opening and closing permissive window, the possibility for the brain to be activated by sensory input. When the incoming sensory input coincides with the window opening the conditions for activation are present. This is one possibility to understand why periodic arousals are so closely associated with K-complexes, appearing in the garment of sleep rhythms. Among pathological arousals the gating effect of the CAP-A-phase is supported by an extended literature. In particular, CAP A-phase is interpreted as a kind of 'gate' through which the pathological events occur more easily. The gating effect had been demonstrated in recent years among several sleep disturbances such as periodic limb movement (PLM), sleep bruxism, sleep apnea syndrome and epilepsy (Terzano and Parrino, 1993).

All these results indicate that both spontaneous and elicited phasic arousals, especially during NREM sleep, have a cyclic nature following the multisecond oscillation. As a translation of fluctuating arousal, CAP offers a favorable background for sleep-disorder manifestations (e.g., epileptic abnormalities, PLM, nocturnal apneas, NREM parasomnias, insomnia) which are related to a condition of unstable sleep during which CAP cycles play a promoting (phase A) or an inhibitory (phase B) gating action on the single EEG, behavioral and autonomic events. Accordingly, a number of sleep disorders can be classified pathophysiologically on the basis of their relationship with CAP and non-CAP. In particular, PLM, sleep bruxism and epileptic manifestations can be considered as phase A-related disorders, while sleep apneas are a typical expression of a phase-B related disturbance.

8.13. CAP as a marker of non-restorative sleep

There is a great body of evidence that sleep fragmentation – punctuation of sleep with frequent, brief arousals – diminishes its recuperative value. This statement is valid even when arousals do not alter the standard 30-s epoch sleep stage scoring. Correlation between the number of arousals and daytime sleepiness in OSAS patients has been reported, but phasic

delta activities during sleep (with diurnal consequences) can also exert activating effects. Airway opening may occur in UARS subjects with a predominant increase in delta power (Poyares et al., 2002). In other words, reopening of the airway at wakefulness and disappearance of abnormal UARS are not necessarily associated with an arousal. Reopening of the airway with an EEG pattern of delta has been also observed in OSAS patients. Involvement of either slow or fast EEG responses depends on the regulation of upper airway patency. Respiratory patterns that need correction activate the CNS. This activation varies, depending on the sensory recruitment and the adequacy of the response. A respiratory challenge can be resolved by CNS activation without involving a cortical arousal. The latter is triggered only when thalamo-cortical structures fail to modulate breathing or when ascending reticular volleys are required to restore respiration. According to the amount of recruitment and numbers of neural structures involved, the CNS activation will be variable. The autonomic nervous system is enhanced when an arousal occurs, which explains the greater increase in heart rate with EEG arousal than without EEG arousal (Black et al., 2000). Anyway, the problem is quantitative not qualitative in the sense that also delta bursts can determine heart rate acceleration and autonomic activation. Generally, the slow and the fast components of EEG activation have different latencies, with the delta portion preceding the rapid activities. This probably determines a graduated impact on the autonomic system. The slow waves determine a softer vegetative reaction, which in certain pathologic conditions may be strong enough to overcome a disturbing factor, e.g., an obstructive event. Otherwise, the slow rhythms are immediately replaced by faster EEG activities, which guarantee a more powerful activation of autonomic functions. Probably the effects on daytime function are not linked to a single phase A subtype but to the reciprocal amount and distribution of the single subtypes. In OSAS patients treated effectively with nasal CPAP, the ventilatory-induced reduction of CAP rate, which correlated significantly with daytime sleepiness, was associated with a robust curtailment of subtypes A3 and an expansion of the A1 percentage (Parrino et al., 2000b).

8.14. The role of CAP in primary insomnia

Primary insomnia appears to be the exaggeration of a physiological rhythm ordinarily involved in the sleep

process. Previous studies have ascertained that acoustic stimuli enhance the physiological amount of CAP rate and determine poor sleep and daytime dysfunction even without an increase of sleep fragmentation. In this perspective, CAP operates as a 'double-edged sword'. While limited quantities of CAP mediate physiological effects, larger quantities reflect the brain difficulties to consolidate and preserve sleep and therefore may be associated with detrimental consequences. Because primary insomnia is not supported by any other sleep, medical, psychiatric or substance-induced problem there is no evidence of an organ disorder. In any case, whatever the nature of disturbance, the outcome is the amplification of an otherwise physiological process. A recent PSG study based on an extensive sample of patients affected by primary insomnia demonstrated that CAP parameters reflect consistently the reduced quality of sleep in insomnia complainers and can substantiate the efficacy of hypnotic medication (Terzano et al., 2003a). Compared to controls, insomniac patients under placebo showed a significant increase of CAP rate, phase A subtypes (A1, A2, A3), EEG arousals, nocturnal wakefulness and stage 1, associated with reduced values of total sleep time and slow-wave sleep (stages 3 and 4). In insomniac patients, sleep quality was significantly improved by hypnotic treatment. Compared to placebo, active medication significantly reduced CAP rate, subtypes A1 and A2, but had only marginal effects on subtypes A3 and on EEG arousals. The most significant correlation between sleep quality and PSG variables was found for CAP rate ($P < 0.0001$).

Sleep is a dynamic process with a self-regulating character. The nightly recurring sleep process is organized into consecutive cycles in which the sequence of NREM stages and the alternation between NREM and REM sleep show a quite stable tendency and a largely predictable pattern. These constraints produce the macrostructural development of sleep. However, transient EEG changes can interact with the expected development of sleep and ensure adaptation to both internal and external conditions. CAP and arousals represent rapid adaptive adjustments of vigilance during sleep. Failure of these compensatory processes conduces to non-restorative sleep. Therefore, assessment of sleep quality relies on a variety of PSG measures including sleep duration (quantified by total sleep time and sleep efficiency), sleep intensity (reflected by stages 3 and 4), sleep continuity (altered by nocturnal awakenings and arousals) and sleep

stability (impaired by excessive amounts of CAP). These PSG measures are susceptible to deterioration in varying ways and proportions in accordance to the manifold clinical manifestations of insomnia. In the hierarchy of PSG measures, CAP variables appear to be the most sensitive to any source of internal or external perturbation during sleep. Anyway, regardless of the specific characteristics of sleep alteration, insomnia ceases to be an indefinite mental disorder but emerges as a subjective disturbance supported by measurable neurophysiological changes.

8.15. Automatic analysis of CAP

There is consolidated evidence that CAP parameters provide more detailed information and are significantly more sensitive than conventional sleep measures. However, the visual scoring of CAP is time-consuming and this can compromise an extensive utilization of the method. In other words, only the availability of an adequate system for the automatic detection of CAP can really make it an easily exploitable tool. To date, various softwares have been carried out with different degrees of development. Jobert et al. (1994) suggested the application of the Wavelet Transform to the analysis of transient events and supported this idea with significant preliminary results. The method introduced by De Carli et al. (1999) was based on the application of the Wavelet Transform to two bipolar EEG traces and one EMG derivation; for the purposes of the analysis, six frequency bands were considered: slow delta, delta, theta, alpha, sigma and beta. Rosa et al. (1999) proposed an automatic system for the detection of the CAP sequences consisting of three parts: a model-based maximum likelihood estimator, a variable length template matched filter and a state machine rule-based decision subsystem. De Carli et al. (2004) added to the above quoted method based on the Wavelet Transform a comparison between the mean power values during: (a) each entire arousal as automatically recognized, (b) the 3.5 seconds immediately preceding the arousal and (c) the 20 seconds which on turn preceded the 3.5 second pre-arousal epoch. Huupponen et al. (2003) identified, via a mean frequency measure and FFT, sleep oscillations with period times of 50–150s having a relatively large amplitude. Barcaro et al. (1998) and Navona et al. (2002) proposed a method based on the computation of five band-related descriptors, which give a measure of how much the amplitude in a band activity is

‘instantaneously’ different from the background activity. These can be viewed as ‘continuous’ descriptors, although no significant information is lost if they are calculated every half second. Mathematically, they are given by the normalized difference between the average band activity amplitude over a ‘short’ interval (two seconds) centered on the instant considered and the average amplitude over a ‘long’ interval, i.e. in the order of the minute. Of course, the latter average depends mainly on the background signal. The basic idea is the following: any microstructure phenomenon can be traced back to the fact that at least one descriptor provides values remarkably higher (i.e. above a certain threshold, called the ‘existence threshold’) than the background value. After the recognition of an event, the length of the corresponding epoch can be simply recognized applying a second threshold, called the ‘length threshold’. The various events are then discriminated according to the bands involved. Finally a computer-assisted system for the detection of different A phases and the topographic representation of CAP spectral components have been described by Ferri et al. (2005).

8.16. Conclusions

The monitoring of sleep is generally accomplished using a variable number of EEG leads in combination with electro-oculographic (EOG) and submental electro-myographic (EMG) signals. These variables are scored in combination using the R&K system described in 1968 to yield NREM stages 1–4 and REM sleep. Although this system has proved useful over the last 35 years and tells us a great deal about many aspects of sleep, it also has many weaknesses. The principal drawback is the consideration of sleep as a stepwise process. Another defective aspect is the lack of any information on perturbed and unrefreshing sleep. The definition of EEG arousals scored independent of R&K rules was certainly an important advance in the measurement of sleep fragmentation. The CAP methodology collects all the information supplied by EEG arousals in NREM sleep and provides additional information on poorly consolidated and unstable sleep.

The perspectives for the exploitation of CAP are promising in several fields. The age-related changes of CAP parameters reflect consistently the maturational processes from childhood to senescence. The sensitivity of CAP to sensorial perturbations and to drugs can make it a reliable tool in the evaluation of

single compounds endowed with hypnotic properties. In particular, the EEG morphology of the different phase A subtypes can allow discrimination between benzodiazepine and non-benzodiazepine agents both in experimental (Parrino et al., 1997) and clinical (Parrino et al., 1999) settings. In addition, monitoring of CAP has been usefully applied in the evaluation of hypnotic treatment both in regimens of intermittent (Terzano et al., 2003b) and chronic medication (Parrino et al., 1998b). Moreover, the close relation between CAP and sympathetic activation (Ferri et al., 2000) can improve our knowledge on the biological cost of persistent insomnia. It is known that CAP is deeply implicated in mood disorders (Parrino et al., 1994; Farina et al., 2003), in the modulation of epileptic phenomena and movement disorders during sleep and promising benefits can derive also from the use of CAP in the diagnosis and management of OSAS. CPAP titration detached from the concomitant assessment of CAP can jeopardize the effectiveness of ventilatory treatment (Thomas, 2002; Thomas et al., 2004). The persistence of CAP and arousals even when respiratory events are controlled by an autoadjust equipment indicates an incomplete titration procedure (Marrone et al., 2002). In other words, the occurrence of CAP is the marker of the system instability, which may be caused by a number of internal or external factors. Through the increase of CAP, the sleeping brain cannot reveal the nature of perturbation but it is certainly indicating that one or more factors are interfering with the processes of sleep consolidation. In contrast, the presence of non-CAP is closely related to a global condition of stability when all the subsystems that control and influence the sleep mechanisms have achieved a reciprocally balanced interaction. The availability of reliable automatic systems will allow us to confirm these findings and open new perspectives on the investigation of CAP in the basic mechanisms of sleep and in the pathophysiology of sleep disorders.

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CHAPTER 9

Scalp topography and cortical generators of the spectral components of the cyclic alternating pattern (CAP)

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9.1. Introduction

Since the first description of the so-called 'cyclic alternating pattern' (CAP) by Terzano et al. (1985, 1988), the CAP phase A patterns have been characterized as phasic events peculiar to the single sleep stages:

- (1) intermittent alpha rhythms (EEG synchronization) and sequences of vertex sharp waves (EEG synchronization), in stage 1;
- (2) sequences of two or more K-complexes alone (EEG synchronization) or followed by alpha-like components (EEG desynchronization) and beta rhythms (EEG desynchronization), in stage 2;
- (3) delta bursts (EEG synchronization) which exceed by at least one third the amplitude of the background activity, in stages 3 and 4;
- (4) transient activation phases (EEG desynchronization) and EEG arousals (EEG desynchronization), in all the stages.

With the terms synchronization and desynchronization, Terzano et al. (1985, 1988) referred mostly to the frequency content of CAP A phases; synchronization was expressed by the low-frequency components of K-complexes and delta bursts, during sleep stages 2–4 and desynchronization was reflected by the high-frequency components (in the alpha and beta bands) in all sleep stages.

The different frequency content of CAP A phases is one of the most important features allowing their

visual subclassification into three subtypes (Terzano et al., 2001):

- Subtype A1: A phases with synchronized EEG patterns (intermittent alpha rhythm in stage 1; sequences of K-complexes or delta bursts in the other NREM stages), associated with mild or trivial polygraphic variations.
- Subtype A2: A phases with desynchronized EEG patterns preceded by or mixed with slow high-voltage waves (K-complexes with alpha and beta activities, k-alpha, arousals with slow-wave synchronization), linked with a moderate increase of muscle tone and/or cardiorespiratory rate.
- Subtype A3: A phases with desynchronized EEG patterns alone (transient activation phases or arousals) or exceeding two-thirds of the phase A length, and coupled with a remarkable enhancement of muscle tone and/or cardiorespiratory rate.

In this chapter we present the results of the analysis of the CAP A phases by means of a computerized approach in order to define quantitatively their spectrum content, their scalp topography and their probable cortical generators.

9.2. Spectral analysis of CAP a phase subtypes

Power spectra were calculated for the C4 channel using the sleep analysis software Hypnolab 1.0 (SWS Soft, Italy), after Welch windowing, by means of the fast Fourier transform (Cooley and Tukey, 1965), on 4-second artefact-free epochs from the different CAP A phase subtypes and plotted for frequencies between 0.25 and 32.0 Hz.

Figure 9.1 shows an example of the results obtained with this analysis, in one normal subject; only

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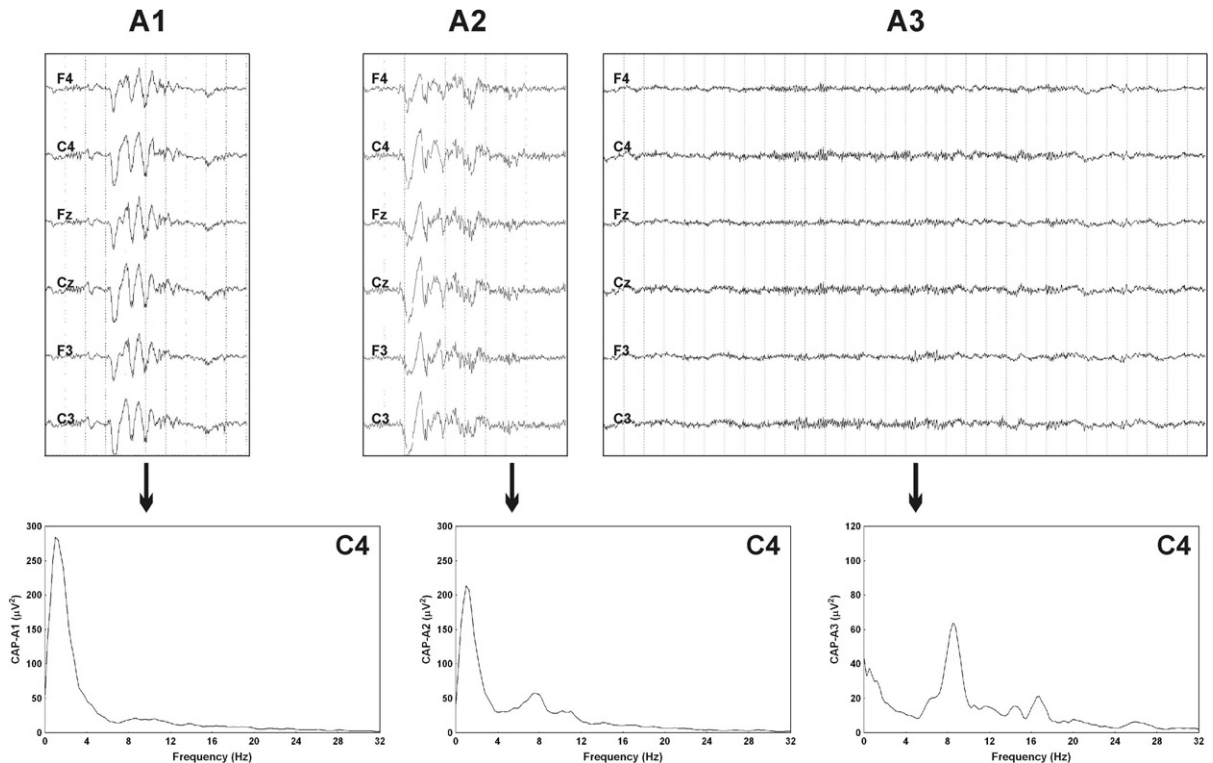


Fig. 9.1. Results of the power spectrum analysis in a normal subject; only a few EEG channels are shown in order to simplify the figure. Spectra were obtained from the C4 channel.

a few EEG channels are shown in order to simplify the figure.

This simple analysis clearly shows that, as expected from the visual detection rules, the spectrum of the A1 subtype is characterized by a prominent peak in the low delta range, between 0.25 and 2.5 Hz. The same peak is also evident in the spectrum obtained from the A2 subtype, with slightly smaller height than in the spectrum of the A1 subtype. In this case, however, also more power is evident in the frequencies ranging approximately between 7–13 Hz. The last spectrum, obtained from the A3 subtype, is dominated by the presence of an evident peak in the alpha band, at around 9 Hz, followed by some power expressed in the high alpha and low beta bands (up to 15–16 Hz).

These results confirm the visual rules for CAP detection based on the presence of two fundamentally distinct frequency bands which are expressed individually (A1 and A3) or in association (A2) in the different CAP A phase subtypes. Also from the quantitative spectral point of view, these bands seem to be well separated and not overlapping between them.

For this reason, in this study we have directed our attention to the computerized analysis of these two frequency components rather than that of the CAP A phase subtypes, the detection of which is based on visually rather than automatically extracted features.

9.3. Scalp topography of the spectral components of CAP

The analysis of the so-called ‘cyclic alternating pattern’ (CAP), a phenomenon which is typical of NREM sleep, has been previously confined to its first-order time features and particular attention has been paid to its rate which is the percentage of each sleep stage occupied by CAP sequences (Terzano et al., 1985, 1988). This type of approach has been conditioned by the common practice in sleep labs of including only a limited number of EEG channels in the polysomnographic recordings, because of the need of simplicity and the requirement of only one EEG channel by the internationally accepted rules of recording sleep (Rechtschaffen and Kales, 1968). However, the significant advancements in computer

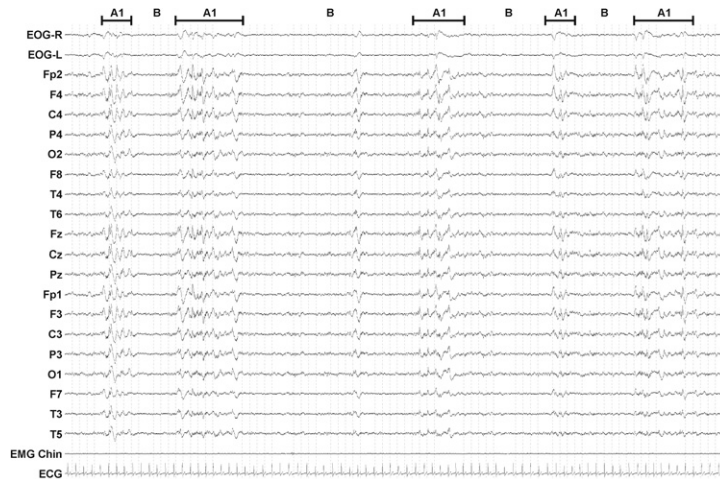


Fig. 9.2. Example of our multichannel polygraphic recordings in which a typical sequence of CAP A1 phases is evident, marked on the top; 90 seconds of recording are shown.

technology of recent years now allows the recording and analysis of a large number of channels with limited additional effort. This allows us to have a better representation of the EEG over the scalp, also during sleep.

Figure 9.2 shows an example of multichannel polygraphic recordings (19 scalp EEG channels from our normal subjects, placed according to the 10–20 international system) in which a typical sequence of CAP A1 phases is evident. The collection of such a number of EEG channels allowed us to study the topographic distribution of the two frequency bands described above, drawing color maps of the scalp obtained by means of the so-called four-nearest neighbors method.

Figure 9.3 displays the results of such an analysis; in particular, the low-frequency band (0.25–2.5 Hz) showed, in the different subjects, a clear prevalence over the anterior frontal regions, mostly over the midline and symmetrically spreading over the two hemispheres. On the contrary, the high-frequency band (7–15 Hz) involved mostly the parietal-occipital areas; also in this case, a symmetrical distribution was evident with the peak over the midline. In this band, a more variable distribution than that of the low-frequency band was detectable in the different subjects.

Also, this approach indicates that the two frequency components recognized by the visual and spectral analysis are distinct and map over clearly different areas of the scalp.

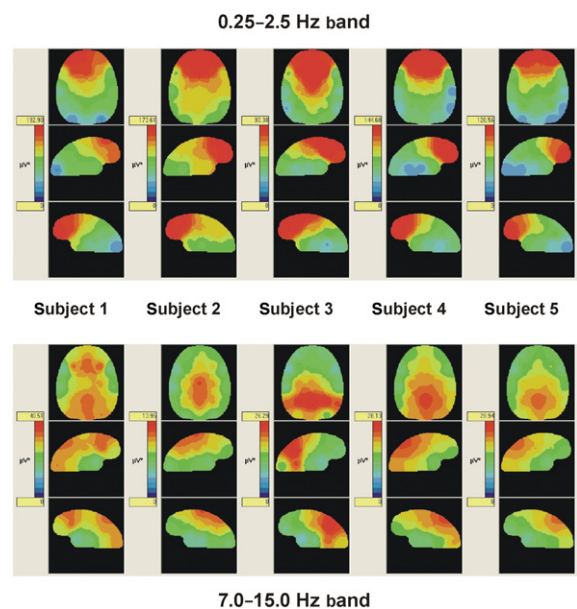


Fig. 9.3. Scalp topographic mapping of the two frequency components of CAP considered in this study.

9.4. Cortical source analysis of the spectral components of CAP by LORETA

We employed the so-called low-resolution brain electromagnetic tomography (LORETA) functional imaging for the source analysis of the two EEG frequency components of CAP A phases, which has been extensively tested with simulation paradigms

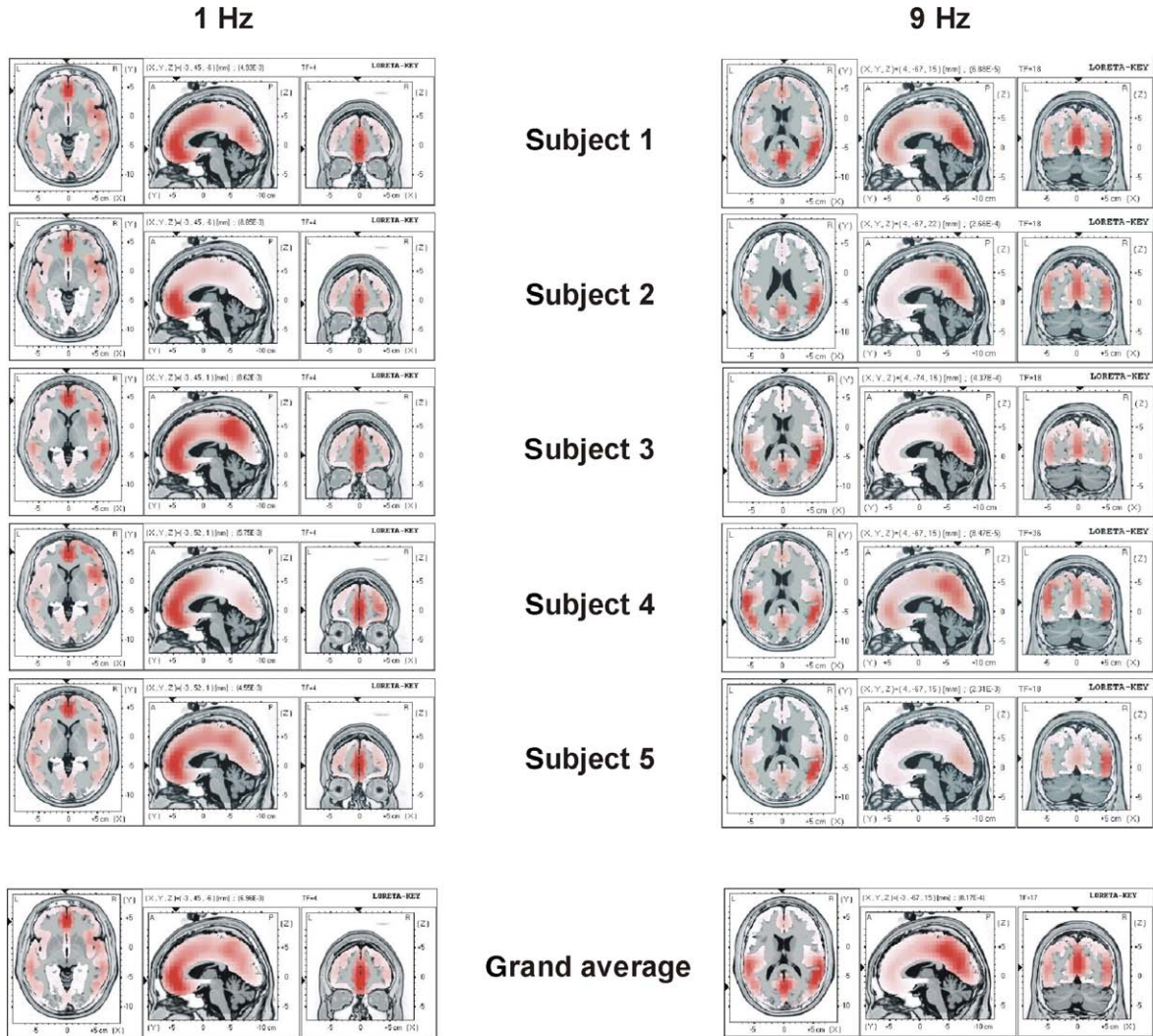


Fig. 9.4. Low-resolution brain electromagnetic tomography (LORETA) functional imaging for the source analysis of the two EEG frequency components of CAP, at 1 Hz and 9 Hz.

(Pascual-Marqui et al., 1994, 1999) and is presently used by several independent laboratories worldwide. LORETA computes 3-D linear solutions (LORETA solutions) for the EEG inverse problem within a three-shell spherical head model including scalp, skull and brain compartments. The brain compartment is restricted to the cortical gray matter/hippocampus and is coregistered to the Talairach probability brain atlas, digitized at the Brain Imaging Center of the Montreal Neurologic Institute (Talairach and Tournoux, 1988). This compartment includes 2394 voxels (7-mm resolution), each voxel containing an equivalent current dipole. LORETA solutions consist of voxel current density values able to predict EEG spectral power density at scalp electrodes.

Solutions of the EEG inverse problem are under-determined and ill-conditioned when the number of spatial samples (electrodes) is lower than that of the unknowns (current density at each voxel). To account for that, cortical LORETA solutions predicting scalp EEG spectral power density are regularized to estimate distributed rather than punctual EEG sources (Pascual-Marqui et al., 1994, 1999). As a result, the spatial resolution of regularized LORETA solutions is much lower than that of SPECT or PET.

Figure 9.4 shows, in the left column, the results of this analysis at 1 Hz, representative of the probable cortical generators of the slow-frequency component of CAP obtained in five normal subjects; the grand average of these subjects is also shown. With this approach, the gen-

erators of the low-frequency component of CAP seem to be localized mostly over the frontal midline cortex. The same figure shows, in the right column, the results of LORETA at 9 Hz, representative of the probable cortical generators of the high-frequency component of CAP which involve both midline and hemispheric areas within the parietal and occipital areas.

Once again, our results indicate that the two distinct frequency bands characterizing the different CAP A phase subtypes are different not only from the frequency and scalp distribution points of view but also their probable cortical generators are well separated and distinct.

This is also evident in the single CAP A2 phase subtypes (Figure 9.5) which show in their first part (part x in Figure 9.5) a cortical distribution not distinguishable from that of the low-frequency component of CAP (A1 phases) and in their last part (part y in Figure 9.5) probable cortical generators not distinguishable from those of the high-frequency component of CAP (A3 phases). It is important to emphasize that this association is not casual and that the low-frequency component of CAP precedes the occurrence of the high-frequency rhythms in the vast majority of CAP A2 phases.

9.5. Discussion

First of all, we must underline that our results seem to be in agreement with those obtained by other authors who did not point their attention on the CAP phases but analyzed phasic activities most of which were part of CAP sequences, such as the study by Happe et al. (2002) who focused their attention on spontaneous K complexes and delta waves; also these authors found that the power of the slow component of these waves shows a peak over the medio-frontal regions. Interestingly, these authors found that the delta frequency components of K complexes and delta waves are unaffected by spindles; spindles are not considered in the scoring of CAP (Terzano et al., 2001). Also, evoked K complexes seem to map over the midfrontal areas (Gora et al., 2001) and the same frontal predominance of the delta band was reported in another study by Finelli et al. (2001) in which spectra were obtained by averaging a large number of epochs.

Averaging sleep epochs can induce a serious distortion of the results because sleep is rich in phasic events which, by definition, have a short duration and their contribution to average results can be very variable, depending not only on the sleep stage but also

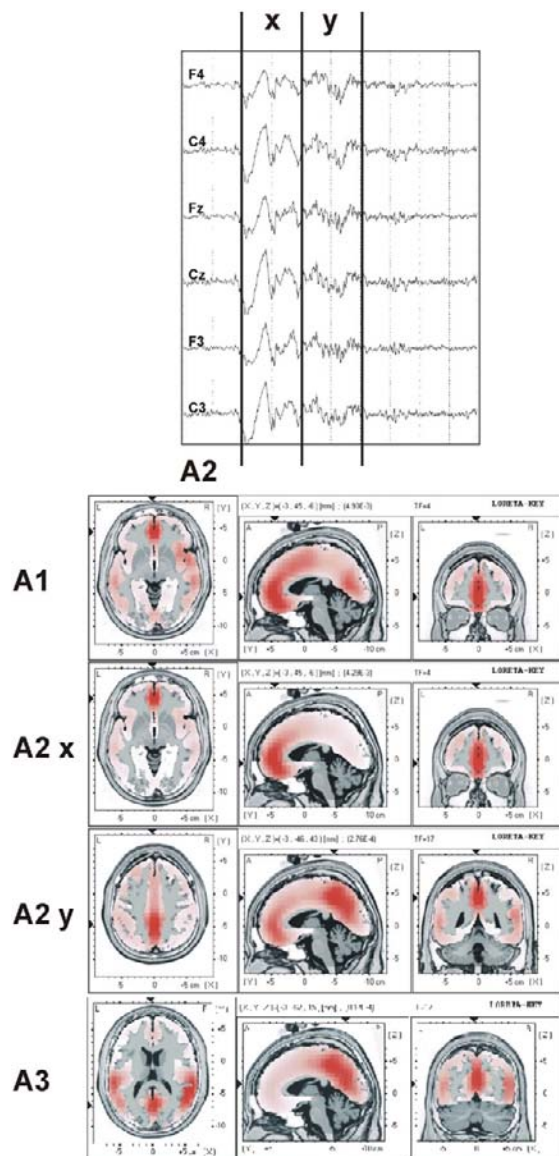


Fig. 9.5. Low-resolution brain electromagnetic tomography (LORETA) functional imaging for the source analysis of the two EEG frequency components of CAP, at 1 Hz (indicated as A2 x and A1) and 9 Hz (indicated as A2 y and A3). In particular, A2 x refers to the first 2 seconds of activity of the A2 CAP phase shown on the top and A2 y indicates the following 2 seconds.

on the presence or absence of CAP sequences; moreover, in these studies A3 phases are usually marked as artifacts and excluded from analysis. We think that this problem affected seriously the results obtained by Coatanhay et al. (2002) who applied LORETA to the study of sleep potentials but averaged a large number of epochs from REM, stage 2 and slow-wave sleep and indicated the left inferior temporal lobe as the

cortical generator of delta waves during slow-wave sleep and the left inferior frontal cortex as the cortical generator of delta waves during sleep stage 2.

Synchronizing mechanisms during sleep are usually thought to be subserved by thalamocortical pathways and, as an example, there is experimental evidence that thalamocortical neurons may oscillate either in the delta or sigma frequency range depending on their membrane potential (Steriade et al., 1993; Contreras and Steriade, 1995) during non-REM sleep. We think that, based on our results, the CAP slow component is the cortical expression of this cortical-subcortical interaction. However, delta waves can also be generated at the level of the cortex and are not always under the control of thalamocortical pathways. In fact, it is known that delta waves can be seen in athalamic cats (Villablanca, 1974) and, even if this kind of experiment does not represent final evidence of cortical generation for delta potentials, it is believed that EEG delta waves can be generated by summation of afterhyperpolarization produced by different potassium currents in deep pyramidal neurons (Steriade et al., 1990). Probably, a combination of two mechanisms such as the thalamocortical modulation of cortically generated slow waves can be invoked in order to explain the regional and not diffuse distribution of the probable generators of the low-frequency component of CAP, as seen in our study.

On the other hand, the high-frequency CAP component seems to be the expression of the activity located at the level of the same structures thought to generate alpha waves during wakefulness within the cerebral cortex at the level of the pyramidal neurons in layers IV and V (Lopes da Silva and Storm van Leeuwen, 1977) with a system of surface-parallel intracortical neurons involved in its spread (Lopes da Silva and Storm van Leeuwen, 1978; Lopes da Silva et al., 1980).

The evidently non-random association between the two different frequency components of CAP, the generators of which are located in clearly different structures, seem to indicate that these structures are in functional intercoupling which allows them to organize the occurrence of the two different frequency components of CAP in a predetermined way.

The superior longitudinal (arcuate) fasciculus is the largest of the fiber bundles (Klingler and Gloor, 1960; Williams and Worwick, 1980) that together with the uncinate and fronto-occipital fasciculi constitute the longitudinal association fiber system that connects each frontal lobe with its respective hemisphere

(Gloor, 1997; Kiernan, 1998). We think that these important bundles are of crucial importance for the integration of the activity of frontal generators and parieto-occipital generators of CAP which seems to be generated by the same intrinsic mechanisms of sleep and wakefulness interacting in a complex but highly integrated way. In this respect, it should be noted that through these bundles nervous signals can be transferred from the frontal lobes to the parietal and occipital areas (and vice versa) in as few as 15 ms or less (Zappoli, 2003); this speed might account for the probable reciprocal inhibition during A1 and A3 CAP phases which might be so fast that only one frequency component is evident on the scalp. However, these considerations can be viewed as speculative and more research is needed in order to clarify the complex interactions between sleep and wakefulness neurophysiological mechanisms, probably taking place during CAP in human sleep.

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CHAPTER 10

Quantitative analysis of the sleep electroencephalogram

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10.1. Introduction

Despite the considerable controversy regarding the clinical utility of quantitative EEG (qEEG) techniques in position papers published by various professional organizations (Duffy et al., 1994; Nuwar 1997; Hoffman et al., 1999) over the past decade (Hughes and John 1999), certain aspects of this technology, including the paperless acquisition of data (digital EEG) and various methods of signal analysis have clearly proven useful in the diagnosis and assessment of neurologic, psychiatric and developmental disorders. Such techniques have also been useful when applied to the sleep EEG, in contributing not only to the fundamental characterization of normal human sleep, but also in facilitating investigations into several sleep disorders (Corsi-Cabrera et al., 2000).

10.2. Neurophysiologic basis of the wake and sleep EEG

The standard clinical EEG represents a visual description of brain electrical activity obtained through arrays of electrodes placed across the scalp (Holschneider and Leuchter, 1999). Providing excellent temporal resolution for assessing such activity on the order of time frames of neuronal events (e.g., milliseconds), the EEG can rapidly detect acute changes in brain function (such as those which occur at sleep onset and during rapid eye movement (REM) sleep) as well as examine the temporal sequencing of brain processes during brain activation. Recorded electrical activity results from the extracellular flow of current associated with summated excitatory postsynaptic poten-

tials (EPSPs) and inhibitory postsynaptic potentials (IPSPs). Although much of the amplitude of brain electrical activity derives from cortical neurons underlying the scalp electrodes, subcortical sites modulate the synchrony of the recorded activity. Specifically, pacemakers in the thalamocortical neuronal circuitry produce rhythmic synchronous activity, which is reduced by arousal and increased with reduced vigilance. Desynchronization of brain electrical activity following neocortical activation is mediated by afferents from the brainstem reticular formation and basal forebrain, which are in turn modulated by noradrenergic, cholinergic and GABAergic neuronal systems.

As human EEG activity shows a range of frequency, voltage, morphology, reactivity and regional predominance, it has been traditionally divided fundamentally into broad bands established by visual inspection (Corsi-Cabrera et al., 2000). Brain electrical frequencies are therefore generally reported in the delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12 or 13 Hz and higher) bands. Sigma activity (12–14 Hz, occasionally to 16 Hz) which overlaps beta, has also been described, consisting mainly of sleep spindles (periodic phasic events observed mainly during NREM sleep, thought to promote sleep continuity) (Bove et al., 1994; Uchida et al., 1994; Halsaz 1998). While delineation of these broad frequency bands has allowed for the characterization of human brain action during normal wakefulness and sleep and in the setting of associated pathologic conditions, it should be noted that while most researchers conform somewhat closely to the above identified frequencies within each respective band, the limits and ranges of each band often vary slightly from one investigator to another and, at times, from one project to another. We have therefore in this chapter chosen, when referencing work in the field, to refer to frequency bands by the traditional name followed by the specific frequency range identified by the investigator in parentheses (e.g., delta (0.3–3.0 Hz)).

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In the normal adult, wakefulness (W) is characterized by either alpha or beta rhythms. Alpha rhythms represent waxing and waning, sinusoidal oscillations resembling spindles with a frequency ranging from between 7–8 Hz and 11–12 Hz, limited in duration to between 0.5–2 seconds. They can appear isolated or in trains, and predominate in posterior and occipital regions when the eyes are closed. These alpha rhythms are produced by efferent projections distributed throughout the cortex, originating from pacemaker neurons in the thalamus which normally oscillate synchronously in approximately the 7.5–12.5 Hz frequency range. With the eyes open, the dominant EEG activity is characterized by lower-voltage, higher-frequency waves (from 12–13 Hz to frequencies much higher) with irregular morphology that have been termed beta waves, low-voltage fast activity, or desynchronized EEG activity. This beta band is thought to reflect corticocortical and thalamocortical transactions related to specific information processing (Hughes and John 1999).

In contrast, sleep is a behavior normally characterized by relaxation of the antigravity musculature with decreased responsiveness to external stimuli (Peigneux et al., 2001). Sleep is preceded by the sleep-onset period (SOP), and is followed by the return to wakefulness, or the sleep inertia period (SIP) (Ogilvie, 2001). In general terms, sleep begins electrophysiologically after the SOP has been terminated by the appearance of sleep-specific spindles and K-complexes, oscillates between NREM and REM stages with a somewhat irregular periodicity (ultradian cycle) that averages roughly 90 minutes, and ends with a return to wakefulness. REM sleep is characterized by the presence of rapid eye movements (REMs) despite global muscular atonia, and is also known as paradoxical sleep (PS) because of the phasic activity of the eye muscles and high-frequency wake-like pattern of the EEG. NREM sleep is divided somewhat arbitrarily in primates into several stages (1 through 4), corresponding with increasing sleep ‘depth’. This is based on the visual detection of the predominant EEG activity over a limited period of time or ‘epoch’ (usually of 20 or 30 seconds), together with electromyographic activity and eye movements (Rechtschaffen et al., 1968; Corsi-Cabrera et al., 2000). Stage 1 is defined by low voltage, mixed frequency with predominance of activity from 2–7 Hz, and alpha during less than 50% of the epoch and stage 2 by the presence of K-complexes, sleep spindles, and slow activity of 2 Hz or less during less than 20% of

the epoch. While sleep deepens, the amount of slow oscillations increases leading to stages 3 and 4 sleep, collectively termed slow-wave sleep (SWS). Stage 3 is characterized by high-amplitude slow activity between 20 and 50% of the epoch, and stage 4, by high amplitude slow activity greater than 50% of the epoch. In humans, SWS is most abundant during the first half of the night (up to 80% of the sleep time), while REM sleep dramatically increasing during the second half of the night (alternating with stage 2 sleep).

However, visual scoring of the NREM EEG into discrete and arbitrary stages in reality, distorts the true physiological continuum of cellular activities which define the sleep state (Steriade and Amzica, 1998; Peigneux et al., 2001; Tan et al., 2001). While such ‘macrostructural’ characteristics of sleep are often depicted in a graph of sleep stage over time across the night – yielding the so-called ‘hypnogram’ (Figure 10.1 (Halasz 1998)), this macrostructure has an underlying ‘microstructural’ basis, as sleep is a dynamic process in which different degrees of distinct arousal-dependent phasic changes are embedded (Halasz 1998). Figure 10.1 shows the distribution of micro-arousals (MA) along the hypnogram of a young healthy individual after placebo and psychostimulant (amphetamine derivative) administration. Under the latter condition, MA became more frequent and impacted into the ‘descending’ phase of the sleep cycles.

Indeed, arousability is the main feature that distinguishes sleep from the comatose state, in which arousals represent sudden changes in ongoing EEG activity, both in amplitude and morphology, and are thus a measure of sleep continuity. Arousal-dependent

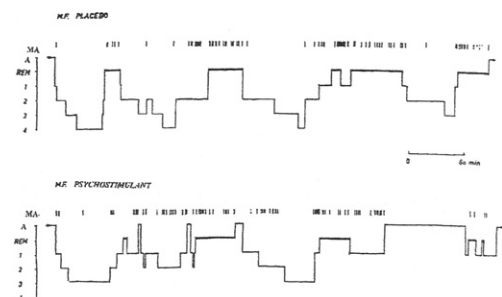


Fig. 10.1. Macrostructural and microstructural aspects of sleep. This figure shows the distribution of micro-arousals (MA) along the hypnogram of a young healthy individual after placebo and psychostimulant (amphetamine derivative) administration. Under the latter condition, MA became more frequent and impacted into the ‘descending’ phase of the sleep cycles (Halasz, 1998).

changes appear spontaneously or may be elicited by several kinds of sensory stimuli, and have been categorized into several groups based on published criteria (ASDA, 1992; Halasz, 1998; Sforza et al., 2000b); these include 'phases of spontaneous transitory activation (PAT)', microarousals (MA), 'K-bursts' (a sequence of two or more K-complexes without alpha activity), and delta bursts (D-bursts). However, 'arousal equivalents' have also been described, which do not fit into current definitions, but share common physiologic sequelae. Such arousal phenomena appear to result from two competing physiological forces – the afferent activity generated by the stimulus with its potential to disrupt the sleep process, and the cortical and subcortical mechanisms which function to maintain sleep (Sforza et al., 2002). In particular, brain activity promoting sleep maintenance may produce the phenomenon of sleep spindles, which are periodically recurring phasic events observed during NREM sleep. They show the greatest power over the vertex of the skull, and recent studies have shown bimodal peaks in spindle frequency with a different distribution over the scalp (faster spindles situated more anteriorly with slower ones dominating centro-parietally). Spindles are believed to result from inhibitory gating of sensory input to the cortex, which may serve to promote sleep continuity (Bove et al., 1994).

Another microstructural measure of sleep continuity is the so-called 'cyclic alternating pattern' (CAP) of the sleep EEG (Terzano, 1985), which represents a pattern of putative arousal-related phasic events appearing throughout NREM sleep. Appearing in sequences across the conventional sleep stages, CAP is the translation of a normal oscillatory process between presumed conditions of greater arousal (A phase) and lesser arousal (B phase), occurring with a periodicity of 20–40 seconds (Parrino et al., 2000; Terzano et al., 2003).

Finally, superimposed upon this macrostructural and microstructural electrophysiologic activity are several integrated regulatory mechanisms which influence not only the sleep process itself, but sleep propensity as well (Nobili et al., 2001). The concept of slow-wave activity (SWA, or power density of the EEG delta band between approximately 0.25 and 4 Hz, related to SWS), has been instrumental in the formulation of a model of sleep regulation in which the interaction of a homeostatic process (termed process S) and circadian process (process C) together determine the propensity for sleep (Borbely 1982). Process S increases gradually during the waking state, resulting

in an initial elevation of SWA once asleep, which then progressively decreases throughout the sleep period; furthermore, the temporal positions of SWS during the initial cycles of sleep at the beginning of the night further reflect the condition of this homeostatic process. However, as will be discussed, a more precise measure of homeostatic integrity can be obtained through the qEEG technique of spectral analysis (specifically, the exponentially declining trend in SWA over successive sleep cycles) (Nobili et al., 2001).

10.3. Quantitative EEG: nomenclature and definitions

To facilitate the discussion of the quantitative analysis of the sleep EEG, several terms (Nuwar, 1997) are defined below with representative examples (figures), where appropriate.

10.3.1. Digital EEG/paperless

This refers to the paperless acquisition, recording and waveform display of the EEG using computers, with waveform storage in a digital format on electronic media (Nuwar, 1997). In contrast to EEG recorded on paper which cannot be changed, digital EEG data can be filtered, re-formatted, re-referenced, transformed spatially and subjected to computational algorithms (Scherg et al., 2002).

10.3.2. Quantitative EEG (QEEG) analysis

QEEG refers to the mathematical processing of digitally recorded EEG data in order to highlight or examine specific features of the EEG. This can be done in several ways.

10.3.2.1. Signal analysis

Signal analysis is the quantitative measurement of specific EEG properties or transformation of raw digital data into numerical parameters other than the traditional amplitude vs time. Several types of measurements and analyses can be performed as detailed below.

10.3.2.1.1. Automated event detection. Automated event detection employs mathematical algorithms to detect or identify events or abnormalities that the computer has been programmed to bring to one's attention. As applied to the sleep EEG, attempts have been made to automate the processes of sleep staging

and the detection of discrete events such as respiratory events, leg movements, eye movements and spindle activity (Agarwal and Gotman, 2002). However, these methods cannot be applied without human validation for two reasons. The first is that these methods are imperfect, and are prone to errors due to the presence of artifacts or unexpected event configurations. The second, and most important, relates to a fundamental problem of computer-based analysis – a computer program must have a precise definition of a problem to encode it into an algorithm. However, many of the definitions related to sleep staging or polysomnographic events are imprecise. For example, the universally accepted rules of state (R&K) (Rechtschaffen and Kales, 1968): ‘Stage 1 is defined by a relatively low voltage . . . The transition from an alpha record to stage 1 is characterized by a decrease in the amount, amplitude and frequency of alpha activity,’ require subjective interpretation and therefore cannot be perfectly transformed into a fixed rule for computer interpretation.

10.3.2.1.2. Monitoring and trending EEG. This is a technique which uses mathematical algorithms to extract parameters from the raw data that summarize the important aspects of the EEG (Nuwar, 1997).

10.3.2.1.3. Source analysis. Source analysis is a form of mathematical analysis in which the recorded EEG values (typically scalp voltage values from an epileptiform abnormality) are compared with predetermined models of possible CNS generators of the EEG signal. The analysis is aimed at specifying the location, orientation, strength and number of the possible sources of the analyzed spike or other EEG features (Nuwar, 1997).

10.3.2.1.4. Frequency analysis. Frequency analysis converts the original EEG data into a representation of frequency content. The magnitude corresponds to the amount of energy that the original EEG possessed at each frequency. Such analyses can be linear or non-linear.

10.3.2.1.4.1. Linear

(1) Basic definitions

- ‘Absolute power’ in each band is one of the most fundamental qEEG measures. Power (or amplitude squared) is a measure of the intensity of energy measured and calculated in a series of frequency bands (the ‘power spectrum’) for

a discrete time interval (Holschneider and Leuchter, 1999; Hughes and John, 1999).

- ‘Relative power’ in each band (percentage of total power in each channel) is a measure of the percent of total power in a specific frequency band. Whereas absolute power can add to essentially any magnitude across the frequency spectrum, relative power must add to 100%, with the relative power in any one band representing some fraction of the total power. Evaluation of relative power may improve the detection of subtle shifts in brain function over time by normalizing fluctuations in total power seen across individuals or within one individual across several recordings.
 - ‘Coherence’ is a measure of the functional connectivity between brain regions calculated by measuring the phase consistency of two signals, or the extent to which EEG signals from different brain regions have common, time-locked frequency components. Coherence varies between 0 and 1 and is analogous to a correlation coefficient of the signal between two brain regions.
 - ‘Cordance’ is an integration of absolute and relative power into a single measure; specifically, it characterizes both the magnitude of and the relationship between, absolute and relative power at each recording electrode (Leuchter et al., 1999). Normalizing power across electrodes and frequency bands, it has been reported to show a stronger association with cerebral perfusion (measured with ¹⁵O-PET) than with either power measure alone (Holschneider and Leuchter, 1999).
- (2) Fast Fourier Transform (FFT)/spectral analysis (Figure 10.2 (Landott et al., 1999)): one of the most used techniques for qEEG analysis, spectral analysis involves signal parametrization using the Fast Fourier Transform (FFT) to quantify the power at each frequency of the EEG averaged across an entire sample, or power spectrum (Jobert et al., 1994; Hughes and John, 1999). By decomposing a complex signal into series of sine and cosine waves, the energy or power (μV^2) accumulated over a period of time for every frequency within a given band can be calculated (Corsi-Cabrera et al., 2000). In this process, one tries to fit, with the least possible error, a series of continuous (periodic) sinusoidal functions to the whole length of the data in the EEG epoch under

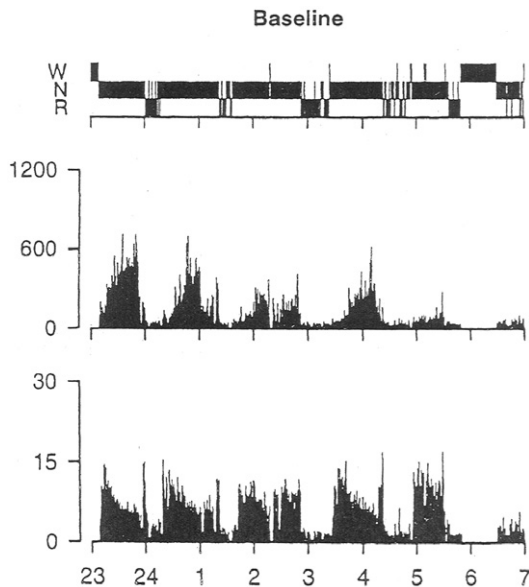


Fig. 10.2. Fast Fourier transform (FFT)/spectral analysis (Landolt et al., 2000). This figure illustrates the distribution of wakefulness, NREM sleep (stages 1, 2, 3 and 4) and REM sleep, and the time course of slow-wave activity (top panel) (SWA in μV^2 , power within 0.75–4.5 Hz; C3A2-derivation) and spindle frequency activity (lower panel) (SFA in μV^2 , power within 12.25–15.0 Hz) for one individual during a baseline night of sleep. W = waking state, N = NREM sleep, R = REM sleep.

investigation (Ktonas, 1981); ‘frequency’ in this context refers to frequency of the periodic sinusoidal wave, which is fitted to the whole length of the data. This process incorporates information about both amplitude and prevalence of activity within a specified frequency band, to yield a single value per a discrete time interval. The data ‘window’ interval impacts time and frequency resolution; specifically, a data window of longer duration yields poorer time resolution, but enhanced frequency resolution – the converse is true for a shorter interval window (Jobert et al., 1994).

- (3) Period amplitude analysis (PAA) (Figure 10.3 (Ktonas and Gosalia, 1981)): In period amplitude analysis, individual half- or full-waves of the EEG are examined for duration and amplitude (Ktonas and Gosalia, 1981). The EEG is treated as a superposition of waves with particular individual periods and amplitudes, and can be used for detailed EEG quantification by measuring the EEG duration and peak amplitude between suc-

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Fig. 10.3. Period amplitude analysis (PAA) (Ktonas and Gosalia, 1981). This figure compares period-amplitude analysis to power spectral analysis (PSA). (a) Shows the 16-second EEG epoch (analog prefiltered data) analyzed; (b) shows the percentage of occurrence of the EEG half-waves in each of the five frequency bands of interest; (c) shows the average of the half-wave peak amplitudes in each of the five frequency bands; (d) shows the power spectrum of the EEG epoch in (a). Frequency band numbers correspond to the following frequency bounds: (c) period-amplitude analysis (Hz): 1 = 0–0.28, 2 = 0.28–0.85, 3 = 0.86–1.42, 4 = 1.45–2.00, 5 = 2.06–2.56; (d) spectral frequency (Hz): 1 = 0–0.28, 2 = 0.28–0.84, 3 = 0.84–1.4, 4 = 1.40–1.96, 5 = 1.96–2.53.

cessive zero-crosses below PSA power of 2 Hz; above 2 Hz, zero-derivative measures of peak–trough amplitude correlate better with PSA power (Uchida, 1999). Therefore, PAA can be used to measure time-domain characteristics within a narrow EEG frequency band, and has been useful in the detection of EEG transients such as K-complexes and spindles (Ktonas, 1981).

- (4) Principle component analysis (PCA): Principle component analysis enables grouping of variables that co-vary together and separates them from others that are orthogonally independent. Variables grouped together in the same eigenvector are therefore responding to, or reflecting, some common influence, while independent from those gathered in a different eigenvector. Therefore, PCA can be used to investigate how EEG waves of various frequencies may be associated (Corsi-Cabrera et al., 2000).
- (5) Wavelet transform (WT) (Figures 10.4A and 10.4B (Jobert et al., 1994)): The wavelet transform was developed as an alternative to the classical Fourier transform in order to overcome the limitation of the latter with regard to the

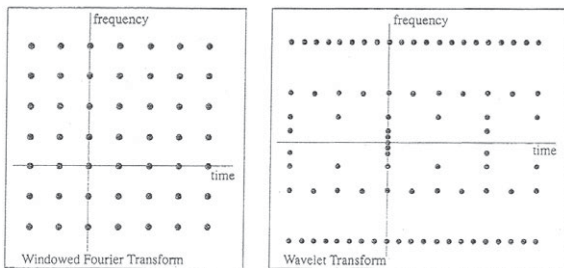


Fig. 10.4A. Wavelet transform (WT) (Jobert et al., 1994). This figure illustrates the fundamental difference between FFT and WT. The left diagram shows the centers (or computed point) of the time-frequency localization for the discrete implementation of a short-time FFT, whereas the right diagram represents that of a wavelet transform. In contrast to the FFT in which time and frequency are evenly spaced, the WT has better time resolution for high frequencies; time resolution increases with frequency.

strong inverse relationship between time and frequency resolution, and the choice of an appropriate data window (Jobert et al., 1994). With FFT, as noted above, if the data window is broad (i.e. data length is long), good frequency resolution is achieved, but time resolution suffers, and vice versa. With WT however, variable time-frequency resolutions are used. When applied to the sleep EEG, the same method can be used for very different time scales (from seconds to hours), enabling the exploratory analysis of various aspects of the micro- and macro-structure of sleep. Unlike FFT, concurrent signal analysis in the time-frequency domains, with optimal resolution in both time and frequency, is possible.

- (6) Matching pursuit (MP) parameterization of time series: The matching pursuit (MP) algorithm was devised to overcome the inherent limitations of both FFT and WT; specifically, FFT gives a poor representation of functions well localized in time, whereas WT is not adequate in representing functions whose Fourier transforms have a narrow frequency of support. In contrast, MP relies on the decomposition of signals into linear expansion of waveforms belonging to a very broad class of functions. These waveforms are adaptively matched to the local signal patterns, and thus the MP approach is particularly useful for characterizing transient activity appearing randomly in the signal, such as sleep spindles and K-complexes (Durka, 1995; Zygierewicz, 1999).

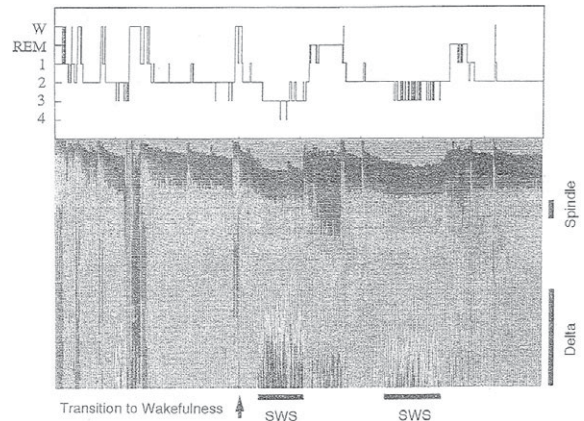


Fig. 10.4B. This figure illustrates how the WT can be applied not only to a scale of a few seconds, but also to several hours of recording time, such as a full night's sleep (Jobert et al., 1994). Thus, the micro- and macrostructural aspects of the sleep process can be analyzed. The top panel represents the sleep profile of a 72-year-old individual with psychophysiological insomnia treated with a benzodiazepine, while the bottom panel represents the WT representation of EEG (lead C3-A1) activity (by integrating the information collected on the basis of epochs of 10 s duration). Although not specifically shown, the time resolution is represented by the x-axis, and the frequency component by the y-axis (higher frequencies at the top, lower frequencies at the bottom). Wakefulness at the beginning of the recording shows high-frequency (20–40 Hz) EEG activity, and stage 2 has frequency components in the range below 5 Hz and distinct activity between 10–20 Hz, which is more evident in the second half of the night. Episodes of SWS peak in the frequency range of 0.625–1.24 Hz. The increased occurrence of SWS during the second half of the night is apparent, as are the multiple awakenings (transition to wakefulness) during the first half of the night, characterized by the abrupt power decrease in the entire frequency range below 20 Hz.

10.3.2.1.4.2. Nonlinear: dimensional complexity.

In addition to the traditional linear analysis of the sleep EEG, methods involving non-linear dynamics have also been applied to the EEG, as electrical activity of the brain exhibits strong non-linear and dynamical properties (Zhang, 2001; Kobayashi et al., 2001). Such complex, aperiodic patterns in the human EEG are produced by the collective activity of interconnected cortical neurons (Anokhin et al., 2000), and thus, dimensional complexity (DCx) analysis may provide a more accurate method of quantifying the gross activity of this complex system, than the more

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Fig. 10.5. Correlation dimension (D_2) (Kobayashi et al., 2001). This figure illustrates the application of D_2 to the sleep state (D_2 versus time). The D_2 significantly decreases from the awake stage to the sleep stages 1, 2, 3 and 4, and increases during REM sleep; this is apparent in each sleep cycle throughout the entire night. Thus, the complexity of the human sleep EEG may be low during SWS and high during REM, and D_2 may be a useful method for analyzing the entire sleep EEG.

traditional linear methods described above (Anokhin et al., 2000). Indeed, human studies have shown that DCx varies with state and sleep stage (Matousek et al., 1995). One measure of system dimensional complexity which has been extensively studied is correlation dimension (D_2), in which the D_2 of a dynamic system is the number of state variables used to describe the dynamics of the system, and is thus an estimate of the complexity of that system (Kobayashi et al., 2001). When applied to the sleep state (Kobayashi et al., 2001) as seen in Figure 10.5 (D_2 versus time), the D_2 significantly decreases from the awake stage to the sleep stages 1, 2, 3 and 4, and increases during REM sleep; this is apparent in each sleep cycle throughout the entire night. Thus, the complexity of the human sleep EEG may be low during SWS and high during REM, and D_2 may be a useful method for analyzing the entire sleep EEG (Kobayashi et al., 2001).

10.3.2.2. Coherence analysis

Coherence analysis uses calculations similar to frequency analysis to obtain information about the temporal relationships of EEG activity frequency components at two or more recording sites (Nuwar, 1997). Data may be displayed as a table or numbers, a multidimensional graph, or topographically.

10.3.2.3. Topographical EEG

Topographical EEG is a visual representation of the spatial characteristics of raw EEG data (i.e., voltage amplitude) or a derived parameter, such as spectral power or peak latency (Nuwar, 1997). Amplitude at a given anatomic site is ordinarily represented as a color

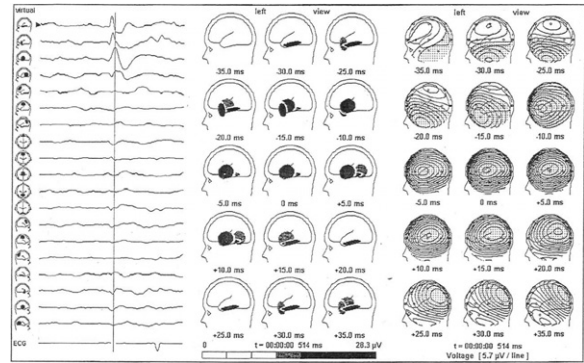


Fig. 10.6. Topographical EEG (Scherg et al., 2002). This figure depicts the whole-head voltage maps (right) viewed from the left in a man with left temporal lobe epilepsy. Inferior-temporal spike activity is shown, with the basal surface of the left temporal lobe being the most likely origin of the spike-wave propagation. The source montage is shown (left), and shows spike-wave patterns at three sublobar aspects of the left temporal lobe: basal, polar and antero-lateral. The amplitudes of the source montages can be translated into color-coded intensities at the 'virtual source electrodes' and displayed as a sequence of source activity images (middle). The timing of spike onset and peaks from both the source waveforms and images, indicate propagation from the basal to the polar and the anterolateral aspects of the temporal lobe. The source activity images (middle) and the vertical dipole topography 30ms before the spike peak in the scalp maps (right) show how the initial basal activity is followed by a complex overlap of nearby temporal areas with different orientations, which accounts for the constantly changing pattern in the whole-head voltage maps (right).

or intensity, and amplitudes at unmeasured sites are interpolated to present a smooth display. These displays can highlight some spatial features of the EEG, and are often called EEG brain maps (Nuwar, 1997). However, this should not be confused with functional cortical brain mapping by direct electrical cortical stimulation or with brain mapping by neuroimaging techniques, which have no direct relationship to EEG brain mapping. More advanced techniques now allow for 'virtual source montages' (Figure 10.6) which can imply activity from different brain regions with various orientations (Scherg et al., 2002).

10.3.2.4. Statistical analysis

Statistical analysis compares variables derived from the digitally recorded EEG between groups of people or between a patient and a group. These comparisons may be carried out on individual variables (e.g., alpha frequency) or on many variables (including spatial

aspects) using appropriate multifactorial statistical methods. In addition to comparisons to normative values, diagnostic discriminant analyses can also be performed.

10.4. Applications of qEEG to the fundamentals of sleep

Quantitative EEG analysis techniques allow for the characterization of sleep and the sleep EEG, beyond that which is possible with more conventional electrophysiological methods. However, it should be noted that the overwhelming majority of work in clinical quantitative sleep EEG analysis has employed FFT analysis in various forms. The following discussion, then, represents a very brief summary of certain highlights of this work and, by default, will appear to focus almost exclusively on work based on FFT.

10.4.1. Cortical topography and the local nature of sleep

While initially regarded as a global brain process, early observations of variations in EEG patterns based on placement of surface electrodes suggested that there were regional differences in brain activity. In the waking state, alpha activity is most apparent in the occipital region of the brain, but once asleep, highly stable, frequency-specific individual patterns of EEG power distribution in NREM sleep have been identified (Finelli et al., 2001).

Specifically, the power spectra along the antero-posterior axis have been shown to exhibit frequency-specific and state-dependent gradients (Finelli et al., 2001); SWA and K-complexes exhibit a frontal predominance, while fast sleep spindles (14 Hz) predominate centroparietally and slow (12 Hz) sleep spindles frontocentrally (Wichniak et al., 2002). Furthermore, SWA during NREM sleep shows the highest power over the frontal cortex and is believed to reflect activity particularly involved in sleep homeostasis (Werth et al., 1997a). The frontal predominance of low-frequency activity (SWA) after sleep deprivation further supports the hypothesis that sleep has a local, use-dependent characteristic (Finelli et al., 2001). Similarly, with the transition to REM sleep, broad changes in the EEG are noted, including a posterior shift in the relative power of almost all frequencies, although most markedly for alpha activity (De Gennaro et al., 2002).

As will be discussed in subsequent sections, these topographic features of the sleep EEG have proven

essential in our understanding of other aspects of the sleep process, including those related to the SOP and 'arousal' equivalents during REM sleep.

10.4.2. Sleep onset determination

Described as a process in which arousal is reduced, the SOP is physiologically characterized by the disappearance of eye movement saccades, a reduction of endogenous blinking, the appearance of slow rolling eye movements, a decrease in electromyographic amplitude, respiratory slowing, and a fall in body temperature (De Gennaro et al., 2001). The EEG typically shows a decrease in fast, low-voltage beta-activity as well as in the regularity and frequency of alpha activity, and increases in slow delta and theta activities (Alloway et al., 1999). Behavioral changes include a decrease in responsiveness to external sensory stimuli culminating in general unresponsiveness (De Gennaro et al., 2001).

Clinically relevant, several sleep disorders involve difficulties in sleep initiation, and the SOP is scrutinized in the clinical evaluation of physiologic sleepiness – in the form of the multiple sleep latency test (MSLT). While the EEG remains the most commonly used measure to describe this process (De Gennaro et al., 2001), the R&K scoring system (Rechtschaffen and Kales, 1968), with its 30-second scoring of epochs, has proven insufficient in monitoring the SOP due to poor time resolution. Traditional macrostructural EEG dynamics shift rapidly during this transition period, and thus important microstructural changes are lost in most types of time-averaging processes (Ogilvie, 2001). A common example of such rapid EEG changes is the waxing and waning of alpha activity just before and after stage 1 is entered. In contrast, quantitative EEG analysis with high time resolution can reveal characteristic changes in power during the SOP, when applied in this setting. In normal sleepers (Hori, 1985), delta (1–3 Hz) and theta (4–7 Hz) power increase during the SOP; alpha (8–12 Hz) power decreases rapidly in the 10-minute period following stage 1 onset, while sigma (13–15 Hz) power decreases immediately after stage 1 begins. However, beta (16–19 Hz) activity (also characteristic of the awake state), does not show any significant changes (Lamarche, 1997).

Clinically, the examination of the SOP has been integral to the study of disorders of 'hyperarousal' such as primary insomnia (De Gennaro et al., 2001), as well as disorders of excessive daytime sleepiness,

including idiopathic hypersomnia (IH) and narcolepsy. Furthermore, it has been suggested that a more valid estimate of physiologic sleepiness during MSLT may be obtained by evaluating the magnitude of delta activity during the SOP, rather than visually scored sleep onset latency (De Gennaro et al., 2001; Alloway et al., 1999). However, further research is required in order to assess the practicality of such a spectral-based MSLT protocol in the measurement of physiologic sleepiness.

10.4.3. Sleep staging and spectral power

While the identification of vigilance states – NREM, REM and waking – has traditionally required human pattern recognition, quantitative analysis has been shown to be useful in making these distinctions. In addition to the well-known oscillating pattern of delta (0.3–3 Hz), sigma (1–15 Hz, which mainly reflects sleep spindle activity) and higher frequency beta (20–28 Hz) frequencies also exhibit strong oscillatory patterns during the night; furthermore, the relative activity of these frequency bands within epochs has been used to differentiate NREM from REM sleep (Uchida et al., 1994). Specifically, while sigma and delta have been found to oscillate reciprocally within NREM periods, both are at their lowest values during REM. In contrast, high-frequency beta exhibits higher values during REM sleep than in NREM. Thus, beta activity is more prominent in the REM EEG and its relationship to sigma may help to discriminate NREM from REM sleep, as illustrated in Figure 10.7 (Uchida et al., 1994) in which the patterns of delta, sigma and beta EEG spectral power for an individual during one night of study are shown. Each point is an average of nine consecutive epochs (3 min) converted to standard scores to provide a common range for these three measures. All three frequency bands oscillate strongly across the night. Sigma and beta oscillate in phase during NREM and out of phase in REM sleep; sigma exhibits its lowest levels during REM while beta reaches its highest values during this stage of sleep.

However, it has become apparent with the advent of qEEG techniques, that such scoring has significant limitations in describing the true continuum of NREM sleep stages (Steriade and Amzica, 1998; Armitage, 1995; Peigneux et al., 2001). By assuming the existence of a discontinuity among stages, a tremendous amount of information is lost in the process of traditional visual scoring of the sleep EEG. Furthermore, the same visual stage score can represent very differ-

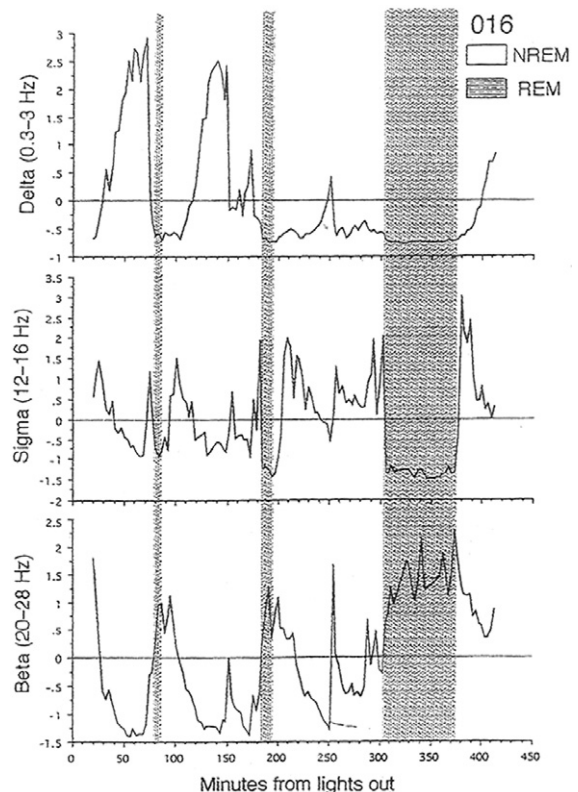


Fig. 10.7. Sleep staging and relative spectral power (Uchida et al., 1994). This figure illustrates how sigma (least prominent during REM, along with delta activity) and beta (more prominent in REM) activity can discriminate between NREM and REM sleep. The patterns of delta, sigma and beta EEG spectral power for an individual during one night of study are shown. Each point is an average of nine consecutive epochs (3 min) converted to standard scores to provide a common range for these three measures. All three frequency bands oscillate strongly across the night. Sigma and beta oscillate in phase during NREM and out of phase in REM sleep.

ent EEG patterns. For example, an epoch scored as stage 4 in an 8-year-old child may have five times the spectral power as that same stage scored in an adult (Tan et al., 2001). Thus qEEG is particularly useful in the investigation of the microstructural organization of sleep – specifically phasic events and transient states with a time resolution on the order of seconds (Rosa, 1999). A variety of approaches have been employed to identify or characterize discrete sleep EEG activity or events utilized in traditional sleep EEG staging (e.g., spindle detection, K-complex recognition) with generally good reliability. Studies to date suggest that computer-quantified sleep EEG

measures are remarkably stable across baseline nights (Armitage, 1995; Tan et al., 2001).

10.4.4. Microstructural aspects of the sleep EEG: arousals and spindle activity

10.4.4.1. Arousals: NREM hierarchy of cortical and subcortical arousals and REM alpha-burst activity

Arousals occur throughout the night and characterize the sleep EEG, serving as a measure of sleep continuity. Using quantitative EEG techniques, arousal equivalents during both NREM and REM sleep have been identified.

10.4.4.1.1. NREM hierarchy. During NREM sleep, arousals can vary from brief increases in myographic activity or subtle changes in respiratory and/or cardiac activity, to sleep stage shifts, significant and abrupt changes in EEG activity, to full awakening. While arousals have been traditionally defined by EEG desynchronization (e.g., microarousals (MA) (ASDA, 1992) and phases of transitory activation (PAT) (Sforza et al., 2000b), using more sophisticated methods of arousal detection, it has been postulated that certain forms of uncommonly highly synchronized EEG activity, as well as subtle changes in signals of autonomic function, may also represent forms of arousal responses in humans. Furthermore, arousal responses appear to be graded, as studied using spectral analysis of cardiac activation during NREM sleep in the setting of the four previously described types of arousals: D-bursts (delta-bursts), K-bursts (sequence of two or more K-complexes without alpha activity), MA and PAT. Specifically, when an arousal stimulus occurs during sleep, brainstem centers may be activated first, which drive tonic neuronal activity and induce coupled alterations in peripheral autonomic tone, tachycardia and synchronized EEG arousal. Afferent information from these neuronal structures may then be carried to the CNS, leading to EEG cortical MA, PAT or awakening. As the arousal threshold is higher in rostral cerebral areas, when the arousal stimuli is of low intensity or when sleep is 'deeper', the cortical areas may not be activated and thus the resulting partial nervous system response may manifest only in autonomic activation and D- or K-bursts. When the stimulus is greater or when sleep is lighter, there may be delayed cortical activation, evidenced by fast desynchronized EEG activity, MA or PAT, and a more significant impact on heart rate. Therefore, it is believed that a continuum

may exist among arousal responses, beginning with brainstem activation (surges in sympathetic activity, cardiac activation) progressing to synchronized EEG-sleep patterns (D- and K-bursts), and ending in cortical EEG desynchronized activation (MA) (Halasz, 1993; Sforza et al., 2000b).

10.4.4.1.2. REM-alpha bursts. The arousal response manifests quite differently during REM sleep. In humans, REM is defined by the appearance of mixed-frequency electroencephalographic (EEG) activity, rapid eye movements and muscular atonia. However, as depicted in Figure 10.8, spectral analysis of REM sleep separates this 'mixed frequency' into four components: a delta power component, theta power (the result of sawtooth waves and REMs), activity in the beta range (minimal and, in part, derived from desyn-

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Fig. 10.8 REM spectral components (Cantero and Atienza, 2000). Spectral analysis of REM sleep separates this 'mixed frequency' into four components: a delta power component (A), theta power (A + B; the result of sawtooth waves and REMs), activity in the beta range (D; minimal and, in part, derived from desynchronized tonic REM activity), and alpha activity (C) (Cantero and Atienza, 2000). The alpha range (approximately 8–12 Hz) activity contributes significantly to the spectral power of REM sleep, and is believed to be predominantly caused by the spontaneous and transient bursts of alpha activity during tonic and phasic REM.

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Fig. 10.9. REM-alpha bursts (Cantero et al., 2000). Distinct phenomena called 'alpha-bursts' (seen on visual inspection in this figure, but not lasting long enough (<3 s) to constitute a true arousal and not associated with submental electromyographic activity (ASDA, 1992)) have been described using FFT. These alpha-bursts are thought to represent a form of microarousal in REM sleep.

chronized tonic REM activity) and alpha activity (Cantero et al., 2000). The alpha range (approximately 8–12 Hz) activity contributes significantly to the spectral power of REM sleep, and is believed to be predominantly caused by the spontaneous and transient bursts of alpha activity during tonic and phasic REM. While this background REM alpha activity has been characterized, more recently, distinct phenomena called 'alpha-bursts' (seen on visual inspection but not lasting long enough (<3 s) to constitute a true arousal and not associated with submental electromyographic activity (ASDA, 1992)) have been described using FFT (Figure 10.9). These alpha-bursts are thought to represent a form of microarousal in REM sleep (Cantero et al., 2000).

10.4.4.2. Slow-wave activity (SWA) and spindle frequency activity (SFA)

Another characteristic of the sleep EEG is the presence of SWA and sleep spindles. Both generated by thalamocortical mechanisms, EEG slow-wave activity (SWA) and spindle frequency activity (SFA) are prominent features of the NREM sleep EEG and inti-

mately involved in sleep homeostasis (Knoblauch et al., 2002).

10.4.4.2.1. Slow-wave activity (SWA) and the homeostatic process. The 'deepest' NREM sleep stages in humans (stages 3 and 4, or SWS), are defined by the presence of a significant amount of large amplitude ($\geq 75 \mu\text{V}$) slow waves, with a frequency of approximately 0.25–2 Hz. In humans, SWS is at a maximum toward the beginning of the night and progressively declines across the sleep period. Furthermore, in all mammalian species studied to date, SWS increases dramatically following sleep deprivation and it is therefore believed that SWS reflects the homeostatic component (the so-called 'process S') of NREM sleep (Littner, 2001). More precisely, slow-wave activity (SWA), measured by spectral analysis, is considered a measurement of sleep intensity and as such, putatively, a more accurate and objective measure of process S than conventional subjective sleep staging (Heinzer et al., 2001).

FFT analysis of delta power, independent of visual scoring of NREM sleep episodes, has thus been important in the characterization of process S (Feinberg, 1993). Characteristic frequency changes can be seen not only during the course of one night of sleep, but also among successive sleep cycles and after sleep deprivation. Figure 10.10 shows density plots for successive 1 Hz or 2 Hz frequency bands across the range of 0.25–17.0 Hz during a baseline night of sleep. The two initial large peaks in the delta frequency bands correspond to slow-wave sleep (stages 3 and 4), whereas alpha peaks corresponding to wake are evident between 7 and 13 Hz. Peaks in the 13–15 Hz band predominantly during stage 2 seem to reflect spindle activity (Borbely et al., 1981).

Figure 10.11 shows the frequency distribution of the relative power density of successive NREM–REM sleep cycles during a baseline night of sleep, expressed relative to the values of the first cycle (horizontal line). For total sleep time (TOT), there is a significant decrease in the 1–8 Hz and 16–20 Hz range between the first and second cycles and between the second (S2) and third (S3) cycles. For stages 3 and 4 combined (S3 & S4) and for stage 4 alone (S4), the values for the second cycle are generally lower than for the first cycle (Knoblauch et al., 2003).

Figure 10.12 represents the frequency distribution of the EEG power density for the first and second recovery nights after 40.5 hours of sleep deprivation (SD); the values are expressed as percentages of the baseline values (arithmetic mean of the two baseline

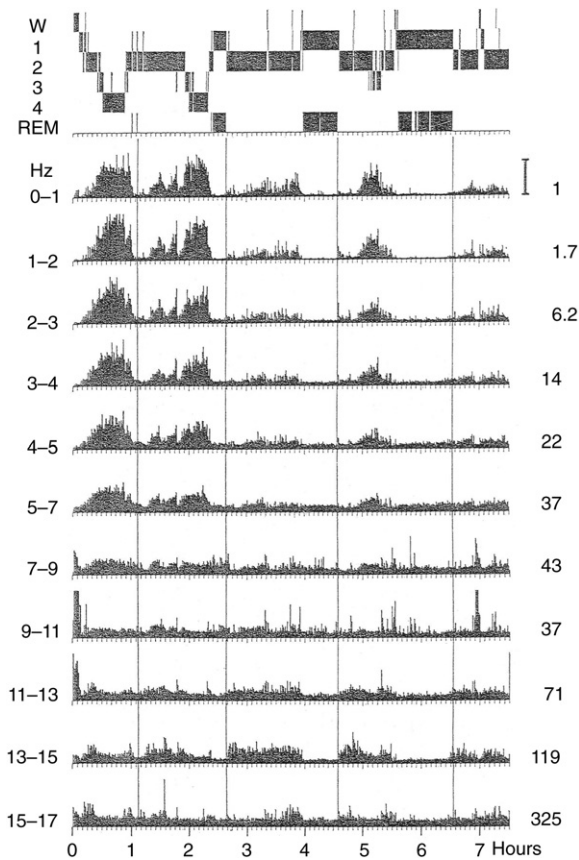


Fig. 10.10. FFT analysis of delta power and process S (Borbely et al., 1981). This figure shows density plots for successive 1 Hz or 2 Hz frequency bands across the range of 0.25–17.0 Hz during a baseline night of sleep. The two initial large peaks in the delta frequency bands correspond to slow-wave sleep (stages 3 and 4), whereas alpha peaks corresponding to wake are evident between 7–13 Hz. Peaks in the 13–15 Hz band predominantly during stage 2 seem to reflect spindle activity.

nights). The first recovery sleep period is characterized by a significant increase in EEG power density in the 1–7 Hz range with the highest values located in the delta band (TOT, as well as when sleep stages were separated, S3 & S4, S4, S2, SREM). However, the enhancement of the EEG power density after SD is not restricted to the delta band, but extends to higher frequencies; specifically, a second peak in the alpha range is evident in stage 3 and 4 and stage 4. In contrast, a significant reduction in power density in the range of spindle activity is seen in stage 2 (15–16 Hz) and for total sleep time (15 Hz) (Borbely et al., 1981).

These data therefore suggest that continuous trends, rather than discrete changes, occur across the

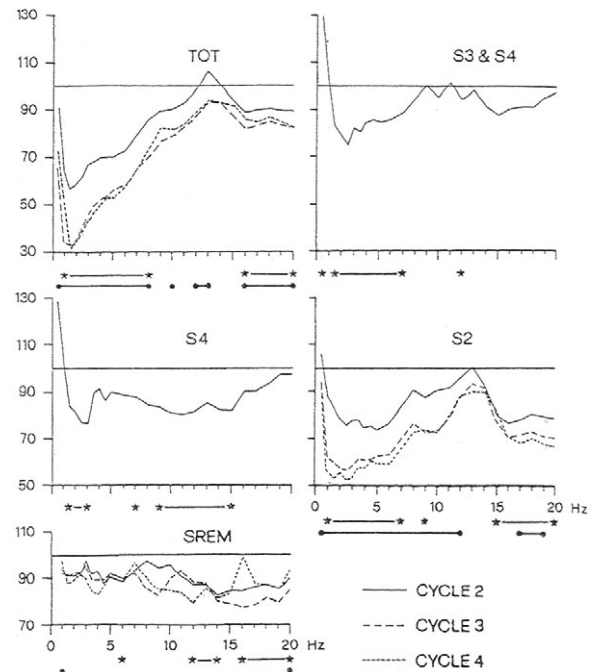


Fig. 10.11. FFT analysis among successive sleep cycles (Borbely et al. 1981). This figure shows the frequency distribution of the relative power density of successive NREM-REM sleep cycles during a baseline night of sleep, expressed relative to the values of the first cycle (horizontal line). For total sleep time (TOT), there is a significant decrease in the 1–8 Hz and 16–20 Hz range between the first and second cycles and between the second (S2) and third (S3) cycles. For stage 3 and 4 combined (S3 & S4) and for stage 4 alone (S4), the values for the second cycle are generally lower than for the first cycle.

frequency spectrum, which are inadequately described by conventional frequency categories, and that the effects of sleep deprivation on sleep are not adequately reflected by the time spent in the various sleep stages (Borbely et al., 1981).

Specifically, neither the progressive reduction in the power density during normal nights (baseline), nor its enhancement after sleep deprivation is limited to the delta band, but rather includes a significant portion of the theta band. Sleep therefore appears more like a unitary process when studied using qEEG, rather than a sequence of well-defined stages (Borbely et al., 1981).

10.4.4.2.2. Sleep spindles, spindle frequency activity (SFA) and processes C and S. Based in part on the above findings, one of the functions of CNS processes that produce sleep spindles has been hypothesized to

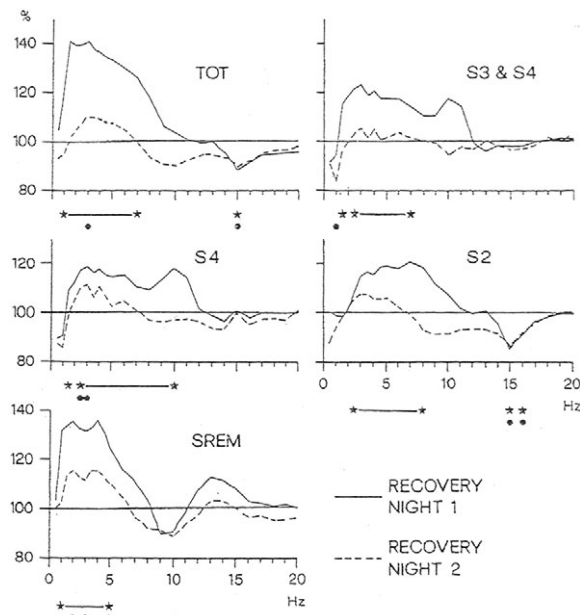


Fig. 10.12. FFT analysis of recovery sleep after sleep deprivation (Borbely et al., 1981). This figure represents the frequency distribution of the EEG power density for the first and second recovery nights after 40.5 hours of sleep deprivation (SD); the values are expressed as percentages of the baseline values (arithmetic mean of the two baseline nights). The first recovery sleep period is characterized by a significant increase in EEG power density in the 1–7 Hz range with the highest values located in the delta band (TOT, as well as when sleep stages were separated, S3 & S4, S4, S2, SREM). However, the enhancement of the EEG power density after SD is not restricted to the delta band, but extends to higher frequencies; specifically, a second peak in the alpha range is evident in stage 3 and 4 and stage 4. In contrast, a significant reduction in power density in the range of spindle activity is seen in stage 2 (15–16 Hz) and for total sleep time (15 Hz).

be to reduce sensory transmission and thus protect the cortex from arousing stimuli (Bove et al., 1994; Knoblauch et al., 2003). However, through qEEG techniques, a clear modulation of SFA (EEG power density in the 11–16 Hz range) by circadian process C and homeostatic process S has also been identified. Of fundamental importance in this endeavor has been the description of a characteristic regional topography to sleep spindles, as well as the identification of a bimodal distribution of spindle frequencies – low (LSFA) and high spindle frequency activity (HSFA) (Werth et al., 1997b). This consists of a lower peak between 11–12 Hz, and higher peak between 12.5–13.5 Hz, respectively. Furthermore, whereas the LSFA

peak is maximal at F3–A2, the HSFA peak is more widely distributed and dominant at C2–A2, P3–A2 and O1–A2. These differences in cortical distribution of SFA may be due to unique generators for these subdivided sigma frequencies (Ogilvie, 2001).

The circadian rhythm of SFA is frequency specific, such that SFA in the 12.25–13 Hz range coincides with the peak and the SFA in the 14.25–15.5 Hz range with the nadir of the endogenous rhythm of melatonin secretion (Knoblauch et al., 2003). A frequency-dependent homeostatic function (process S) of SFA has also been demonstrated (Dijk et al., 1987) as well as frequency-specific topographic variability (Knoblauch et al., 2002).

Regarding the latter, EEG spectra during recovery sleep after either 40 hours of total sleep deprivation or a 75/150 minute short sleep–wake cycle paradigm under constant posture conditions (consisting of ten alternating cycles of 75 minutes of scheduled sleep and 150 minutes of scheduled wakefulness) was examined in ten individuals (Knoblauch et al., 2002).

The accumulation of sleep pressure with extended wakefulness was found to be significantly attenuated by intermittent naps and the differential sleep pressure conditions induced frequency- and topographic-specific changes in the EEG slow wave range (0.5–5 Hz) as well as in the low (LSFA, 12.25–13.25 Hz) and high spindle frequency activity range (HSFA, 13.75–16.5 Hz) during non-REM sleep. EEG activity, particularly frontal SWA and centro-parietal HSFA, was observed to be under a clear sleep–wake-dependent homeostatic control, implying a reciprocal relationship in the homeostatic regulation of SWA and HSFA, but with different spatio-temporal aspects (Knoblauch et al., 2002).

10.5. Selected applications of qEEG in sleep medicine and sleep disorders

Rather than summarize in any comprehensive fashion the vast work of qEEG in clinical sleep medicine, the brief descriptions which follow illustrate how the fundamental concepts of sleep uncovered by computer-based EEG analysis have been applied to clinical practice, in improving our understanding of various pathologic conditions related to the sleep process. Concepts such as slow-wave sleep intensity (SWI) and the various forms of arousal have proven particularly relevant in this regard. The impact of various types of drugs on the sleep EEG as measured quanti-

tatively, while relevant, is beyond the scope of this chapter and will not be addressed.

10.5.1. Symptoms of sleep-related breathing disorder (SRBD) including upper airway resistance syndrome (UARS) and response to treatment

10.5.1.1. Symptomatology related to SDB

Obstructive sleep apnea syndrome (OSAS), central sleep apnea and upper airway resistance syndrome (UARS) are sleep disorders characterized by repetitive cessations (apneas) or limitations in airflow (hypopneas) and/or increased respiratory effort, associated with arousal responses; they are collectively called the sleep-related breathing disorders (SRBD) (Parrino et al., 2000; Ondze et al., 2003). These disorders result in unstable and poorly consolidated sleep, resulting in a marked alteration in sleep architecture (Heinzer et al., 2001; Parrino et al., 2000); clinical features may include snoring, frequent arousals and nocturnal hypoxemia. Individuals with SRBD also may experience excessive daytime sleepiness (EDS) and impairment of cognitive functions, such as deficits in memory, attention, and visual-constructive abilities (Morrison et al., 2001). In such patients, significant reductions in slow-wave sleep (SWS) and rapid eye movement (REM) sleep are often observed, although sleep efficiency (the measure of time asleep versus time in bed) may be preserved or minimally reduced (Heinzer et al., 2001).

10.5.1.1.1. Correlates of excessive daytime sleepiness and cognitive impairment. Quantitative EEG techniques have been particularly helpful in characterizing the nature and neurological correlates of daytime sleepiness and neurocognitive deficits associated with SRBD.

10.5.1.1.1.1. SWA and excessive daytime sleepiness (EDS). Daytime sleepiness has been correlated with increased respiratory effort (Zamagni and Sforza, 1996), parasympathetic activation (Pressman and Fry, 1989) and oxygen desaturation (Mendelson, 1992) in SRBD, although study results have been inconsistent (Colt et al., 1991; Guilleminault et al., 1988). Yet while a correlation clearly exists between the number of arousals due to respiratory events during the night and the severity of EDS measured by MSLT (Sforza and Lugaresi, 1995; Chervin and Aldrich, 1998), current methods by which arousals are measured may be inadequate in assessing the true extent of sleep

fragmentation in these patients, as studies have demonstrated an incomplete accounting of variance in MSLT results (Poceta et al., 1992; Roehrs et al., 1989). Indeed, it has been shown that the normal dynamic of SWA decline across the night is disrupted by arousals in these patients; specifically, there is a lower amount of SWA across the night in patients with SRBD, particularly in the first two NREM episodes. Therefore, it is not the total amount of SWA that is best correlated with the daytime vigilance, but rather the peak of SWA noted in the first part of the night. However, it should be noted that the first NREM episode is also that part of sleep which is most affected by age, sleep loss or sleep extension (Heinzer et al., 2001).

10.5.1.1.1.2. The cyclic alternating pattern (CAP) rate and EDS. Another method by which the fragmentation of sleep caused by SRBD can be described is through the examination of the so-called 'cyclic alternating pattern', or CAP of sleep EEG activity (Rosa et al., 1999; Navona et al., 2002). CAP is organized in sequences embedded within and across the conventional sleep stages, and is a translation of an oscillatory process between a condition of greater arousal (A phase) and lesser arousal (B phase) which recurs with a periodicity of 20–40 seconds (Terzano et al., 1990; Parrino et al., 2000). CAP is therefore a marker of unstable sleep, whereas the absence of CAP (non-CAP) reflects a condition of consolidated sleep. Both experimental and clinical studies have demonstrated a significant inverse correlation between an increase in CAP rate (the ratio of CAP time to non-REM sleep time) and the subjective estimates of sleep quality (Terzano et al., 1990) and sleepiness (Parrino et al., 2000). Regardless of any concomitant disorder or other changes in the PSG measures, the higher the CAP rate, the poorer the quality of sleep. Accordingly, any sleep-improving treatment reduces the amount of CAP and potentiates sleep stability or an increase of non-CAP (Terzano et al., 2003).

10.5.1.1.1.3. The awake EEG and residual neurocognitive dysfunction. The examination of the wake EEG has also been helpful in characterizing possible correlates of cognitive impairment including deficits in memory, attention and executive function (planning, programming, regulation and verification of goal-directed behaviors), which are known to be dependent upon the integrity of the frontal lobe. Specifically, it has been hypothesized that the cognitive function

alterations in OSAS may result from apnea-related hypoxemic frontal lobe dysfunction apart from, or in addition to, compromised sleep function and continuity (Morrison et al., 2001). During wakefulness, apneic patients show EEG slowing, manifested by a higher ratio of delta + theta frequencies (DT) to alpha + beta frequencies (AB) spectral power for all regions pooled. Specifically, EEG measurements of awake, untreated OSAS patients are characterized by a higher slow-wave activity to fast activity ratio (DT/AB), which is mostly due to higher delta activity in the frontal regions (Morrison et al., 2001).

10.5.1.1.2. Sleep disruption and non-visible arousals

10.5.1.1.2.1. Detection of arousals. As mentioned, cortical arousals induced by apneas and hypopneas during sleep are believed to play an important role in the sleep fragmentation, daytime sleepiness, impaired cognitive function, and reduced concentration capacity in patients with OSAS. However, previous studies have found incomplete correlations between the severity of clinical symptoms or objective sleepiness and polygraphic findings (such as apneas, hypopneas and cortical arousals) (Dingli et al., 2002). Furthermore, a substantial subset of apneas and hypopneas are not terminated by visible or conventionally established cortical arousals (ASDA, 1992). However, using quantitative EEG, an increase in the delta band amplitude with or without the occurrence of arousal-related fast EEG activity, starting before apnea event termination, has frequently been documented in NREM sleep. The occurrence of these brief bursts of hyper-synchronous delta activity supports the hypothesis that bursts of SWA occurring toward the end of apneas are a manifestation of a perturbation of cortical sleep activity and may therefore reflect activity similar to that of arousals (Dingli et al., 2002). This has been corroborated in several studies, examining the EEG of sleep apneics (Berry et al., 1998) as well as those with UARS (Black et al., 2000). Others (Dingli et al., 2002) have noted the additional finding of a simultaneous characteristic decrease in theta power – although this is not a consistent finding (Black et al., 2000). In addition, K-complexes, which are excluded from the conventional rules for scoring arousals, are often seen preceding conventional arousals and are also believed to represent possible ‘arousal equivalents’ (Parrino et al., 2000).

Given these findings, quantitative EEG techniques, including power spectral analysis, have greatly improved the detection of arousals or arousal-like

activity, in that most apneas and hypopneas which are not terminated by visually scored arousals are in fact, associated with significant spectral power changes. Specifically, there is an increase in delta power toward the end of such events with or without the occurrence of an increase in faster activity at event termination (Dingli et al., 2002).

10.5.1.1.2.2. CAP and respiratory events. In addition to changes in spectral power occurring toward the end of respiratory events in SRBD, alterations in CAP have been identified. An arousal-related phenomenon which correlates with the recurrence of respiratory events and with post-apneic breathing resumption, the majority of respiratory events in patients with SRBD occur in close temporal association with the B phase of CAP, whereas the recovery of airflow after such events is characterized by a concomitant A phase. Thus patients with SRBD have increased CAP rates (Parrino et al., 2000).

10.5.1.2. Response to nasal continuous positive airway pressure (NCPAP) therapy

The beneficial effects of nasal continuous positive airway pressure (CPAP) therapy on SRBD are well known. However, despite the significant changes in sleep architecture that occur before and after CPAP use in SRBD, several studies have failed to show a strong relationship between normalization of conventional sleep measures and daytime functioning in patients (Parrino et al., 2000). In contrast, abnormalities described though qEEG techniques have been found to trend toward normal, if not normalize, after treatment with CPAP.

10.5.1.2.1. Slow-wave activity to fast activity ratio (DT/AB) in the wake EEG. The DT/AB EEG ratio (ratio of delta + theta frequencies (DT) to alpha + beta frequencies (AB)) decreases significantly in the waking EEG of SRBD patients after treatment with CPAP. Also, absolute delta and theta activity during wake significantly decreases in all regions, to normal values (Morrison et al., 2001). Thus, CPAP treatment is not only effective in reversing respiratory impairments during the night but also in normalizing EEG patterns during wakefulness.

However, neurocognitive deficits may persist after treatment with CPAP, even with normalization of EEG activity, suggesting that the EEG slowing described prior to treatment may not reflect all changes in neurocognitive function associated with this sleep

disorder. For example, hypoxemic damage related to SRBD may not only affect cortical, but also subcortical regions.

10.5.1.2.2. CAP. Nasal CPAP therapy dramatically reduces the number of arousals in patients with SRBD, and is associated with recovery of normal durations of CAP cycle components (A and B phases) (Parrino et al., 2000). Thus, the disappearance of CAP (i.e. non-CAP) with CPAP treatment suggests a normalization of both sleep structure and autonomic activity as a result of the reduction or elimination of recurring respiratory events (Parrino et al., 2000).

10.5.1.3. Differentiating between OSAS and UARS

Finally, quantitative EEG techniques have been used to differentiate UARS from OSAS. While it is believed by some that these disorders are two differing manifestations of the same pathophysiological process, others (Guilleminault et al., 2001) feel that they are distinct entities with different underlying pathophysiologies. Specifically, UARS subjects do not show the usual decline in delta power seen normally from the beginning to the end of the night, and thus have higher delta power at the end of the night when compared to controls. This absence of a clear decline is similar to what is seen in normal subjects submitted to repetitive auditory stimulation leading to sleep fragmentation (Philip et al., 1994). UARS subjects also exhibit a significantly higher amount of alpha power (Guilleminault et al., 2001). In contrast, those with OSAS, have lower alpha and delta power when compared to those with UARS, and normal subjects have more delta power and less alpha power than both groups of patients with sleep-disordered breathing (Mene Gutierrez et al., 2001).

Therefore, it has been suggested that individuals with OSA and UARS may exhibit different cortical responses to similar abnormal respiratory challenges during sleep. Specifically, UARS subjects may have a much lower 'arousal threshold' to such challenges, yet maintain an exquisitely intact mechanoreceptor response resulting in higher amounts of alpha frequency activity. In contrast, OSAS patients may not be as responsive, and therefore exhibit lower amounts of alpha power (Guilleminault et al., 2001).

10.5.2. Idiopathic hypersomnia and narcolepsy

While qEEG has helped to characterize EEG abnormalities in SRBD, such quantitative techniques have also been instrumental in the investigation of disorders

related to central causes of pathologic sleepiness, such as idiopathic hypersomnia and narcolepsy.

10.5.2.1. Causes of sleepiness

In normal individuals, underlying physiologic sleepiness depends on two main factors: prior sleep (duration and quality) and the phase of the circadian rhythm (Wichniak et al., 2003). More specifically, the level of daytime sleepiness is directly related to the amount and continuity of preceding nocturnal sleep; partial or total sleep deprivation leads to an increase in daytime sleepiness the following day, whereas increasing sleep time leads to an increase in alertness. However, brief arousals resulting in fragmented and discontinuous sleep normally may lead to an increase in daytime sleepiness even without concomitant reduction in total sleep time.

In disorders of central hypersomnia, increased daytime sleepiness may occur in the absence of a shortened total sleep time or sleep fragmentation, which is characteristic of idiopathic hypersomnia (IH). Although narcoleptics may experience significant sleep fragmentation, their daytime sleepiness appears to be at least somewhat independent of nocturnal sleep quantity or quality.

10.5.2.1.1. Idiopathic hypersomnia (IH). Individuals with IH often sleep longer than narcoleptics and normal individuals. Using qEEG techniques, it has been demonstrated (Sforza et al., 2000) that individuals with IH have less SWA in NREM sleep, especially during the first two sleep cycles; therefore, it has been postulated that the excessive sleepiness experienced by these individuals may be related to a deficit in SWA.

10.5.2.1.2. Narcolepsy. In contrast, narcoleptics may exhibit more SWA. Unlike those with IH, polysomnography usually reveals frequent sleep onset REM (soREM) periods, decreased sleep efficiency, increased sleep fragmentation and awakenings during the night and increased amounts of stage 1 sleep (Mukai et al., 2003). While both delta and beta power have been found to be elevated during REM sleep in narcoleptics (Tafti et al., 1992a), delta and sigma power as well as higher alpha band frequencies have also been found to be elevated during NREM sleep in these individuals when compared to controls (Tafti et al., 1992a; Mukai et al., 2003). Although this finding has not been replicated in all studies (Guilleminault et al., 1998), it has been suggested that the observed elevated spindle activity (sigma band) may be in response to an increased demand for sleep main-

tenance, implying the presence of an underlying inadequacy of sleep homeostatic mechanisms in these individuals (Mukai et al., 2003). The finding of an even temporal distribution of SWS during nocturnal sleep in narcoleptics (Broughton et al., 1988; Nobili et al., 2001) appears to support this theory.

Subsequent studies using two approaches have helped to clarify this issue; the first (Tafti et al., 1992a,b) involved examining the response of SWA to increased wakefulness (or sleep deprivation), while the second study (Nobili et al., 1995) focused on the response to decreased wakefulness (bed-rest conditions) and the effects of prior sleep duration on subsequent nocturnal sleep (Besset et al., 1994). While an exaggerated homeostatic response to 16 and 24 hours of sleep deprivation in eight narcoleptics was suggested by an increased delta band spectral frequency using the former approach (Tafti et al., 1992a,b), the same exponential decaying trend in SWA was observed in narcoleptics as in controls. Using the second approach (Nobili et al., 1995), nine narcoleptics and nine control subjects were subjected to 16 hours of sleep deprivation, followed by 32 hours of bed-rest protocol in a sensory-attenuated room. Narcoleptics did not differ in total sleep time over the entire 32 hours compared to controls, but did spend more time sleeping during the day. In addition, while both groups exhibited a similar exponential decay in SWA during the first night (N1), only the controls exhibited a similar SWA trend during the second night of study (N2). Additionally, in contrast to the circadian–circasemidian distribution of SWA seen in controls, narcoleptics showed no circadian pattern and only a modest ultradian distribution of SWA with a periodicity of 4 hours during the day and N2. These findings suggest that the coupling between processes C and S is different in narcoleptics; specifically, the effects of ultradian drives to sleep may be stronger due to an active (stronger drive to sleep) or passive mechanism (weaker wake-promoting mechanism) (Nobili et al., 1995). Alternatively, narcoleptics are also known to suffer a dysfunctional hypothalamic orexin/hypocretin system (Nishino, 2003), and this defect may result in a disconnect from suprachiasmatic nuclei (the CNS circadian rhythm generator) output and sleep–wake-promoting centers yielding non-circadian sleep–wake activity.

10.5.2.2. *Sleep onset in narcolepsy*

Narcoleptics often enter directly into REM sleep at sleep onset (soREM), with very short sleep-onset latencies. Yet, contrary to what would be expected, no increase in pressure for REM sleep compared to

NREM sleep has been identified and mean delta, theta, alpha, sigma and beta power has not been found to differ significantly between the sleep onset periods (SOP) of narcoleptic REM and NREM naps (Alloway et al., 1999). However, there is evidence that spectral differences exist within the sleep onset period of narcoleptic naps containing REM sleep and normal (non-narcoleptic) naps containing NREM sleep. While the EEG of REM sleep and stage 1 sleep appears nearly indistinguishable when assessed using visually based sleep-scoring techniques, EEG spectral analysis has revealed increased delta and theta power, and decreased alpha and sigma power throughout the SOP of narcoleptic REM naps compared to normal stage 1 naps. In addition, delta power is higher during the SOP of narcoleptic REM naps compared to normal stage 2 naps. These findings suggest that there is a physiologic difference within the microstructure of the narcoleptic sleep onset period during REM naps in comparison to normal stage 1 and 2 naps.

10.5.3. *Periodic limb movement disorder (PLMD)*

Periodic limb movements (PLMs) are described as repetitive, stereotyped leg movements, which occur predominantly during NREM sleep. Surface EMG of the anterior tibialis reveals bursts of muscle activity of 0.5–5 s duration with an inter-burst interval of 5–120 s (Sforza et al., 1999). When associated with daytime symptoms of sleepiness or fatigue in the absence of other causes of such movements, the diagnosis of periodic limb movement disorder (PLMD) can be made, which has been reported to occur in 13% of patients complaining of insomnia and 6% of those being evaluated for excessive sleepiness (Mendelson, 1996).

10.5.3.1. *PLMS and their relationship to arousals*

PLMs are often accompanied by EEG signs of microarousals (MA), which have in the past been assumed to be responsible for the non-restorative sleep and daytime fatigue sometimes reported by these patients (Sforza et al., 1999). However, recent studies (Coleman et al., 1982; Rees et al., 1995; Mendelson, 1996) have suggested that this may not be the only cause for patient symptoms, in that the PLM index (number of PLMs per hour of sleep) has not consistently correlated with excessive daytime sleepiness or sleep latency on MSLT. It is possible that these findings are due to the lack of sensitivity of the current ASDA criteria used to quantify MA and associated sleep disruption (Sforza et al., 1999). Indeed, as in SRBD, quantitative EEG analysis has revealed

significant changes in EEG spectral activity and heart rate during a majority of PLMs without MA, despite the lack of visually identifiable EEG changes (Black, 1998); this is characterized by an increase in the absolute delta and theta activity, but not in the other frequency bands (Halasz et al., 1985).

However, it has been alternatively postulated that PLMs do not in fact lead to arousals, but rather, that PLMs and arousals are manifestations of a primary gating mechanism. In patients with PLMs, the time-correlation of these EEG arousals with leg movements varies from individual to individual; they may precede or follow leg movements, or occur simultaneously. Specifically, it has been suggested that the approximately 20–40 s periodicity of PLMs is regulated by endogenous cerebral and brainstem-activated mechanisms (Karadaniz et al., 2000), or CAP, very similar to the relationship with respiratory events observed in SRBD. In one study (Parrino et al., 1996), 92% of leg movements which occurred during NREM sleep occurred in the setting of CAP, with most of the leg movements (96%) being associated with the A phase. It is postulated that periodic activation may lead to movements with or without associated transient arousal. The periodic generator may trigger EEG arousals and these in turn facilitate the occurrence of leg movements, or the leg movements and the arousals may be independent phenomena.

10.5.4. Sleepwalking

Sleepwalking is a parasomnia (Espa et al., 2000), defined as a dissociative process involving both motor and cortical activity, but most specifically described as a disorder of partial arousal. Conventional polysomnographic studies have shown that sleepwalking mainly occurs during SWS, either in the first or subsequent sleep cycles, with hyper-synchronous high-voltage slow-wave (1–3 Hz) activity lasting 10–30 s immediately preceding the muscular activation characteristic of this behavior. It should be noted that both an increased pressure for delta sleep as well as the presence of arousals or intrusions into SWS are commonly observed in sleepwalkers. Quantitative EEG methods have helped to further characterize this condition.

10.5.4.1. SWA and arousals

New insights into SWS have been made possible by computer-based EEG analyses using either PAA (Church et al., 1975) or FFT (Borbely, 1982) methodologies. One of the most relevant contributions of

these methods is the concept of SWS intensity (SWI), which can be quantified by the level of slow-wave activity (SWA, power density of the EEG delta band between approximately 0.5–4.0 Hz). Accordingly, it has been postulated that a very strong SWI reflected by both an increased level of SWA and an abnormal distribution and/or reduction of sleep spindles during the night could reflect the processes underlying the difficulty parasomnic subjects experience in waking from SWS, which may play a role in the precipitation of parasomnia episodes. In one study (Espa et al., 2000), the power density during NREM sleep, REM sleep and the spindle activity in adults with sleepwalking were compared to control subjects, and the time course of delta power density and spindle activity were analyzed. All episodes of parasomnias were found to occur exclusively during SWS, and the majority of them occurred during the first NREM sleep episode. Sleep fragmentation was the most important difference observed in the sleep architecture of parasomniacs when compared to control subjects, and occurred mainly in SWS. Furthermore, SWS interruptions occurred approximately every 13 minutes in parasomniacs, while they occurred approximately every 25 minutes in controls, and the analysis of sleep microstructure by CAP analysis (Zuconni et al., 1995) showed an increase in sleep instability and arousal oscillations, particularly during delta sleep. Fifty percent of arousal reactions during SWS and 100% of the episodes of parasomnias were associated with hypersynchronous high-voltage delta waves which were not seen in controls (Espa et al., 2000). Therefore, it has been suggested that these EEG patterns are characteristic of adult sleepwalkers. Furthermore, sleepwalkers exhibit a more evenly distributed SWA throughout the night, with a less pronounced SWA decay. This abnormal distribution is likely due to recurrent awakenings from SWS interruptions, leading to continued SWA reappearance later in the sleep period (Espa et al., 2000).

10.5.5. Insomnia and hyperarousal

Insomnia is a complaint of difficulty initiating or maintaining sleep or of non-restorative sleep, associated with complaints of daytime functional decrements. When these symptoms persist for more than a month, the insomnia is termed chronic. Delayed sleep initiation, disrupted sleep, early morning awakening, and inadequate sleep quality are among the main sleep complaints in insomnia. Although insomnia fre-

quently occurs in conjunction with psychiatric, medical or substance-abuse conditions, insomnia can occur independently and is termed 'primary' insomnia. Chronic insomniacs typically display characteristics that are indicative of a heightened somatic arousal response such as faster heart rates, higher electromyographic activity levels and higher body temperature (Lamarche and Ogilvie, 1997; Perlis et al., 2001). This hyperarousal is exhibited not only at night before sleep onset but also during the day, and in studies assessing daytime sleepiness, primary insomniacs do not manifest greater sleepiness than controls and, in fact often demonstrate lower sleep propensity during the day (Terzano et al., 2003).

Several PSG studies have revealed differences in many chronic insomniacs consistent with their complaints of disrupted or inadequate sleep, but others have also shown no difference between insomniacs and those without complaints of difficult sleep initiation or maintenance. This has been referred to as a split between objective (PSG) and subjective (complaints) indicators of sleep disturbance, or sleep 'misperception' (Krystal et al., 2002), and is reflected in the *International Classification of Sleep Disorders (ICSD)* (ASDA, 1997); three subtypes of chronic intrinsic insomnia are distinguished, based in part on PSG findings: idiopathic, psychophysiological (associated with PSG abnormalities), and sleep-state misperception (associated with a normal PSG) (Krystal et al., 2002). In those with sleep state misperception, another type of arousal – CNS arousal (Perlis et al., 2001) may explain their subjective symptoms of sleep disturbance. The use of computer-based techniques to examine electrophysiological indices of arousals (Freedman, 1986) has been particularly useful in this regard. It has been demonstrated that during wakefulness, insomniacs have significantly more beta activity, more 1 Hz activity, and less 9 Hz activity (in alpha range) than normals. During the SOP, stage 1 and rapid eye movement (REM) sleep, insomniacs also have significantly more beta activity than normals, and it has therefore been suggested that CNS arousals, as manifested by EEG beta activity, may be higher in insomniacs than in normals (Merica and Gaillard, 1992; Lamarche and Ogilvie, 1997; Perlis et al., 2001). This has been corroborated in a recent study (Krystal et al., 2002) using FFT, which showed that subjective insomniacs had a lower relative delta power and significantly greater relative sigma and beta power when compared to normal subjects. These differences may therefore serve as objective correlates to subjective sleep com-

plaints in those individuals with otherwise normal PSG studies (Krystal et al., 2002).

Similarly, it has been suggested that insomniacs with sleep maintenance issues may manifest a chronic slow-wave sleep (SWS) deficiency (Besset et al., 1998). Through assessment of SWA, it has been hypothesized that in such patients, an alteration in the homeostatic process, due to hyperactivity of arousal systems of the CNS, may be responsible for an insufficient sleep pressure and therefore, an inability to maintain sleep for an extended period of time (Besset et al., 1998). Finally, primary insomnia has also been associated with another measure of sleep instability – CAP, in which alterations in CAP variables has been consistent with subjective reports of poor sleep quality (Terzano et al., 2003).

10.6. Conclusions

The quantitative analysis of both the sleep and waking EEG has unquestionably advanced the field of sleep medicine. While the most popular technique applied in this field has been FFT, the development of more complex non-linear quantitative techniques such as dimensional complexity analysis as well as topographic EEG brain mapping offers new and exciting avenues for further research. Fundamental techniques such as spectral analysis have identified fundamental concepts such as SWA and SWI, which have made possible the characterization of sleep regulation and homeostasis. As such, researchers have been able to look beyond the oversimplified and rather arbitrary concept of sleep staging based on visual scoring, upon which much of the early research in sleep medicine was based. Indeed, it has been the identification and subsequent characterization of the microstructural aspects of the sleep state, which has led to a more complete understanding of cortical arousals, related microarousals, 'arousal equivalents', and associated sleep spindle activity. Based on these fundamental concepts, the pathophysiologic basis and clinical manifestations of several sleep disorders are now better understood.

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CHAPTER 11

Evoked potentials during non-REM sleep: utility and functional significance

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11.1. Introduction

Very early in the history of sleep research, it became apparent that evoked EEG responses could be elicited during non-REM sleep. The first evoked response observed was the K-complex. This was seen in response to a tone played during an afternoon nap when the subject was in what we would now call stage 2 sleep (Loomis et al., 1938). This was indeed one of the earliest reports of evoked EEG activity in any arousal state, appearing just 9 years after Berger's first report of scalp recorded EEG in the human (Berger, 1929). The K-complex was an obvious candidate to be the first evoked response as it is extremely large relative to the size of the background EEG and thus has an intrinsically good 'signal-to-noise' ratio. Over the succeeding decades, better amplifiers, better filters, signal averaging, digital recording and the use of multi-electrode arrays have all enabled the investigation of additional evoked responses in non-REM and REM sleep states, as a measure of CNS function during sleep. Ironically, however, despite these technological advances, the K-complex is still the most studied sleep-related evoked EEG phenomenon making the statement in the original Loomis et al. paper that 'the interpretation of these K waves is difficult and demands further investigation' (p. 429) unusually prescient.

Reasons to evaluate event-related potentials (ERPs) during sleep are many and varied. A substantial body of work has focused on the sleep onset

period, with the goal of characterizing the loss of wakeful consciousness. Yet other studies have used ERPs during sleep as a way to evaluate the impact of aging or of different pathologies on the sleeping brain. Regardless of the motivation, the use of averaged ERP methods to evaluate sleep EEG is a departure from the standard observational mode of sleep research and provides the opportunity to 'probe' the sleeping nervous system and evaluate responses under a high level of experimental control.

The vast majority of studies evaluating evoked responses during sleep have used auditory stimuli. However, other studies have used stimuli of different modalities including externally applied increases in respiratory loads, in an attempt to evaluate the mechanisms involved in the CNS response to physiological and pathological increases in upper airway resistance during sleep. This review will discuss how both auditory- and respiratory-evoked potentials change with non-REM sleep, with a particular focus on two components: the N350 and N550. For recent reviews of the relatively small number of studies evaluating REM sleep see Cote (2002) and Bastuji et al. (2002). For reviews of other sleep-related components in non-REM sleep see Bastien et al. (2002) and Crowley and Colrain (2004).

11.1.1. Auditory-evoked potentials (AEP)

During wakefulness a characteristic set of evoked potential components is elicited by auditory stimuli. The 'early' latency components occur within the first few milliseconds following the stimulus, and reflect activity within brain stem relay nuclei (Jewett et al., 1970). These are unaffected by sleep (Campbell and Bartoli, 1986; Bastuji et al., 1988), presumably indicating that initial signal transduction and transfer to the CNS occur in all arousal states. 'Middle' latency

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responses occur between 10–50 ms and reflect activity in higher points in the auditory pathway and initial cortical responses. The effect of sleep on these components is somewhat equivocal, with some studies failing to observe an effect and others demonstrating a reduction in the amplitude of various components, particularly if stimuli are presented rapidly (Linden et al., 1985; Erwin and Buchwald, 1986; Jones and Baxter, 1988). However, it should be noted that middle latency components are very difficult to measure at the scalp and few sleep studies have used appropriate recording procedures to carefully evaluate them.

‘Long’ latency-evoked responses follow the middle latency components and can be recorded up to several hundred ms post stimulus. These are thought to reflect different aspects of attentional and cognitive processing of the stimulus and depend on the specific type of stimulus and the nature of the processing involved. Of particular interest to sleep researchers are the N1 component seen at approximately 100 ms, and thought to index attention, and the P300 seen at approximately 300 ms post stimulus and thought to index aspects of decision making, stimulus recognition and memory, in short, ‘higher cognitive processes’. The long-latency components seen in wakefulness are much affected by sleep, and a number of evoked potentials unique to sleep begin to emerge in the sleep onset period and peak from 300–900 ms following stimulus onset.

11.1.2. Respiratory-related evoked potentials (RREP)

During wakefulness, RREPs are formed of early and late components (Davenport et al., 1986). The most prominent early components are P1 and Nf, which are positive and negative components respectively, typically occurring between 40–80 ms after the start of a pressure change induced by an occlusion or load stimulus (Davenport et al., 1996). They are thus analogous to the ‘middle latency’ auditory-evoked potential components, and appear to be maintained during sleep (Webster and Colrain, 1998).

In addition to the early components, the RREP has consistently been shown to also have an N1 and a P300 during wakefulness (Webster and Colrain, 1998) that are thought to relate to attention and higher cognitive processing of airway occlusions. As with AEPs, these are replaced by sleep-specific components that start to appear early in the sleep onset period.

11.2. The sleep onset transition period

The sleep onset period has been studied to determine the role of wakeful consciousness in the production of the long latency ‘cognitive’ evoked potential components. It is a period that is subject to substantial flux in terms of EEG states and the experienced level of consciousness. Rather than a smooth movement from active wakefulness/consciousness to stable sleep/unconsciousness, there are changes from wake EEG frequencies to sleep EEG frequencies that show rapid reversals back to the wake levels. The reaction time to stimuli presented during the sleep onset period also varies substantially, and appears to relate to both EEG frequencies and evoked potentials (Ogilvie et al., 1991; Harsh et al., 1994).

ERPs averaged over all of stage 1 sleep are typically reported as being intermediate in appearance between those of wakefulness and stage 2 sleep. This has been shown for auditory (Ogilvie et al., 1991; Harsh et al., 1994; Niiyama et al., 1994; de Lugt et al., 1996) and respiratory-related evoked potentials (Webster and Colrain, 1998). Specifically, the N1 has a smaller amplitude and the P300 has a smaller amplitude and longer latency relative to wakefulness (Cote et al., 2002).

However, given the heterogeneous nature of stage 1 sleep, it is more enlightening to look at responses to stimuli that are sub-classified as being presented in states more or less similar to wakefulness or sleep, based on either behavioral or EEG criteria. For example, Harsh et al. (1994) and Ogilvie et al. (1991) both reported that the N1 component diminished with increased reaction time and was virtually absent when subjects did not respond to stimuli.

Niiyama et al. (1994) subdivided stage 1 into an early stage 1a and a later stage 1b. Subjects detected 93% of targets in stage 1a and only 1.5% of targets in stage 1b. From a behavioral perspective, the authors’ stage 1b appears to be much closer to definitive stage 2 sleep than traditional stage 1. P300 was apparent in stage 1a and its scalp distribution was similar to that in wakefulness, but its amplitude was much reduced in stage 1b.

Harsh et al. (1994) used an auditory oddball task in which targets were presented on 20% of trials. Stage 1A contained between 50 and 80% alpha while stage 1B contained less than 50% alpha (i.e., the usual standard criterion for the definition of stage 1). Subjects either attended to the stimuli and were asked to finger lift upon detection of the target or in a separate condition, to ignore the stimuli. The percentage of

detected targets diminished from 83% in stage W, to 65% in stage 1A, and finally to 30% in stage 1B. A large parietal maximum P300 was apparent during wakefulness and to detected targets in stage 1A. In stage 1B, P300 was much later and its scalp distribution was markedly posterior.

Gora et al. (1999) analyzed RREP responses in stage 1 sleep based on whether the dominant EEG frequency preceding the stimulus was in the alpha or theta bands. They reported that the N1 decreased in amplitude in theta trials relative to alpha trials, but the alpha N1 was already significantly diminished relative to wakefulness. The stage 2 N1 displayed a further significant decrease relative to that seen in stage 1 theta. P300 displayed a 100 ms increase in latency in theta trials compared with alpha trials, and a shift to a more occipital topographic focus.

Colrain et al. (2000a) also used the stage 1-alpha and stage 1-theta sub-division to examine changes in AEPs at sleep onset. An oddball paradigm was used with a 1000-Hz standard, a 2000-Hz target and a 500-Hz non-target 'deviant' being presented on 60%, 20% and 20% of trials. N1 was near baseline when the subject entered stage 2 of sleep. The stage 1-alpha and stage 1-theta N1 did not, however, vary in amplitude from that recorded in the waking state. This could be because as de Lugt et al. (1996) noted, stimuli that are presented slowly are particularly obtrusive and difficult to ignore. A large P300 was recorded in wakefulness and stage 1-alpha and their scalp distributions did not vary. A later positive wave occurred later in stage 1-theta (450 ms) and its topographical distribution was different to that seen for the P300 during wakefulness and stage 1-alpha.

There is thus a consensus over many studies that sleep onset is associated with diminished N1 and P300 components (see Cote (2002) for a detailed review of sleep studies evaluating P300), reflecting a rapid reduction in the capacity to attend to the external environment and engage in higher cognitive processing of stimuli. One caveat needs to be mentioned in this context, however. There remains the possibility that a P300-like component can be elicited in stage 2 sleep to the presentation of a subject's own name (Perrin et al., 1999; Pratt et al., 1999).

11.3. The evoked Vertex Sharp Wave and the N350 component

One of the most striking effects of sleep onset is the appearance of a negative wave peaking between

250–400 ms. This N350 wave is not observed in the waking state. Its appearance appears to begin during the transition from a drowsy state to that of sleep. Harsh et al. (1994) reported that it generally first appeared during their stage 1B of sleep although there was wide inter-subject variability. It more consistently appeared when subjects were no longer able to overtly respond to an external stimulus. Ogilvie et al. (1991) also observed that this late negativity was associated with a behavioral failure to respond to external stimuli. Colrain et al. (2000a) and Gora et al. (1999) indicated that the N350 in AEPs and RREPs is difficult to observe in stage 1-alpha but is readily apparent in stage 1-theta. A highly consistent finding among the various laboratories is therefore that the N350 begins to emerge just prior to definitive stage 2 sleep (unless stimuli are presented with a rapid inter stimulus interval (de Lugt et al., 1996)). It is thus one of the most reliable markers that sleep is imminent.

Many authors have suggested that the N350 may be related to the vertex sharp wave (Harsh et al., 1994; Sekine et al., 1998; Colrain et al., 2000b). As its name implies, the vertex sharp wave is maximum over central areas of the scalp. Its amplitude is so large that it can be seen in the raw EEG during the sleep onset period (Yasoshima et al., 1984).

Colrain et al. (2000b) were the first to indicate that vertex sharp waves could be systematically elicited by stimuli. In two experiments they demonstrated that vertex sharp wave responses were seen in response to 10% of rare auditory stimuli, 9% of frequent auditory stimuli and 5% of inspiratory occlusion stimuli. Gora et al. (2001) were also able to show evoked vertex sharp waves to 4.4% inspiratory occlusion stimuli. They also identified trials in which both a vertex sharp wave and a K-complex were evoked, reporting that 5.1% of responses fitted this category. The presence of evoked vertex sharp waves in isolation and in combination with K-complexes has been confirmed in several more recent studies (Crowley et al., 2002a; Nicholas et al., 2002a; Nicholas et al., 2002b; Afifi et al., 2003).

The N350 also appears as a component in the averages of K-complexes during stage 2, 3 and 4 of sleep (see Figure 11.1). Colrain et al. (2000b) employed a large 29-channel recording to map the scalp distribution of these N350s. They noted that the N350 occurs to both auditory and respiratory stimuli and to frequently occurring standards and infrequently occurring deviants. They separated and averaged single trials containing only vertex sharp waves, a combina-

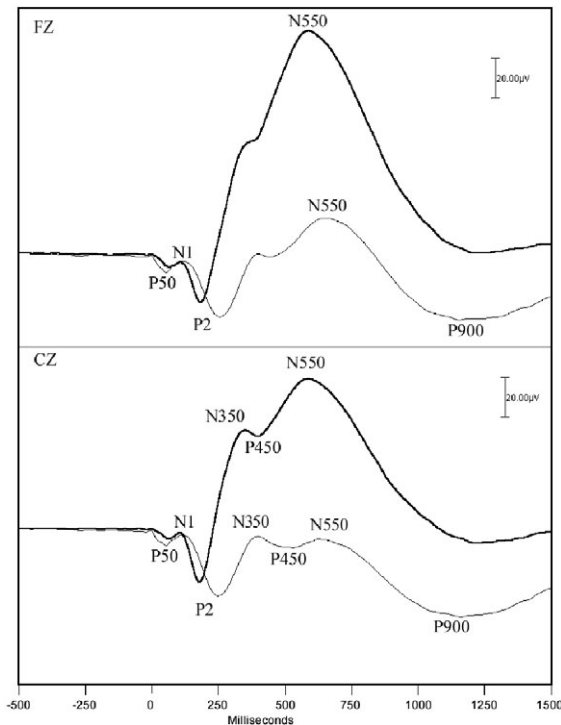


Fig. 11.1. Averaged auditory ERPs from stage 2 non-REM sleep in young (dark lines) and elderly (light lines) healthy subjects, adapted from Crowley et al. (2002a). Data are presented from Fz (upper panel) and Cz (lower panel) electrode sites, and are based on the averages of only those responses containing K-complexes (KC+). The waveforms display small P50 (middle latency) and N1 components, and a prominent P2, that is larger in the elderly. N350 is more prominent at Cz, and N550 more prominent at Fz. Negative is plotted up the Y axis.

tion of vertex sharp waves and a K-complex, or none of these waveforms. When the stimulus elicited only a vertex sharp wave, a large negativity peaking at about 300–350 ms was apparent, with a distinctive vertex maximum scalp distribution. The N350 also occurred when a K-complex was also elicited, and indeed when no obvious phasic responses were observed. These latter N350s were reduced in amplitude but their scalp distribution was not different from that observed when only vertex sharp waves were elicited. The topographic data clearly indicate that despite the rarity of the event, the modality of the stimulus or the nature of the immediate phasic response to the stimulus, the same intracerebral generators are most probably producing the N350. Thus the N350 can be viewed as a sleep specific, multi-modal response.

Bastien and Campbell (1992) hypothesized that the N350 might act as a trigger for the much larger amplitude N550 (related to the K-complex, as indicated below). In their study, stimulus intensity was manipulated. On trials in which the K-complex could not be elicited, N350 amplitude was larger following high-compared to low-amplitude tone pips. The amplitude of the N350 on trials in which the K-complex could be elicited was larger than on trials in which it could not be elicited, a commonly reported finding (Bastien and Campbell, 1994; Harsh et al., 1994; Niiyama et al., 1994, 1995; Sallinen et al., 1994). The nature of the interrelationships between the vertex sharp wave-related N350 and the K-complex-related N550 remains to be fully determined.

11.4. The evoked K-complex and the N550 evoked potential component

The accepted definition for K-complexes is ‘EEG waveforms having a well delineated negative sharp wave which is immediately followed by a positive component. The total duration of the complex should exceed 0.5 s.’ (Rechtschaffen and Kales, 1968). While the definition also states that ‘The K-complex is generally maximal over vertex regions’, a number of studies have now shown it to be largest over frontal EEG sites (Niiyama et al., 1995; Colrain et al., 1999; Cote et al., 1999). Indeed, Paiva and Rosa (1991) reported that 57% of spontaneous K-complexes had a frontal or fronto-central maximum as compared to 30% maximal at Cz.

Davis et al. (1939) observed that the K-complex can be evoked by different stimuli independently of their modality. Roth et al. (1956) also observed that the K-complex could be generalized to different stimuli by delivering acoustic, visual, painful shock and tactile stimuli. Their results showed that the K-complex remained morphologically invariant under the influence of the different stimuli but that it was easier to elicit with an auditory stimulus. Several recent studies have however indicated that the K-complex is also readily elicited by a sudden increase in inspiratory load (Colrain et al., 1999; Gora et al., 1999, 2001, 2002; Afifi et al., 2003).

It is clear from the published literature that K-complexes have an extremely variable morphology (Halasz et al., 1985; Ujjasz and Halasz, 1986, 1988) and in 1991, Paiva and Rosa proposed six different morphological variations of the isolated, spontaneous K-complex. Single K-complexes are, of course,

embedded in the ongoing EEG. The background EEG in stage 2 can exceed $100\mu\text{V}$ and in stage 4 can be even larger. It is quite possible that a portion of the apparent polyphasic activity might be due to summation with background EEG activity. It is for this reason that Bastien and Campbell (1992) proposed the use of averaging to extract the signal (pure K-complex) from the noise of the unrelated random EEG.

Early studies in which responses to all stimuli were averaged produced a waveform dominated by a large negative component at about 550 ms (N550). Bastien and Campbell (1992) were the first to separately average groups of responses that did (KC+) and did not (KC-) involve K-complexes. Importantly, N550 is absent or greatly diminished in KC- averages of responses to both auditory and respiratory stimuli (Colrain et al., 1999; Cote et al., 1999). Bastien and Campbell (1992) argued that the N550 in the KC+ average gives a very good estimate of the properties of the 'pure' K-complex (see Figure 11.1). A by-product of the averaging process is the determination of the proportion of trials in which a K-complex is produced. Thus it is also possible to easily derive a measure of the elicibility of K-complexes. As will be argued below, the amplitude of the N550 component and the proportion of K-complexes produced are probably indexing different aspects of CNS function.

Several papers have used some form of an 'oddball' paradigm to evaluate the extent to which K-complexes are reflective of some form of endogenous or cognitive processing of stimuli during sleep. The amplitude of the N550 component is typically reported as being larger to rare or deviant auditory tones identified as 'target' stimuli during wakefulness (Salisbury et al., 1992; Niiyama et al., 1994; Bastuji et al., 1995; Colrain et al., 1999). However, as indicated by Colrain et al. (2000a) this is most likely reflecting a stimulus probability effect rather than some residual recognition of 'target' status during sleep.

There is now a substantial literature indicating that the AEP N550 measured in either the average of all responses or in the KC+ averages, has a topographic distribution indicating frontal or fronto-central maxima, bilateral symmetry, and a gradual fall off in voltage from the midline frontal/fronto-central area to the posterior and lateral scalp regions (Niiyama et al., 1995; Colrain et al., 1999, 2000a; Cote et al., 1999; Nicholas et al., 2002b). Importantly, the topography is the same for the RREP N550 (Colrain et al., 1999; Gora et al., 2001; Afifi et al., 2003). Thus, like the

N350, the N550 can be viewed as a sleep-specific but modality-independent response.

11.4.1. *Functional significance of the K-complex*

The functional significance of the K-complex (spontaneous or evoked) has long been a source of debate. One of the major disagreements has been whether they represent an arousal response or are markers of a brain state conducive to the production of delta EEG activity, and thus reflect a sleep maintenance process.

The view that K-complexes are reflective of a brain state that is conducive to sleep has recently gained currency (Bastien and Campbell, 1992; Wauquier et al., 1995; Bastien et al., 2000; De Gennaro et al., 2000; Crowley et al., 2002a; Nicholas et al., 2002b, particularly following the anatomical studies conducted by Steriade's group outlined below (Amzica and Steriade, 1997, 1998a, 1998b; Steriade and Amzica, 1998). Several human experimental studies are supportive of this view. For example, K-complex densities are increased prior to transition to slow-wave sleep compared to transitions to REM sleep (Cote and Campbell, 1999; De Gennaro et al., 2000). This increase prior to SWS was modeled by a linear regression and decreased with successive sleep cycles across the night following the established pattern of delta waves and slow-wave activity originally proposed by Borbely (1982, 1998). Spontaneous and evoked K-complexes are significantly more likely during a night of recovery sleep following a night in which sleep was fragmented, when compared to baseline, and paralleled an increase in slow-wave sleep and in delta power (Nicholas et al., 2002b). Finally, both spontaneous (Crowley et al., 2002a) and evoked K-complexes are more rare in the elderly (Crowley et al., 2002b), and the elderly and alcoholics have smaller N550 components (Crowley et al., 2002b; Nicholas et al., 2002a). In both subject populations, the K-complex findings parallel their decreased levels of SWS, and are in opposition to their increased likelihood of arousal from sleep, when compared with healthy controls.

There is, however, evidence specifically supporting the notion of the K-complex being a non-specific arousal response. K-complexes have been found to be associated with brief bursts of sympathetic activity (Hornyak et al., 1991; Okada et al., 1991; Takeuchi et al., 1994; Tank et al., 2003), and changes in body position (Roth et al., 1956) and skin resistance (Roth et al., 1956). The definition of cyclic alternating patterns

(CAPS) uses K-complexes in one of the subtypes, but only if two or more of them occur in rapid succession (Terzano et al., 2002).

The arousal view of the K-complex is often expressed in the context of K-complexes and sleep spindles being antagonistic processes or 'different sides of the same coin', with sleep spindles and K-complexes reflecting inhibitory and excitatory microstates respectively (Halasz, 1993). This view is supported by data from benzodiazepine administration studies indicating increased spindle production but decreased K-complex production (Gaillard and Tissot, 1975; Johnson et al., 1976; Kubicki et al., 1987; Naitoh et al., 1982; Halasz, 1993). Such a view would predict that the presence of sleep spindles coincidental with stimuli would decrease the likelihood of a K-complex being evoked by that stimulus. In a recent study, we sought to test this hypothesis by comparing responses from stimuli presented during a spindle (SP+) to those presented in the absence of a spindle (SP-). No differences were apparent in either the proportion of stimuli producing a K-complex or in the amplitude of the KC+ N550 component (Crowley and Colrain, 2003). Not only do the data fail to support the hypothesis that sleep spindles are antagonistic to the production of K-complexes, they indicate that the two processes are independent, with sleep spindles produced within the thalamus and K-complexes being a cortical phenomenon possibly generated via an extra-thalamic or non-specific thalamic pathway. This view is supported by the scalp topography of the evoked K-complex being the same for auditory and respiratory stimuli, despite the thalamo-cortical relay projecting to very different areas of cortex (Colrain et al., 1999). The fact that K-complexes in the human are generated within the cortex rather than the thalamus has recently been confirmed by Wennberg and Lozano (2003), who show polarity inversion in simultaneous recordings of K-complexes at the scalp and deep thalamic electrodes. These findings thus argue for a separate pathway being used for K-complex generation.

11.4.2. A model for K-complex generation

To date, our best understanding of the mechanisms underlying the production of the K-complex comes from the elegant work of Steriade's group. Amzica and Steriade have argued that the K-complex is rhythmic at the pace of the cortically generated slow oscillation. This novel slow oscillation (<1 Hz) was first described

in intracellular recordings from cortical neurons in anesthetized animals (Steriade et al., 1993b) and was subsequently found during natural slow-wave sleep in cats (Steriade et al., 1996) and naturally sleeping humans (Achermann and Borbely, 1997; Amzica and Steriade, 1997). This slow oscillation has been characterized by membrane potential alternations between depolarized and hyperpolarized states in simultaneous recordings of cortical, thalamic reticular and thalamo-cortical neurons. The cortical nature of the slow oscillation was demonstrated by its survival in athalamic preparations (Steriade et al., 1993a), its absence in the thalamus of decorticated cats (Timofeev and Steriade, 1996), and the disruption of its long-range synchronization after disconnection on intracortical synaptic linkages (Amzica and Steriade, 1995).

Amzica and Steriade (1997, 1998a) have hypothesized that each depolarizing-hyperpolarizing cycle of the slow oscillation corresponds to a spontaneous K-complex in the cortical EEG. More specifically, in cats, the intracellular depolarization of cortical neurons corresponds to the large-amplitude negative peak of the K-complex and that the intracellular hyperpolarization of cortical neurons corresponds to the slow-wave shape of the positive peak of the K-complex. In other words, spontaneous K-complexes are the expression of the spontaneously occurring, cortically generated slow oscillation in the 0.2–0.4 Hz range that occurs in cortical cells.

Delta EEG reflects EEG synchronization produced at least in part by thalamocortical cells operating in a burst-firing pattern following hyperpolarization (Steriade et al., 1991) or possibly by cortical cells operating in this manner independent of the thalamus (Steriade et al., 1993b). The slower frequency of delta as compared to spindles is the result of a greater level of hyperpolarization.

As indicated above, the independence of spindle and K-complex generation (Crowley and Colrain, 2003) and the similarity in the scalp topography of the AEP and RREP N550 (Colrain et al., 1999) both provide evidence that K-complex production does not involve the sensory relay thalamo-cortical pathway. Another pathway must therefore be subserving the production of evoked K-complexes.

One possible pathway may involve the cholinergic basal forebrain, which serves as a ventral extrathalamic relay between the reticular formation and the cortex (Moruzzi and Magoun, 1949; Shute and Lewis, 1967; Jones, 1991, 1993). The cholinergic basal forebrain may play an important role in the regulation of

the sleep–wake cycle, exerting its afferents via a dual mechanism (Buzsaki et al., 1988). First, during wakefulness, the cholinergic input from the basal forebrain to the reticular nucleus of the thalamus inhibits the rhythmic oscillations of the ‘pacemaker’ neurons of this thalamic nucleus. Thus, increased activity of the basal forebrain, particularly the nucleus basalis of Meynert (NB), ensures cortical activation by direct release of acetylcholine in the cortex and by dampening the oscillatory influences of the thalamus. During sleep when the reticular nucleus is released from the inhibitory effects of the cholinergic basal forebrain, the synchronized rhythmic discharges of the GABAergic reticular neurons phasically inhibit the thalamocortical neurons. Hyperpolarization and phasic release from inhibition, result in rhythmic rebound bursting of thalamocortical cells and consequent rhythmic depolarization and firing of neocortical neurons. Second, and arguably more important in this context, recent *in vivo* studies (MacFarlane et al., 1996; Manns et al., 2000, 2003) have demonstrated that the cholinergic neurons of the NB discharge in a rhythmic bursting mode, which is subtended by calcium conductances when cells are hyperpolarized (Khateb et al., 1992; Alonso et al., 1996). Hyperpolarization is likely to be due, at least in part, to the withdrawal of afferent inputs from both the ascending reticular activating system and the lateral hypothalamic hypocretin/orexin system (Chemelli et al., 1999; Lin et al., 1999; Peyron et al., 2000; Xi et al., 2001; Mignot et al., 2002).

We have recently tested this model of the role of the cholinergic basal forebrain in evoked K-complex production, by investigating evoked K-complexes in a population of mild Alzheimer’s disease (AD) patients compared to age-matched normal aging controls (Crowley et al., 2005). AD patients had significantly smaller K-complex proportions than controls. The N550 component in AD also showed a decrease in amplitude particularly in frontal scalp regions.

To a large extent this model enables an incorporation of most of the data supporting both the arousal and sleep-conducive arguments of K-complex function. By proposing that K-complex generation is a function of a ventral pathway from the brain stem to the basal forebrain, it is clear to see why stimuli eliciting K-complexes might produce indications of autonomic activation, such as transient increases in heart rate and blood pressure (Monstad and Guilleminault, 1999). However, if it is indeed the case that the widespread burst firing of cortical cells required for a K-

complex to be produced can only occur when cholinergic basal forebrain cells are hyperpolarized, it is not surprising that the activation does not spread to the CNS.

It should be emphasized that the proportion of stimuli producing K-complexes and the amplitude of the KC+ N550 component are probably indexing different aspects of CNS structure and function. The proportion measure is probably indexing the functional integrity of the triggering mechanism, hypothesized above to involve the cholinergic basal forebrain. N550 amplitude is measuring the ability of large numbers of cells to be synchronized by the ‘trigger’. This measure should be impacted by the total number of neurons available to be synchronized and the extent to which they are interconnected (e.g. dendritic arborization). This would predict a relationship between cortical gray matter volume and N550 amplitude. Preliminary evidence from MRI data is supportive of this (Nicholas et al., 2003), but more extensive investigation is required.

11.5. Summary and conclusions

The use of evoked potential methods to study brain function during sleep provides opportunities to evaluate the functional integrity of the sleeping nervous system in ways that are more controlled and efficient than traditional observational measures. This is clearly seen in the studies of aging, where in relatively short periods of time, the capacity of a subject’s nervous system to produce delta frequency EEG can be assessed, even in those with little or no slow-wave sleep.

They also provide a mechanism for studying the CNS during the time in which sleep-specific pathology occurs. In two recent studies we have been able to demonstrate that obstructive sleep apnea syndrome (OSAS) patients have altered CNS responses that are specific to inspiratory occlusion stimuli during sleep (Gora et al., 2002; Afifi et al., 2003). Awake RREPs and AEPs, and sleep AEPs, were found not to be different between OSAS patients and controls.

Studies of the sleep onset period have highlighted that the CNS oscillates between two quite different states as part of the process of falling asleep. Recent and ongoing work is attempting to capitalize on the knowledge gained from these investigations of falling asleep to evaluate the nature of CNS function during brief arousals from sleep (Ferrara et al., 2001; Kleverlaan et al., 2003). Such studies, in conjunction

with recent uses of evoked potential during wakefulness to evaluate the impact of sleep disturbances (Ferrara et al., 2002; Cote et al., 2003), provide yet further promise for these techniques to make significant contributions to sleep research in the future.

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CHAPTER 12

Epidemiology of sleep disorders in the general population

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12.1. Introduction

Sleep disorders encompass a broad range of manifestations. They are traditionally divided into two large categories: dyssomnias and parasomnias. Dyssomnias are sleep disorders characterized by abnormalities in the quantity, quality or timing of sleep. As such, they are associated with difficulty initiating or maintaining the sleep or daytime sleepiness. Parasomnias cover abnormal behavioral or physiological events occurring during sleep but do not involve the sleep mechanisms per se.

This chapter reviews the sleep symptoms and disorders most frequently studied in the general population. They have been grouped into four main themes: insomnia and related disorders, excessive daytime sleepiness and related disorders, sleep breathing disorders and parasomnias.

12.2. Dyssomnias

12.2.1. Insomnia and related disorders

Insomnia is one of the most frequently studied sleep complaints in the general population. More than 50 epidemiological studies have assessed its prevalence in different countries. Methodologies have included face-to-face interviews, postal questionnaires, telephone interviews or a combination of two of the above.

12.2.2. What is insomnia?

To date, there is no consensus on how to define and to measure insomnia in epidemiology. As a consequence, epidemiological findings largely vary depending on

the definition used. Nonetheless, the epidemiological approach for measuring insomnia can be summarized in two main categories (al Rajeh et al., 1993): dissatisfaction with quantity of sleep (Ancoli-Israel et al., 1991) and dissatisfaction with quality of sleep.

The dissatisfaction with the quantity of sleep can be expressed as a complaint of sleeping not enough or sleeping too much. Sleeping not enough has been reported with prevalence ranging from 20–41.7% in the general population (Husby and Lingjaerde, 1990; Ohayon et al., 1997a; Ohayon and Roth, 2001). Sleeping too much is far less frequent with prevalence ranging between 2.8–9.5% (Bixler et al., 1979; Ford and Kamerow, 1989; Tellez-Lopez et al., 1995; Ohayon et al., 1997b).

Dissatisfaction with quality of sleep has various definitions. It can be expressed as a complaint of difficulty initiating (DIS) or maintaining sleep (DMS), poor sleep or dissatisfaction with sleep.

12.2.3. Prevalence of difficulty initiating or maintaining sleep

The assessment of DIS or DMS was done mostly according to four strategies: by asking the participants: (a) for the presence of the symptoms; (b) the frequency of the symptoms per week; (c) the severity of the symptoms; (d) if the symptoms were accompanied with any daytime repercussion.

Each of these strategies provided different prevalence. Seven studies have investigated the presence/absence of DIS or DMS. This method gave high prevalence rates ranging between 30–48% (Bixler et al., 1979; Welstein et al., 1983; Klink and Quan, 1987; Quera-Salva et al., 1991; Klink et al., 1992; Mallon et al., 2000; Table 12.1).

Epidemiological studies using frequency to determine the prevalence of DIS or DMS are the most common (Karacan et al., 1976; Karacan et al., 1983; Janson et al., 1995b; Olson 1996; Ancoli-Israel and

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Table 12.1

Epidemiological studies that assessed insomnia symptoms using presence, frequency, severity or sleep dissatisfaction.

Presence	Frequency	Severity	Sleep Dissatisfaction
Bixler et al., 1979, USA (Los Angeles, CA)	Karacan et al., 1976, 1983, USA (Alachua, FL; Houston, TX)	Mellinger et al., 1985, USA	Yeo et al., 1996, Singapore
Welstein et al., 1983, USA (San Francisco, CA)	Janson et al., 1995b, Iceland (Reykjavik), Sweden (Uppsala and Goteborg), Belgium (Antwerp)	Gislason and Almqvist, 1987, Sweden (Uppsala)	Ohayon, 1996, France Ohayon et al. 1997b, United Kingdom
Klink et al., 1987, 1992, USA (Tucson, AZ)	Olson, 1996, Australia (Newcastle)	Liljenberg et al., 1988, Sweden (Gavleborg and Kopparberg)	Kageyama et al., 1997, Tokyo, Maebashi, Nagasaki, Naha and Kawasaki, Japan
Quera-Salva et al., 1991, France	Henderson et al., 1995, Canberra and Queanbeyan, Australia	Weyerer and Dilling, 1991, Germany (Upper Bavarian area)	Ohayon et al., 1997a, Montreal, Canada
Brabbins et al., 1993, Liverpool, UK	Foley et al., 1995, E. Boston, New Haven, Iowa, Washington counties, USA	Tellez-Lopez et al., 1995, Mexico (Monterrey)	Ohayon et al., 2002, Paris, France
Mallon et al., 2000, Sweden	Blazer et al., 1995, NC, USA	Mallon and Hetta, 1997, Sweden	Ohayon and Zulley, 2001, Germany
Babar et al., 2000, Hawaii, USA	Ganguli et al., 1996 Mid-Monon- gahela Valley, Pennsylvania, USA Hoffmann, 1999, Belgium Ohayon et al., 1997b, UK Maggi et al., 1998, Veneto region, Italy Hetta et al., 1999, Sweden Ancoli-Israel and Roth, 1999, USA Vela-Bueno et al., 1999, Madrid, Spain Yamaguchi et al., 1999, Kanazawa, Japan Doi et al., 2000, Japan Leger et al., 2000, France Ohayon, 2001, Germany Ohayon et al., 2002, Italy, South Korea, Finland	Hajak, 2001, Germany Bixler et al., 2002, USA (Central Pennsylvania)	Ohayon & Smirne, 2002, Italy Ohayon and Partinen, 2002, Finland
Prevalence range: 30–48%	Prevalence range: 16–21%	Prevalence range: 15–25%	Prevalence range: 6.8–24.4%

Roth, 1999; Hetta et al., 1999; Hoffmann, 1999; Vela-Bueno et al., 1999; Doi et al., 2000; Leger et al., 2000; Ohayon and Partinen, 2002). In most studies, frequency of the symptoms are assessed on a weekly basis (Janson et al., 1995b; Hetta et al., 1999; Hoffmann, 1999; Vela-Bueno, 1999; Doi et al., 2000; Ohayon and Partinen 2002), for example, five nights or more per week, three or four nights per week, one or

two nights per week, etc.; three nights or more per week being the cut-off score to determine the presence of the symptom. Some studies (Karacan et al., 1976, 1983; Olson, 1996; Ancoli-Israel and Roth, 1999) instead used a qualitative appreciation of the frequency such as never, sometimes, often or always; often or always being the cut-off point to determine the presence of DIS or DMS. The prevalence of DIS or

DMS drops to around 16–21% when frequency is used to determine the presence of insomnia (Table 12.1).

Qualitative assessment of severity of DIS or DMS (for example being bothered a lot; having great or very great DIS or DMS or a major complaint) gave prevalence between 10–28% of the general population (Mellinger et al., 1985; Gislason and Almqvist, 1987; Liljenberg et al., 1988; Weyerer and Dilling, 1991; Tellez-Lopez et al., 1995; Mallon and Hetta, 1997; Hajak, 2001; Bixler et al., 2002).

Some epidemiological studies, in addition to evaluating the presence, frequency or severity of DIS or DMS, asked about daytime repercussions of these symptoms, such as daytime sleepiness, irritability, depressive or anxious mood or needing to seek help. This method gave a much lower prevalence ranging between 8.5–13.0% (Ford and Kamerow, 1989; Breslau et al., 1996; Ohayon, 1997; Hetta et al., 1999; Hoffmann, 1999; Leger et al., 2000; Ohayon and Zulley, 2001).

12.2.4. Prevalence of sleep dissatisfaction

Some studies asked the participants to assess their level of satisfaction with their sleep. The prevalence of individuals reporting being dissatisfied with their sleep ranged from 8–18.5% (Henderson et al., 1995; Yeo et al., 1996; Ohayon et al., 2001; Ohayon and Zulley, 2001; Pallesen et al., 2001; Ohayon and Smirne, 2002; Ohayon and Vecchiarelli, 2002).

Studies that inquired about perception of sleep as being poor or considering oneself as being insomniac reported prevalence between 10–18.1% of the population reported being poor sleepers or being insomniacs (Lugaresi et al., 1983; Asplund, 1996; Kageyama et al., 1997; Vela-Bueno et al., 1999; Kiejna et al., 2003).

Prevalence of DSM insomnia diagnoses also was assessed in some studies ranging from 4.4–11.7% (Kageyama et al., 1997; Ohayon, 1997; Ohayon et al., 1997c; Ohayon and Zulley, 2001; Ohayon and Smirne, 2002).

Unfortunately, chronicity of insomnia complaint is poorly documented. However, studies that measured this aspect (Ohayon, 1996; Ohayon and Smirne, 2002; Ohayon and Zulley, 2001; Ohayon and Roth, 2003), showed that insomnia is mostly chronic, lasting at least one year in 85% of cases (Ohayon and Roth, 2003).

12.2.5. Factors associated with insomnia

Several disorders or conditions other than insomnia disorders can produce insomnia complaints. Sleep-

related breathing disorders such as obstructive sleep apnea syndrome or hypoventilation account for 5–9% of insomnia complaints (Buysse et al., 1994; Jacobs et al., 1988; Ohayon, 1997). Periodic limb movement disorders and/or restless legs syndrome are found in about 15% of individuals with insomnia complaints (Jacobs et al., 1988; Buysse et al., 1994; Edinger et al., 1996; Ohayon and Roth, 2002). Medical or neurological conditions are observed in 4–11% of insomnia complaints (Jacobs et al., 1988; Buysse et al., 1994; Ohayon, 1997; Ohayon et al., 1997d; Ohayon and Partinen, 2002). Poor sleep hygiene or environmental factors account for about 10% of insomnia complaints and substance-induced for 3–7% (Jacobs et al., 1988; Buysse et al., 1994; Ohayon, 1997; Ohayon and Partinen, 2002; Ohayon and Smirne, 2002).

12.2.6. Age and gender

DIS or DMS were found to increase linearly with age reaching close to 50% in elderly individuals in most epidemiological studies (≥ 65 year old) (Bixler et al., 1979; Klink and Quan, 1987; Quera-Salva et al., 1991; Tellez-Lopez et al., 1995; Ohayon, 1996; Ohayon et al., 1997a, 1997b; Ancoli-Israel and Roth, 1999; Hoffmann, 1999; Vela-Bueno et al., 1999; Ohayon and Zulley, 2001). However, the prevalence of DIS or DMS with daytime consequences and the prevalence of sleep dissatisfaction have mixed results. Women are more likely than men to report DIS and DMS (Karacan et al., 1976, 1983; Mellinger et al., 1985; Olson, 1996; Lindberg et al., 1997; Ohayon et al., 1997b; Vela-Bueno et al., 1999; Leger et al., 2000; Bixler et al., 2002), daytime consequences (Ford and Kamerow, 1989; Hetta et al., 1999; Hoffmann, 1999; Leger et al., 2000), dissatisfaction with sleep (Ohayon, 1996; Yeo et al., 1996; Leger et al., 2000) and to have insomnia diagnoses (Ohayon and Zulley, 2001; Ohayon and Hong, 2002; Ohayon and Partinen, 2002). Some studies reported an increase of prevalence in menopausal women compared to their younger counterparts (Mitchell and Woods, 1996; Punyahotra et al., 1997; Owens and Matthews, 1998).

12.2.7. Lifestyle

Several factors related to lifestyle were found to be associated with higher risks of insomnia symptoms in the general population. High level of stress (Ohayon and Zulley, 2001; Ohayon and Hong, 2002; Ohayon and Partinen, 2002; Ohayon and Smirne, 2002),

unemployment (Ohayon et al., 1997a; Chevalier et al., 1999; Hoffmann, 1999; Vela-Bueno et al., 1999), shift/night work (Maartens et al., 2001; Mallon et al., 2002) or sleeping in a bedroom with inappropriate temperature (Ohayon and Zulley, 2001) are among the most frequently reported in the literature.

12.2.8. Physical illnesses and psycho-active substances

Poor health status has been frequently reported in subjects with insomnia symptoms (Blazer et al., 1995; Henderson et al., 1995; Maggi et al., 1998; Chiu et al., 1999; Barbar et al., 2000; Kim et al., 2000; Ohayon and Zulley, 2001; Ohayon and Smirne, 2002). Up to half of subjects with insomnia symptoms have recurrent, persistent or multiple health problems (Bixler et al., 1979; Mellinger et al., 1985). Most frequently reported associations were with upper airway diseases (Gislason and Almqvist, 1987; Klink and Quan, 1987; Ohayon and Zulley, 2001); rheumatic diseases (Gislason and Almqvist, 1987; Hagen et al., 1997; Ohayon and Zulley, 2001; Sutton et al., 2001), chronic pain (Andersson et al., 1999; Sutton et al., 2001) and cardiovascular diseases (Foley et al., 2001; Ohayon and Zulley, 2001; Mallon et al., 2002). Tobacco (Revicki et al., 1991; Wetter and Young, 1994; Janson et al., 1995b; Phillips and Danner, 1995), antihypertensive drugs (Bardage and Isacson, 2000; Gislason and Almqvist, 1987) and alcohol (Pillitteri et al., 1994; Ancoli-Israel and Roth, 1999; Ohayon and Zulley, 2001) have been associated with insomnia symptoms in several epidemiological studies. Alcohol was used as a sleeping aid in four out of ten individuals with sleep disturbances (Johnson et al., 1998; Ancoli-Israel and Roth, 1999; Roehrs et al., 2002).

12.2.9. Mental disorders

Epidemiological studies have consistently reported that a mental disorder is associated with 30–60% of insomnia symptoms (Mellinger et al., 1985; Henderson et al., 1995; Newman et al., 1997; Ohayon, 1997; Maggi et al., 1998; Foley et al., 1999; Hetta et al., 1999; Hoffmann, 1999; Ohayon et al., 2000b; Ohayon and Roth, 2003). In individuals with a current major depressive episode, the presence of insomnia symptoms was found in nearly 80% of the subjects (Olson, 1996; Weissman, et al., 1996; Owens and Matthews, 1998). Four longitudinal studies examined the relationship between the persistence of insomnia symptoms and the appearance of mental disorders

(Breslau et al., 1996; Roberts et al., 2000; Roehrs et al., 2002). The persistence of insomnia over time was associated with a likelihood of four to eight times higher of developing a mental disorder.

12.3. Excessive daytime sleepiness and related disorders

The main problem encountered in the study of excessive daytime sleepiness is the lack of uniformity in the definition of excessive daytime sleepiness (see Table 12.2). One series of epidemiological inquiries, essentially North American, focused on hypersomnia symptoms, such as getting too much sleep or napping, whereas another, this one European, assessed daytime sleepiness and sleep propensity in situations of diminished attention. Consequently, the variance in results across studies does not make it possible to reach any definite conclusions in the matter.

Four U.S. studies that investigated hypersomnia reported rates varying from 0.3–16.3% (Bixler et al., 1979) simply mentioned they assessed hypersomnia and reported a prevalence of 4.2%. In the Ford and Kamerow study (1989), participants were asked whether they had gone a period of 2 weeks or more in which they slept too much (hypersomnia). This yielded a 6-month prevalence of hypersomnia of 3.2%. Using the same definition, Breslau et al. (1996) found a lifetime prevalence of hypersomnia of 16.3% in their young adult sample (21–30 years of age). Klink and Quan (1987) examined how many participants fell asleep during the day and found an overall prevalence of 12%. The Cardiovascular Health Study (Whitney et al., 1998) found a 20% prevalence of participants being 'usually sleepy in the daytime' in a sample of 4578 adults aged 65 and older.

In a Mexican study (Tellez-Lopez et al., 1995), 9.5% of the sample claimed to get too much sleep, and 21.5% claimed to experience a strong need to sleep during the day. A Brazilian community study (Souza et al., 2002) used the Epworth Sleepiness Scale to measure excessive daytime sleepiness in a sample of 408 adults from Campo Grande City. They found a prevalence of 18.9%.

In Europe, the Swedish study by Gislason and Almqvist (1987) yielded a prevalence rate of 16.7% for moderate daytime sleepiness and of 5.7% for severe daytime sleepiness in their male sample. Janson et al. (1995a) found a prevalence of daytime sleepiness occurring at least one day per week of about 40%; daily daytime sleepiness was observed in about 5% of their young adult sample (20 to 44 years of age)

*Table 12.2***Prevalence of narcolepsy.**

Authors	Population	N	Age range	Methods	Prevalence Per 100 000
Solomon, 1945	Black Americans	10 000	16–34	Navy recruit men	20
Dement et al., 1972	North California	Unknown	Unknown	Population sample, newspaper advertisement, telephone interview	50*
Dement et al., 1973	South California	Unknown	Unknown	Population sample, TV advertisement, telephone interview	67*
Honda, 1979	Japan	12 469	12–16	School sample, questionnaire	160
Roth, 1980	Czech Caucasians	Unknown	Unknown	Patient material, polysomnography	20*
Franceschi et al., 1982	Italy	2518	6–92	Unselected in-patients, questionnaire, polysomnography	40
Lavie & Peled, 1987	Israeli Jews and Arabs	1526	30–57	Patient material, polysomnography and HLA typing	0.23*
al Rajeh et al., 1993	South Arabia	23 227	>=1	Face-to-face interviews, subjects with abnormal responses evaluated by a neurologist	40
Hublin et al., 1994	Finland	12 504	33–60	Twin cohort, postal questionnaire, telephone interview, polysomnography, HLA typing	26
Tashiro et al., 1994	Japan	4559	17–59	Sample of employees, questionnaire, personal interview	180
Wing et al., 1994	China	342	>= 18	Patient material, polysomnography and HLA typing	1 to 40*
Billiard, 1996	France	Unknown	Unknown	Male military recruits, 'Le Gard' region	50
Ondzé et al., 1998	France	14 195	>15	Patients of all physicians of 'Le Gard' region. Questionnaire + follow up by phone interview and more detailed questionnaire	21
Han et al., 2001	China	70 000	5–17	Consecutive patients attending to a pediatric neurology clinic. Screening questionnaire + polysomnography, MSLT and HLA typing	40
Ohayon et al., 2001	UK, Germany, Italy, Portugal and Spain	18 980	15–100	Representative sample of general population. Telephone interview with Sleep-EVAL system	47

* Prevalence was extrapolated.

drawn from three different countries. Martikainen et al. (1992), who used a more restrictive definition of excessive daytime sleepiness, found that 9.8% of their 1190 Finnish respondents aged 36–50 years reported being 'clearly more tired than others', experiencing a 'daily desire to sleep in the course of normal activi-

ties', or feeling 'very tired daily'. Hublin et al. (1996) found a prevalence of daytime sleepiness occurring daily or almost daily of 9% in their Finnish twin cohort. Ohayon et al. (1997d) assessed daytime sleepiness on a severity scale in their UK sample of 4972 subjects. Severe daytime sleepiness was observed in

5.5% of their sample, and moderate daytime sleepiness in 15.2%. A Northern Irish community study (Nugent et al., 2001) involving 2364 aged between 18–91 years reported a prevalence of 19.8% of moderate or severe excessive daytime sleepiness.

Two epidemiological studies have linked excessive daytime sleepiness to cognitive deficits. In a study involving 2346 Japanese-American men aged between 71–93 years, Foley et al. (2001) found that men who reported excessive daytime sleepiness at baseline were twice as likely to be diagnosed with dementia 3 years later than those without daytime sleepiness. In another study involving 1026 subjects aged 60 years or older, Ohayon and Vechierrini (2002), found that after controlling for age, gender, physical activity, occupation, organic diseases, use of sleep or anxiety medication, sleep duration and psychological well-being, subjects with excessive daytime sleepiness were twice as likely to have attention-concentration deficits, difficulties in orientation and memory problems than did the others.

Unlike insomnia symptoms, excessive daytime sleepiness is generally not gender-related. Whether its prevalence increases or decreases with age is not clear, as both trends have been observed (Gislason and Almqvist, 1987; Klink and Quan, 1987).

Excessive daytime sleepiness can be caused by various factors such as poor sleep hygiene (Hublin et al., 1996; Ohayon et al., 1997d), work conditions (Ohayon et al., 1997d), and psychotropic medication use (Hublin et al., 1996; Ohayon et al., 1997d). Excessive daytime sleepiness has been found to be associated also with sleep-disordered breathing (Janson et al., 1995a; Hublin et al., 1996; Ohayon et al., 1997d), psychiatric disorders, especially depression (Ford and Kamerow, 1989; Breslau et al., 1996; Hays et al., 1996; Hublin et al., 1997; Ohayon et al., 1997) and physical illnesses (Janson et al., 1995a; Ohayon et al., 1997d).

12.3.1. Narcolepsy

There have been numerous attempts to estimate the prevalence of narcolepsy in different parts of the world. Table 12.3 summarizes the studies of the prevalence of narcolepsy. Most prevalences are derived from clinical samples or non-representative community samples. Two are based on representative community samples. According to these studies, the prevalence varies from 20–67 per 100 000 inhabitants in Europe and North America. A study performed in Japan set this rate at 590 per 100 000 inhabitants

(Honda et al., 1983), and another Japanese study set this rate at 160 per 100 000 inhabitants (Honda, 1979). In Hong Kong, this prevalence was estimated to be between 1–40 narcoleptics per 100 000 inhabitants (Wing et al., 1994), and in Saudi Arabia 40 per 100 000 inhabitants (al Rajeh, 1993). Another study performed with Jews in Israel, a population known for its low rate of human leukocyte antigen (HLA-DR2), a predisposing marker for narcolepsy, set the prevalence at 0.23 per 100 000 inhabitants (Lavie and Peled, 1987).

12.4. Sleep breathing disorders

Few surveys have estimated the prevalence of sleep apnea or obstructive sleep apnea syndrome in community-based samples (Table 12.4). Target population, methods and criteria varied considerably between studies. In all cases, prevalences are estimated because it is virtually impossible to perform polysomnographic recordings on all participants. Therefore screening questionnaires were used to identify participants most likely to have sleep apnea or obstructive sleep apnea syndrome.

The Israeli study by Lavie (1983) was one of the first to explore obstructive sleep apnea in a non-clinical sample. Here, 300 working men were examined, 78 of them with polysomnography. An apnea/hypopnea index (AHI) greater than or equal to 10 was found in 2.7% of the sample and an AHI greater than or equal to 20 in 0.7%. In the Finnish twin cohort study, Telakivi et al. (1987) carried out polysomnographic recordings on 25 snorers and 27 non-snorers selected from among 278 men aged 41–50 years. They estimated that 0.4% of this population had an AHI greater than or equal to 20 and that 1.4% had an AHI greater than or equal to 10, with an oxygenation desaturation index (ODI) of at least 4%.

In Sweden, Gislason et al. (1988) assessed 3201 men aged 30–60 years and conducted polysomnographic recordings on 61 sleepy snorers. They calculated that 0.9% of this population had an AHI greater than or equal to 10 and that 1.4% had an AHI greater than or equal to 20. In a similar survey involving 1505 Icelandic women 40–59 years old, Gislason et al. (1993) found that 2.5% of the sample presented with a sleep apnea syndrome defined as daytime sleepiness with an AHI ≥ 30 .

In Italy, Cirignotta et al. (1989) surveyed 1510 men aged 30–69 years via a postal questionnaire and selected 156 of them for polysomnography. They estimated that 4.8% of this population had an AHI greater than 5, and 3.2% an AHI greater than 10.

Table 12.3**Definitions of excessive daytime sleepiness in the epidemiological surveys.**

Authors	Definitions
Karacan et al., 1976	Hypersomnia
Bixler et al., 1979	Sleeping too much
Klink and Quan, 1987	Falling asleep during the day
Ford and Kamerow, 1989; Breslau et al., 1996	Sleeping too much lasting 2 weeks or more, and professional consultation, sleep enhancing medication intake, or interferes a lot with daily life
Téllez-López et al., 1995	Getting too much sleep Strong need to sleep in the day
Hays et al., 1996	Frequent feeling of sleepiness during the day or evening that necessitates nap
Lugaresi et al., 1983	Sleepiness independent of meal times
Gislason and Almqvist, 1987	Moderate or severe daytime sleepiness
Liljenberg et al., 1988	Daytime sleepiness often or very often
Martikainen et al., 1992	– Considered themselves more clearly tired than others, or – Daily experience of desire to sleep during normal activities, or – Felt tired every day
Hublin et al., 1996	Daytime sleepiness every or almost every day
Janson et al., 1995a	Daytime sleepiness ≥ 3 days/week
Asplund, 1996	– Often sleepy during the day – Often naps in daytime
Ohayon et al., 1997d	Feel sleepy during the day: Moderately, a lot or greatly, ≥ 1 month
Nugent et al., 2001	Moderate daytime sleepiness, i.e. fall asleep when relaxing often/always and at least occasionally sudden attacks of sleep which they can't resist or have to pull of the road while driving because of sleepiness. Severe daytime sleepiness, i.e. fall asleep against their will at least occasionally

Table 12.4**Prevalence of sleep apnea in selected samples.**

Authors	Population	N (n recorded)	Age	Methods	Criteria	Prevalence (%)
Lavie Israel, 1983	Male workers	1 502 (78)	32–67	1) Questionnaire 2) Polysomnography	AI ≥ 10	0.89
Gislason et al., Uppsala, Sweden, 1988	Men, general population	3 201 (61)	30–69	1) Postal questionnaire 2) Polysomnography, sleepy snorers	AHI ≥ 30 + daytime sleepiness	1.3
Cirignotta et al., Bologna, Italy, 1989	Men, general population	1 170 (40)	30–69	1) Postal questionnaire 2) Polysomnography, every-night snorers	AHI ≥ 10	2.7

Table 12.4

Continued

Authors	Population	N (n recorded)	Age	Methods	Criteria	Prevalence (%)
Martikainen et al., Tampere, Finland, 1994	General population	1985: 1190 1990: 626 (22)	36–50	1) Postal questionnaire 2) Polysomnography, habitual male snorers	ODI $\geq 4\%$ > 5 per hour ODI $\geq 4\%$ > 10 per hour	1.8 1.1
Ancoli-Israel et al., San Diego, USA, 1991	General population	615 (427)	65–95	Home Polysomnography	AI ≥ 5 RDI ≥ 10	24.0 62.0
Stradling & Cosby Oxford, UK, 1991	Men, age-sex register of one group general practice	1 001 (893)	35–65	Oximetry	ODI $\geq 4\%$ > 5 per hour ODI $\geq 4\%$ > 10 per hour ODI $\geq 3\%$ > 10 per hour + symptoms	5.0 1.0 0.8
Gislason et al., Reykjavik, Iceland, 1993	Women, general population	1 505 (35)	40–59	1) Postal questionnaire 2) Polysomnography, sleepy snorers	AHI ≥ 30 + daytime sleepiness	2.5
Young et al., USA, 1993	State employees	3 513 (625)	30–60	1) Questionnaire 2) Polysomnography, snorers	AHI ≥ 5 + daytime sleepiness or non-refreshing sleep	4.0 (M) 2.0 (W)
Olson et al., Australia, 1995	General population	2 202 (441)	35–69	1) Questionnaire 2) respiratory measurement, overrepresentation of snorers and sleep complainers	AHI ≥ 10	5.7 (M) 1.2 (W)
Bearpark et al., Busselton, Australia, 1995	Men, general population	486 (294)	40–65	1) Questionnaire 2) Polysomnography	RDI ≥ 5 + at least occasional daytime sleepiness RDI ≥ 5 + at least often daytime sleepiness	12.2 3.1
Bixler et al., Pennsylvania, USA, 1998	Men, general population	4 364 (741)	20–100	1) Telephone interview 2) Polysomnography	AHI ≥ 10 + daytime symptoms	3.3
Bixler et al., Pennsylvania, USA, 2001	Women, general population	12,219 (1000)	20–100	1) Telephone interview 2) Polysomnography	AHI ≥ 10 + daytime symptoms	1.2
Duran et al., Vitoria-Gasteiz, Spain, 2001	Men and women, general population	2 148 (555)	30–70	1) Home interview 2) Portable respiratory recording 3) Polysomnography	AHI ≥ 10	19.0 (M) 14.9 (W)
Ip et al., Hong Kong, 2004	Women, general population	1 532 (106)	30–60	1) Questionnaire 2) Polysomnography	AHI ≥ 5 AHI ≥ 5 + excessive daytime sleepiness	3.7 2.1
Udwadia et al., Bombay, India, 2004	Men, general population	658 (250)	35–65	1) Questionnaire 2) Polysomnography	AHI ≥ 5 AHI ≥ 5 + excessive daytime sleepiness	19.5 7.5

AI, apnea index; AHI, apnea/hypopnea index; ODI, oxygen desaturation index; RDI, Respiratory disturbance index.

In Spain, Duran et al. (2001) interviewed 2148 individuals from the general population and performed polysomnography with 555 of them. The prevalence of $AHI \geq 10$ was at 19% among men and 14.9% among women.

The Wisconsin Sleep Cohort study (Young et al., 1993) looked at 3513 workers aged 30–60 years. Of these, 625 habitual and non-habitual snorers were submitted to a one-night polysomnographic recording. For women, 18.9% of habitual snorers and 5% of non-habitual snorers had an AHI of 5 or greater. For men, the corresponding figures were 34% and 16.1%, respectively. Based on these findings, the prevalence of sleep apnea syndrome (daytime sleepiness and/or non-refreshing sleep and an AHI of 5 or greater) was estimated at 4% among men and 2% among women.

Two studies performed using large community-based samples (Bixler et al., 1998, 2001) screened for possible sleep breathing disorders and recorded 1741 participants. The prevalence of sleep apnea, defined as $AHI \geq 10$ accompanied with daytime symptoms was estimated at 3.3% among men (Bixler et al., 1998) and 1.2% among women (Bixler et al., 2001).

In Australia, the Busselton health survey (Bearpark et al., 1995) found that 12.2% of men aged 40–65 years had at least five respiratory disturbances per hour of sleep ($RDI \geq 5$) along with 'at least occasional' daytime sleepiness, and that 3.1% had an RDI greater than or equal to 5 along with daytime sleepiness 'at least often'. Also in Australia, Olson et al. (1995) queried 2202 subjects aged 35–69 years and monitored 441 of these who complained about their sleep or snored. The rate of obstructive sleep apnea syndrome, based on an AHI of 15 or greater, was estimated at 3.6% overall, and at 5.7% for men and 1.2% for women.

In Hong Kong, Ip et al. (2004) screened 1532 women between 30–60 years and performed polysomnography on 106 of them. They reported a prevalence of $AHI \geq 5$ at 3.7%; an $AHI \geq 5$ accompanied with daytime sleepiness was found in 2.1% of their sample.

Using a similar methodology, Udawadia et al. (2004) screened 658 Indian men aged between 35–65 and performed polysomnography on 250 of them. They reported a prevalence of $AHI \geq 5$ at 19.5%; an $AHI \geq 5$ accompanied with daytime sleepiness was found in 7.5% of their sample.

12.5. Restless legs syndrome

Restless legs syndrome (RLS) was seldom investigated in the general population. RLS studies are

reported in Table 12.5. Existing figures for RLS were estimated using a limited set of questions (one or two questions). The prevalence of RLS symptoms was found to be around 10% (Lavigne and Montplaisir, 1994; Phillips et al., 2000). Three European studies used a set of criteria to assess the prevalence of RLS in the general population. One was done only with men (Ulfberg et al., 2001), another was conducted with elderly (Rothdach et al., 2000) and the other was performed with subjects 15 years of age or over (Ohayon and Roth, 2002). The Rothdach's study (2000) with elderly people found a prevalence of 9.8%. Ohayon and Roth (2002) in the same age group, found a prevalence of 8.6%. The Swedish men study (Ulfberg et al., 2001) reported a prevalence of 5.8%. Ohayon and Roth (2002) found a prevalence of 5.4% in the men of their sample.

In two studies, RLS was not gender related (Ohayon and Roth, 2002) and in two others the prevalence of RLS was about two times higher in women than in men (Lavigne and Montplaisir, 1994; Rothdach et al., 2000). Three studies showed that RLS increased with age (Lavigne and Montplaisir, 1994; Ohayon and Roth, 2002). The prevalence of RLS symptoms is close to 20% in elderly people and around 5% for subjects younger than age 30 (Lavigne and Montplaisir, 1994; Phillips et al., 2000). In the Ohayon study (Ohayon and Roth, 2002), prevalence of RLS diagnosis ranged from 2.7% in the 15–18-year-old group to 8.3% in the group of subjects aged 60 and over (60–69: 8.3%; 70–79: 8.7%; ≥ 80 : 8.2%).

12.6. Parasomnias

Parasomnias are sleep disorders characterized by abnormal behavioral or physiological events occurring at different sleep stages or during sleep–wake transitions. These disorders have seldom been investigated in the adult general population.

12.6.1. Arousal parasomnias

Arousal parasomnias (confusional arousals, sleepwalking and sleep terrors) occur primarily in childhood and normally cease by adolescence. In the adult general population, prevalence of sleepwalking varied between 1.9–3.2% (Bixler et al., 1979; Tellez-Lopez et al., 1995; Hublin et al., 1997; Ohayon et al., 1999b). Sleepwalking is not gender-related but is more common among younger subjects (under 25 years of age) and almost never reported by elderly persons.

Table 12.5

Prevalence for restless leg syndrome or symptoms.

Authors	Population	N	Age	Methods	Prevalence
Lavigne and Montplaisir, 1994	Canada	2 019	≥18	Household interviews, prevalence based on a single question	10.0%
Phillips et al., 2000	Kentucky, USA	1 803	≥18	Telephone interviews, prevalence based on a single question	9.4%
Rothdach et al., 2000	Augsburg, Germany	385	65–83	Face-to-face interview, 3 questions based on criteria described by the International RLS Study group (need positive answers to all questions)	9.8%
Ulfberg et al., 2001	Sweden	2 608 men	18–64	Postal questionnaire, 4 questions based on criteria described by the International RLS Study group (need positive answers to all questions)	5.8%
Ohayon and Roth, 2002	UK, Germany, Italy, Portugal and Spain	18 980	15–100	Telephone interviews, prevalence based on ICSD criteria evaluated by an expert system	5.5%

The prevalence of sleep terrors and confusional arousals in adulthood were seldom investigated. In children, studies have reported prevalence rates for sleep terrors ranging from 1–6.5% (Klackenberg, 1982; Simonds and Parraga, 1982; Salzavulo and Chevalier, 1983). A British epidemiological study (Ohayon et al., 1999b) with 4972 subjects aged between 15–99 years of age reported a 2.2% prevalence of night terrors. As for confusional arousals, a study conducted with 13 057 subjects aged 15 years or older, found a prevalence of 2.9% (Ohayon et al., 2000a).

12.6.2. Sleep–wake transition parasomnias

This group of parasomnias comprises rhythmic movement disorder, sleep starts, sleep talking and nocturnal leg cramps. Epidemiological data on these phenomena are scarce. Téllez-López et al. (1995) reported an overall prevalence of 21.3% for sleep talking and of 3% for frequent sleep talking, with higher rates in the younger age group (30 years or under).

12.6.3. REM-sleep disorder parasomnias

This group of parasomnias includes nightmares, sleep paralysis and REM-sleep behavior disorder. Nightmares have been reported to occur at least once a week in 5% of the adult population (Ohayon et al., 1997e).

Sleep paralysis is one of the main symptoms associated with narcolepsy, but it can also occur individually (i.e., isolated sleep paralysis). Téllez-López et al. (1995) found that 11.3% of their sample had sleep paralysis episodes at least sometimes. Where more narrowly defined populations are concerned, Goode (1962) and Everett (1963) observed rates of 4.7% and 15.4%, respectively, for self-reported sleep paralysis in medical students, and Bell et al. (1984) noted a prevalence of 41% in Black Americans. In a study of adults living on the northeast coast of Newfoundland, Ness (1978) reported a rate of 62% for ‘old hag’ attacks, as sleep paralysis is popularly known in that part of Canada. An epidemiological study (Ohayon et al., 1999a) performed with 8085 subjects between 15–99 years of age found that 6.2% had at least one episode of sleep paralysis in their lifetime; 0.8% experienced severe sleep paralysis (at least one episode per week) and 1.4% moderate sleep paralysis (at least one episode per month). Another study performed with 158 subjects aged 70 years or older reported that 17.7% of them already had experience of ‘ghost oppression’ (Wing et al., 1999).

REM-sleep behavior disorder is characterized by a loss of generalized skeletal muscle REM-related atonia and the presence of physical dream enactment. The phenomenon was first described by Japanese researchers (Hishikawa et al., 1981), but only labeled

as such by Schenck et al. (1986). The prevalence of this sleep disorder in the general population is not well documented. Ohayon et al. (1997c) estimated it at 0.5% based on the minimal criteria proposed by the International Classification of Sleep Disorders.

12.7. Conclusions

Sleep disorders are very frequent in the general population but are under-recognized: less than 20% of individuals with sleep disorders are properly diagnosed and treated, although for a sizable proportion it represents serious sleep disorders that need medical attention.

Insomnia and daytime sleepiness can affect several areas of functioning, including professional, social and marital, and cause diminished concentration and memory problems. In addition, a sleepy individual is at greater risk for road, work-related and household accidents. The high prevalence of insomnia and daytime sleepiness clearly indicates that this is an important public health issue necessitating preventive and educational initiatives and warranting greater attention from public health authorities.

In the coming years, epidemiological research efforts should focus on the following (al Rajeh et al., 1993): greater emphasis should be placed on distinguishing between the various subtypes of insomnia and a better operationalization on how to assess insomnia (Ancoli-Israel et al., 1991); the concept of daytime sleepiness in the general population needs to be properly operationalized; for now, comparison between studies is almost impossible since none of them assess it in the same way (Ancoli-Israel and Roth, 1999); seasonal or transient patterns of insomnia and daytime sleepiness need to be examined (Andersson et al., 1999); longitudinal epidemiological data on the evolution and consequences of insomnia and daytime sleepiness need to be gathered; and finally (APA, 1994) almost all forms of parasomnia need to be investigated.

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CHAPTER 13

Narcolepsy

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13.1. Introduction

The term 'narcolepsy' was first coined by G  lineau in 1880 with the complete description of a patient with excessive daytime sleepiness (EDS), sleep attacks and episodes of muscle weakness triggered by emotions (G  lineau, 1880). In the current international classification, narcolepsy is characterized by 'excessive daytime sleepiness that is typically associated with cataplexy and abnormal REM (Rapid Eye Movement) sleep phenomena such as sleep paralysis and hypnagogic hallucinations'. Narcolepsy is a chronic neurological condition, but is not a progressive disorder (Billiard et al., 1983; Sonka et al., 1991).

Narcolepsy is an under-diagnosed sleep disorder that affects 0.03–0.16% of the general population in various ethnic groups (Guilleminault, 1994; Hublin et al., 1994b; Tashiro et al., 1994). Most cases of human narcolepsy are sporadic. Genetic predisposition and environmental factors are important for the development of narcolepsy and few familial cases of human narcolepsy have been reported (Guilleminault et al., 1989).

Narcolepsy is mainly treated with pharmacological compounds. EDS is typically treated using central nervous system (CNS) stimulants and/or modafinil. These compounds are effective in reducing daytime sleepiness but have little effect on cataplexy, hypnagogic hallucinations and sleep paralysis (Nishino and Mignot, 1997). Antidepressants (one of the most commonly used anticataplectic treatments) alleviate cataplexy and REM sleep abnormalities but have little

effect on daytime sleepiness (Nishino and Mignot, 1997). Sodium oxybate, a newly approved hypnotic (or novel compound), effectively controls cataplexy while also helping relieve daytime sleepiness.

The major pathophysiology of human narcolepsy has been recently elucidated based on the discovery of narcolepsy genes in animals. Using forward (i.e., positional cloning in canine narcolepsy) and reverse (i.e., mouse gene knockout) genetics, the genes involved in the pathogenesis of narcolepsy (hypocretin/orexin ligand and its receptor) in animals have been identified (Chemelli et al., 1999; Lin et al., 1999). Hypocretins/orexins are novel hypothalamic neuropeptides also involved in various hypothalamic functions such as energy homeostasis and neuroendocrine functions (De Lecea et al., 1998; Sakurai et al., 1998). Mutations in hypocretin-related genes are rare in humans, but hypocretin-ligand deficiency is found in many cases (Peyron et al., 2000; Nishino et al., 2001b). This recent discovery is likely to lead to the development of new diagnostic tests and targeted treatments. Since hypocretins are involved in various hypothalamic functions, hypocretin-deficient narcolepsy appears now to be a more complex condition than just a simple sleep disorder. This chapter starts with an overview of the clinical aspects of narcolepsy, followed by an update on the pathophysiology (with emphasis on the role of the hypocretins). Finally, we discuss the expectations from future narcolepsy research.

13.2. Epidemiology

13.2.1. The prevalence of narcolepsy

The prevalence of narcolepsy has been investigated in several ethnic groups and countries. One of the most sophisticated prevalence studies was a Finnish cohort study consisting of 11 354 twin individuals (Hublin et al., 1994b). All subjects who responded to a ques-

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tionnaire with answers suggestive of narcolepsy were contacted by telephone. Clinical interviews were performed and polysomnographic recordings were then conducted in five subjects considered to be narcoleptic. Sleep monitoring finally identified three narcoleptic subjects with cataplexy, thus leading to a prevalence of 0.026% (Hublin et al., 1994b). All three subjects were dizygotic twins and the co-twins were not affected (Hublin et al., 1994b). Other prevalence studies have led to similar prevalence values (0.02–0.067%) in Great Britain (Ohayon et al., 1996), France (Ondzé et al., 1999), the Czech Republic (Roth, 1980), five European countries (Ohayon et al., 2002) and in the United States (Dement et al., 1973; Silber et al., 2002).

A study performed in 1945 in African-American navy recruits also led to 0.02% in this ethnic group for narcolepsy-cataplexy (Solomon, 1945). Narcolepsy-cataplexy may be more frequent in Japan and less frequent in Israel. Two population-based prevalence studies led to a 0.16% and 0.18% prevalence figure in Japan (Honda, 1979; Tashiro et al., 1994). However, these studies used only questionnaires and interviews but not polysomnography to confirm the diagnosis. In Israel, only a few narcoleptic patients have been identified when compared to the large population of subjects recruited into sleep clinics (Lavie and Peled, 1987). This has led to the suggestion that the prevalence of narcolepsy could be as low as 0.002% in this ethnic group.

The age of onset varies, from early childhood to the fifties, with two peaks, a larger one that occurs at around 15 years of age and a smaller peak at approximately 36 years of age (Dauvilliers et al., 2001b). Similar results were found in two different populations but the reasons for this bimodal distribution remains obscure. Incidence of the disease was reported to be 1.37/100 000 per year (1.72 for men and 1.05 for women) in Olmsted County in Minnesota (Silber et al., 2002). The incidence rate was highest in the second decade, followed in descending order by the 3rd, 4th and 1st decade.

13.2.2. Genetic vs environmental factors

A familial tendency for narcolepsy has long been recognized since its description in the late 19th century (Westphal, 1877). Starting in the 1940s, several studies were published which investigated the familial history of small cohorts of narcoleptic probands (Krabbe and Magnussen, 1942; Yoss and Daly, 1960;

Nevsimalova-Bruhova and Roth, 1972; Baraitser and Parkes, 1978; Kessler et al., 1979; Honda et al., 1983). Using standard diagnostic criteria, more recent studies have showed rates of familial cases as 4.3% in Japan (Honda, 1988), 6% in the United States (Guilleminault et al., 1989), 7.6% in France and 9.9% in Canada (Dauvilliers et al., 2001b). In addition to subjects who fulfill all diagnostic criteria for narcolepsy, other relatives may report only recurrent sleep episodes; they may suffer from an incomplete and milder form of the disease (Billiard et al., 1994). Studies also revealed that the risk of a first-degree relative developing narcolepsy-cataplexy is 1–2.0%, a 10–40 times higher risk than in the general population (Billiard et al., 1994; Hublin et al., 1994a; Mignot, 1998).

On the other hand, in the literature, 16 monozygotic (MZ) twin pairs with at least one affected twin have been reported, and only four (or five, depending on the criteria) of these pairs were concordant for narcolepsy (Mignot, 1998). Although genetic predisposition is likely to be involved in the development of narcolepsy, the relatively low rate of concordance in narcoleptic MZ twins indicates that environmental factors also play a role in the development of the disease. The nature of the possible environmental factors involved is not fully understood. Frequently cited factors are head trauma (Lankford et al., 1994), sudden change in sleep/wake habits (Orellana et al., 1994) or various infections (Roth, 1980). While these factors may be involved, there are no documented studies demonstrating increased frequency when compared to control groups.

13.3. Clinical characteristics

13.3.1. Excessive daytime sleepiness and related symptoms

Excessive daytime sleepiness (EDS) and cataplexy are considered to be the two primary symptoms of narcolepsy, with EDS often the most disabling symptom. The EDS most typically mimics the feeling that people experience when they are severely sleep-deprived but may also manifest itself as a chronic tiredness or fatigue. Narcoleptic subjects generally experience a permanent background of baseline sleepiness that easily leads to actual sleep episodes in monotonous sedentary situations. This feeling is most often relieved by short naps (15–30 min), but in most cases the refreshed sensation only lasts a short time after

awaking. The refreshing value of short naps is of considerable diagnostic value. Sleepiness also occurs in irresistible waves in these patients, a phenomenon best described as 'sleep attacks'. Sleep attacks may occur in very unusual circumstances, such as in the middle of a meal, a conversation or riding a bicycle. These attacks are often accompanied by microsleep episodes (Guilleminault, 1987) where the patient 'blanks out'. The patient may then continue his or her activity in a semiconscious manner (writing incoherent phrases in a letter, speaking incoherently on the phone, etc.), a phenomenon called automatic behavior (Broughton and Ghanem, 1976; Dement, 1976; Guilleminault, 1987). Learning problems and impaired concentration are frequently associated (Broughton and Ghanem, 1976; Dement, 1976; Guilleminault, 1987; Cohen and Smith, 1989; Rogers and Rosenberg, 1990), but psychophysiological testing is generally normal.

Sleepiness is usually the first symptom to appear, followed by cataplexy, sleep paralysis and hypnagogic hallucinations (Yoss and Daly, 1957; Parkes et al., 1975; Roth, 1980; Billiard et al., 1983; Honda, 1988). Cataplexy onset occurs within 5 years after the occurrence of daytime somnolence in approximately two thirds of the cases (Roth, 1980; Honda, 1988). Less frequently, cataplexy appears many years after the onset of sleepiness. The mean age of onset of sleep paralysis and hypnagogic hallucinations is also 2–7 years later than that of sleepiness (Kales et al., 1982; Billiard et al., 1983).

In most cases, EDS and irresistible sleep episodes persist throughout the lifetime although they often improve after retirement (possibly due to better management of activities), daytime napping and adjustment of night-time sleep.

13.3.2. Cataplexy

Cataplexy is distinct from EDS and is pathognomonic of the disease (Guilleminault et al., 1974). The importance of cataplexy for the diagnosis of narcolepsy has been recognized since its description (Löwenfeld, 1902; Henneberg, 1916) and in subsequent reviews on narcolepsy (Wilson, 1927; Daniels, 1934). Most authors now recognize patients with recurring sleepiness and cataplectic attacks as a homogeneous clinical entity, and this is now shown to be associated with hypocretin-deficiency (see the section on the pathophysiology of the disease). Cataplexy is defined as a sudden episode of muscle weakness triggered by emotional factors, most often in the context of positive

emotions (such as laughter, having good cards at card games, the pull of the fishing rod with a biting fish, the perfect hit at baseball), and less frequently by negative emotions (most typically anger or frustration). All antigravity muscles can be affected leading to a progressive collapse of the subject, but respiratory and eye muscles are not affected. The patient is typically awake at the onset of the attack but may experience blurred vision or ptosis. The attack is almost always bilateral and usually lasts a few seconds. Neurological examination performed at the time of an attack shows a suppression of the patellar reflex and sometimes a Babinski's sign.

Cataplexy is an extremely variable clinical symptom (Gelb et al., 1994). Most often, it is mild and occurs as a simple buckling of the knees, head dropping, facial muscle flickering, sagging of the jaw or weakness in the arms. Slurred speech or mutism is also frequently associated. It is often imperceptible to the observer and may even be only a subjective feeling that is difficult to describe, such as a feeling of warmth or that somehow time is suspended (Wilson, 1927; Gelb et al., 1994). In other cases, it escalates to actual episodes of muscle paralysis that may last up to a few minutes. Falls and injury are rare and most often the patient will have time to find support or will sit down while the attack is occurring. Long episodes occasionally blend into sleep and may be associated with hypnagogic hallucinations.

Patients may also experience 'status cataplecticus'. This rare manifestation of narcolepsy is characterized by subintractant cataplexy that lasts several hours per day and confines the subject to bed. It can occur spontaneously or more often upon withdrawal from antiepileptic drugs (Passouant et al., 1970; Parkes et al., 1975; Hishikawa and Shimizu, 1995).

Cataplexy often improves with advancing age. In rare cases it disappears completely but in most patients it is better controlled (probably after the patient has learned to control his emotions) (Billiard et al., 1983; Rosenthal et al., 1990).

13.3.3. Sleep paralysis

Sleep paralysis is present in 20–50% of all narcoleptic subjects (Yoss and Daly, 1960; Parkes et al., 1974; Hishikawa, 1976; Roth, 1980). It is often associated with hypnagogic hallucinations. Sleep paralysis is best described as a brief inability to perform voluntary movements at the onset of sleep, upon awakening during the night or in the morning. Contrary to

simple fatigue or locomotion inhibition, the patient is unable to perform even a small movement, such as lifting a finger. Sleep paralysis may last a few minutes and is often finally interrupted by noise or other external stimuli. The symptom is occasionally bothersome in narcoleptic subjects, especially when associated with frightening hallucinations (Rosenthal, 1939).

Whereas excessive daytime sleepiness and cataplexy are the cardinal symptoms of narcolepsy, sleep paralysis occurs frequently as an isolated phenomenon, affecting 5–40% of the general population (Goode, 1962; Fukuda et al., 1987; Dahlitz and Parkes, 1993). Occasional episodes of sleep paralysis are often seen in adolescence and after sleep deprivation, thus prevalence is high for single episodes.

13.3.4. Hypnagogic and hypnopompic hallucinations

Abnormal visual (most often) or auditory perceptions that occur while falling asleep (hypnagogic) or upon waking up (hypnopompic) are frequently observed in narcoleptic subjects (Ribstein, 1976). These hallucinations are often unpleasant and are typically associated with a feeling of fear or threat (Rosenthal, 1939; Hishikawa, 1976). Polygraphic studies indicate that these hallucinations occur most often during REM sleep (Hishikawa, 1976; Chetrit et al., 1994). These episodes are often difficult to distinguish from nightmares or unpleasant dreams, which also occur frequently in narcolepsy.

Hypnagogic hallucinations are most often associated with sleep attacks and their content is well criticized by the patient. The hallucinations are most often complex, vivid, dream-like experiences ('half sleep' hallucinations) and may follow episodes of cataplexy or sleep paralysis, a feature that is not uncommon in severely affected patients. These hallucinations are usually easy to distinguish from hallucinations observed in schizophrenia or related psychotic conditions.

13.3.5. Other important symptoms

One of the most frequently associated symptoms is insomnia, best characterized as a difficulty to maintain night-time sleep. Typically, narcoleptic patients fall asleep easily, only to wake up after a short nap unable to fall asleep again before an hour or so. Narcoleptic patients do not usually sleep more than normal individuals over the 24-h cycle (Hishikawa et al., 1976; Montplaisir et al., 1978; Broughton et al.,

1988b) but frequently have a very disrupted night-time sleep (Hishikawa et al., 1976; Montplaisir et al., 1978; Broughton et al., 1988b). This symptom often develops later in life and can be very disabling.

Frequently associated problems are periodic leg movements (Mosko et al., 1984; Godbout and Montplaisir, 1985), REM behavior disorder, other parasomnias (Schenck and Mahowald, 1992; Mayer et al., 1993), and obstructive sleep apnea (Guilleminault et al., 1976; Mosko et al., 1984; Chokroverty, 1986).

Narcolepsy was reported to be associated with changes in energy homeostasis several decades ago. Narcolepsy patients are frequently: (1) obese (Honda et al., 1986; Schuld et al., 2000); (2) more often have insulin-resistant diabetes mellitus (Honda et al., 1986); (3) exhibit reduced food intake (Lammers et al., 1996); and (4) have lower blood pressure and temperature (Sachs and Kaisjer, 1980; Mayer et al., 1997). These findings however, had not received much attention since they were believed to be secondary to sleepiness or inactivity during the daytime. More recently, however, it was shown that these metabolic changes may be found more specifically in hypocretin-deficient patients (Nishino et al., 2001b), suggesting a direct pathophysiological link. Additional research in this area is warranted to clarify this association (Hara et al., 2001).

Narcolepsy is a very incapacitating disease. It interferes with every aspect of life. The negative social impact of narcolepsy has been extensively studied. Patients experience impairments in driving and a high prevalence of either car- or machine-related accidents. Narcolepsy also interferes with professional performance, leading to unemployment, frequent changes of employment, working disability or early retirement (Broughton et al., 1981; Aldrich, 1989; Alaila, 1992). Several subjects also develop symptoms of depression, although these symptoms are often masked by antiepileptic medications (Roth and Nevsimlova, 1975; Broughton and Ghanem, 1976; Broughton et al., 1981).

13.4. Diagnosis

The clinical diagnosis is based on the presence of EDS and/or sudden onsets of sleep occurring almost daily during a period of at least 6 months and on the presence of a clear clinical history of cataplexy (Honda, 1988). In the current International Classification of Sleep Disorders (ICSD, 1990), diagnosis can be made in the presence of EDS without cataplexy, if one asso-

ciated symptom including sleep paralysis, hypnagogic hallucinations, automatic behaviors, disrupted sleep is present together with one of the following polygraphic abnormalities: night-time sleep latency <10 min, night-time REM sleep latency <20 min, average sleep latency <5 min, or presence of two sleep onset REM periods (SOREMPs) during the multiple sleep latency test (MSLT) (see Figure 13.1). The regular MSLT consists of five naps, scheduled at 2-hour intervals starting between 9 and 10 am (Richardson et al., 1978; Carskadon et al., 1986; Chervin et al., 1995). The test is terminated after a sleep period of 15 minutes or after 20 minutes if the patient did not fall asleep. SOREMPs are defined as the occurrence of REM sleep within 15 minutes after sleep onset.

A nocturnal polysomnogram is useful for eliminating other possible causes of excessive daytime sleepiness such as periodic leg movements and obstructive sleep apnea. The diagnosis of Upper Airway Resistance Syndrome must also be very carefully considered. A multiple sleep latency test (MSLT) is generally performed the following day. Sleep efficiency during nocturnal polysomnography may be normal or low.

The American Sleep Disorders Association recommends that an MSLT be performed for all patients suspected of narcolepsy (American Sleep Disorders Association, 1992). The diagnostic value of the MSLT for narcolepsy has however been recently questioned

by some authors (Lammers and Van Dijk, 1992; Moscovitch et al., 1993). First, approximately 15% of narcoleptic subjects with clear-cut cataplexy do not have a short sleep latency and/or more than two SOREMPs during a single MSLT (Moscovitch et al., 1993; Mignot et al., 2002). Conversely, a small number of patients with abnormal breathing may display typical narcolepsy-like MSLT results. As the prevalence of Upper Airway Resistance Syndrome and sleep apnea is 100 times greater than those with narcolepsy-cataplexy, false positives may be frequent if the test is interpreted without carefully excluding all other causes of excessive daytime sleepiness (Aldrich, 1993).

In a number of countries the MSLT is not commonly performed, especially if clear-cut cataplexy is present. Some investigators rely on the presence of SOREMP during a single night recording, an abnormality present in less than half of narcoleptic patients with cataplexy. A single daytime nap study is also used by some to analyze for the presence of a SOREMP or short sleep latency (Raynal, 1976; Roth et al., 1986; Broughton et al., 1988a) (see Figure 13.1). Other groups have advocated the use of continuous 24-hour or 36-hour polysomnographic recordings (Billiard et al., 1986), ambulatory EEG polygraphic recordings (Genton et al., 1995) but most investigators have found that the MSLT is more predictive than all of the above-mentioned tests for diagnosing narcolepsy.

Other polygraphic methods have been developed to measure EDS in narcolepsy, such as the sleep latency on the maintenance of wakefulness test (MWT) (Mitler et al., 1982). The major difference with the MSLT is the instruction given to the subject. In a MWT the subject is told to attempt to remain awake. Generally, this testing method is not used for the diagnosis but rather to assess the effect of treatment with psychostimulants (Mitler et al., 1998).

In addition to these clinical and polysomnographic criteria, HLA typing showing the association with HLA DQB1*0602 is supportive of the diagnosis, but the specificity of DQB1*0602 positivity is low (Mignot, 1998). Today, CSF hypocretin-1 measurement has become a major diagnostic tool in the diagnosis of narcolepsy and other hypersomnias (Ripley et al., 2001c; Mignot et al., 2002) (see the section of pathophysiology).

13.4.1. Symptomatic narcolepsy

Several cases of narcoleptic patients with brain tumor (most often localized in the posterior hypothalamus

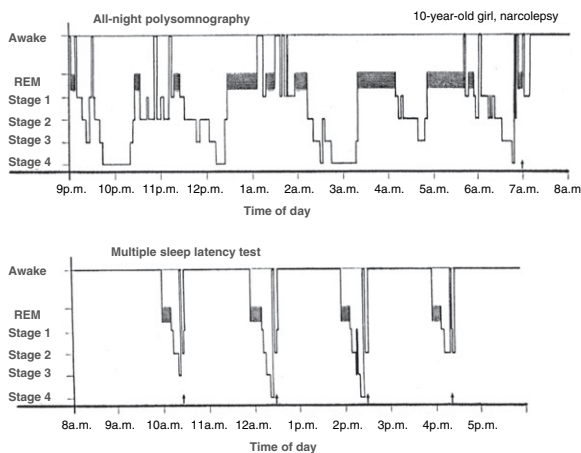


Fig. 13.1. Multiple sleep latency test in a narcoleptic patient. Narcoleptic subjects often show sleep-onset REM periods during night-time polygraph recordings. Sleep-onset REM periods are also seen in daytime short naps (during multiple sleep latency tests), modified from (Honda, 1988).

and the superior part of the brainstem) have been published. Narcolepsy has also been reported in patients with multiple sclerosis, encephalitis, cerebral ischemia, cranial trauma, brain tumor, and cerebral degeneration (Aldrich and Naylor, 1989; Arie et al., 2001; Melberg et al., 2001; Scammell et al., 2001). Hypothalamic sarcoidosis has caused narcolepsy in at least two cases, although neither had cataplexy (Aldrich and Naylor, 1989; Malik et al., 2001). Symptomatic narcolepsies are also present in children affected with the Niemann–Pick disease (Challamel et al., 1994). The diagnosis of symptomatic narcolepsy requires that narcolepsy be developed in close temporal relationship with the neurological disorders since the association may be incidental rather than causal. A recent report described patients with paraneoplastic anti-Ma2 antibodies who have hypothalamic inflammation, sleepiness and cataplexy, but polysomnograms were not reported (Overeem et al., 2001; Rosenfeld et al., 2001). Melberg et al. have described a Swedish family with autosomal dominant cerebellar ataxia, deafness, and narcolepsy (Melberg et al., 2001). Affected members gradually develop chronic sleepiness and cataplexy in young adulthood along with enlargement of the third ventricle suggestive of hypothalamic atrophy. Interestingly, some of these symptomatic cases of narcolepsy are reported to be associated with moderate declines in CSF hypocretin levels (see the section of pathophysiology) (Arie et al., 2001; Melberg et al., 2001; Overeem et al., 2001; Scammell et al., 2001).

13.4.2. Differential diagnosis

Narcolepsy is often misdiagnosed as a psychiatric condition or as an epilepsy variant. It may also be confounded with other forms of hypersomnia, such as sleep apnea syndrome (SAS), idiopathic hypersomnia or hypersomnia associated with depression. The presence of cataplexy is the key factor to single-out narcolepsy from the other forms of hypersomnia. However, when cataplexy is predominant, narcolepsy can be misdiagnosed as syncope, drop attacks, atonic attacks or attacks of histrionic nature. Some well-informed individuals may mimic the symptoms of narcolepsy in order to benefit from a disability, leave from work or to obtain a prescription of psychostimulants. Narcolepsy without cataplexy may overlap with idiopathic hypersomnia, a heterogeneous disorder of chronic sleepiness (Bassetti and Aldrich, 1997). By definition, patients with idiopathic hypersomnia lack cataplexy and have less than two SOREMs on the

MSLT. Some of these individuals have deep, excessively long periods of sleep, difficulty waking from sleep, and long unrefreshing naps, but many have symptoms similar to narcolepsy (Aldrich, 1996; Bassetti and Aldrich, 1997).

13.5. Pathophysiology of narcolepsy

13.5.1. Pathophysiological consideration of symptoms of narcolepsy

The similarity between cataplexy and REM sleep atonia, the presence of frequent episodes of hypnagogic hallucinations and of sleep paralysis, and the propensity for narcoleptics to go directly from wakefulness into REM sleep (SOREMP), suggests that narcolepsy is primarily a 'disease of REM sleep' (Dement et al., 1966). This hypothesis may, however, be too simplistic. This does not explain the presence of sleepiness during the day and the short latency to both NREM and REM sleep during nocturnal and nap recordings. Another complementary hypothesis is that narcolepsy results from the disruption of the control mechanisms of sleep and wakefulness or, in other words, of the vigilance-state boundary problems (Broughton et al., 1986). According to this hypothesis, a cataplectic attack represents an intrusion of REM sleep atonia during wakefulness, while the hypnagogic hallucinations appear as dream-like imagery taking place in the waking state, especially at sleep onset in patients who frequently have SOREMP.

Cataplexy is associated with an inhibition of the monosynaptic H-reflex and the polysynaptic deep tendon reflexes (Guilleminault et al., 1974) and it is only in REM sleep that the H-reflex is totally suppressed. This finding highlights the relationship between the inhibition of motor processes during REM sleep, sudden atonia and areflexia seen during cataplexy. Studies in canine narcolepsy however, suggested that the mechanism for induction of cataplexy is different from those for REM sleep (Nishino et al., 2000b). Furthermore, an extended human study confirmed that cataplexy is very specific to hypocretin-deficient narcolepsy in contrast to other REM-sleep-related phenomena (see below) (Mignot et al., 2002). Cataplexy may thus be separated from other REM-related symptoms and cataplexy considered as a hypocretin-deficient pathological phenomenon. The fact that patients with other sleep disorders, such as sleep apnea, and even healthy controls often have sleep onset REM sleep periods, hypnagogic hallucinations,

and sleep paralysis when their sleep/wake patterns are disturbed (Fukuda et al., 1987; Bishop et al., 1996; Ohayon et al., 1996; Aldrich et al., 1997), yet these subjects never develop cataplexy, further supports this proposal. Although cataplexy and REM sleep atonia have great similarity and possibly share a common executive system, it is not necessary for the regulatory mechanism of both states to be identical. The mechanism of emotional triggering of cataplexy remains undetermined.

13.5.2. HLA typing in narcolepsy

In Japan, Juji et al. (1984) reported that 100% of narcoleptics were positive for HLA DR2, and a tight association subsequently was confirmed in Europe (Langdon et al., 1984; Billiard and Seignalet, 1985) and also in North America (Poirier et al., 1986). However, several DR2-negative cases have also been reported, suggesting the presence of other predisposing genes (Andreas-Zietz et al., 1986; Guilleminault and Grumet, 1986; Mueller-Eckhardt et al., 1986). The HLA gene complex maps on the short arm of the chromosome six. It is divided into three subregions (Figure 13.2), HLA classes I, II and III. HLA plays a key role in the recognition and processing of foreign antigens by the immune system. HLA DR2 is implicated in several autoimmune diseases such as insulin-dependent diabetes mellitus and multiple sclerosis (see the section on narcolepsy and the immune system). More specific antisera were used to better characterize HLA DR2, and it was shown that the serological haplotype, DR15-DQ6 (DR2-DQw1 subtype) was associated with narcolepsy (Honda and Matsuki, 1990). Furthermore, the amplification of the polymorphic exon (second exon) of the HLA DQA and DQB genes by polymerase chain reaction has shown that all Caucasian narcoleptic subjects have the same alleles DRB1*1501, DQA1*0102 and DQB1*0602 (Kuwata et al., 1991). However, in Black American narcoleptics the susceptibility to narcolepsy is more tightly associated with the DQ6 subtype than with the DR15. In fact, only 70% of Black American narcoleptics are DR15 positive, whereas they are almost all positive for the DQ6 (Matsuki et al., 1992; Mignot et al., 1994b, 1997a, 1997b). The most specific marker of narcolepsy in a number of different ethnic groups studied to date is DQB1*0602 (Mignot, 1998) (Figure 13.2).

Studies of HLA association were also conducted in narcoleptic subjects without cataplexy. An association with DQB1*0602 was found in only 40.9% of cases.

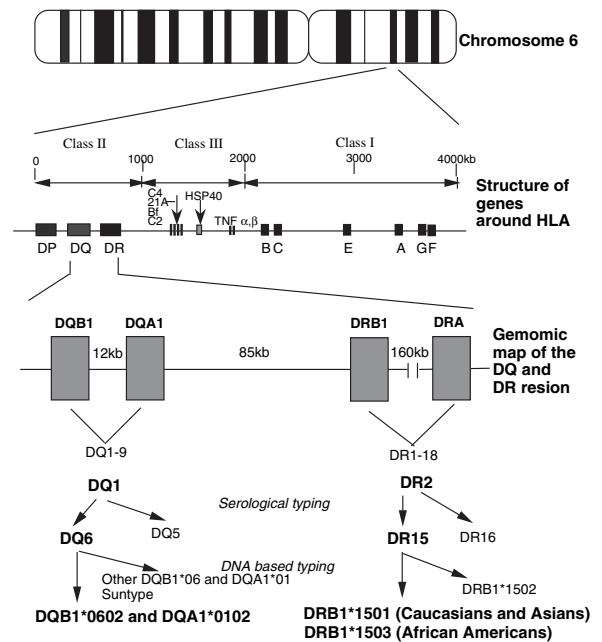


Fig. 13.2. Schematic overview of the location of the human leukocyte antigen (HLA) complex on chromosome 6, including the DQ/DR region with the haplotypes typically associated with narcolepsy. The HLA genes are located on chromosome '6p21' and distributed over more than 4000 kb. The HLA gene family is divided into two classes: class I (A, B and C) and class II (DQ, DR and DP). Close to the HLA genes, there are genes encoding the complement 2 and 4, TNF (tumor necrosis factor), and HSP40 (heat shock protein). The HLA DR and DQ genes are located very close to each other. These genes encode heterodimeric HLA proteins composed of an alpha and a beta chain. In the DQ locus, both the DQ alpha and DQ beta chains have numerous variable residues and are encoded by two polymorphic genes, DQA1 and DQB1, respectively. Polymorphism at the DR level is mostly encoded by the DRB1 gene and thus only this locus is depicted in this figure. DQB1*0602, a molecular subtype of the serologically defined DQ1 antigen is the most specific marker for narcolepsy across all ethnic groups. It is always associated with the DQA1 subtype, DQA1*0102. In Caucasians and Asians, the associated DR2 subtype DRB1*1501 is typically observed with DQB1*0602 (and DQA1*0102) in narcoleptic patients. In African Americans, either DRB1*1503, a DNA based subtype of DR2, or DRB1*1101, a DNA based subtype of DR5, are most frequently observed together with DQB1*0602.

This result clearly shows the close association between DQB1*0602 and the presence of cataplexy (Mignot et al., 1997a). In normal subjects, a significant reduction in REM sleep latency was noted when they were DQB1*0602 positive (Mignot, 1998).

Furthermore HLA-DQB1*0602 homozygosity doubles to quadruples the risk for narcolepsy (Pelin et al., 1998), and the relative risk for narcolepsy varies in DQB1*0602 heterozygote subjects according to the second allele located in *trans* to DQB1*0602 (Mignot et al., 2001).

However, it was reported that approximately 25% of familial narcoleptic cases (including narcoleptic subjects and subjects presenting with only recurrent isolated sleep episodes) are negative for DQB1*0602 (Mignot et al., 1996), supporting the existence of one or more genes with high penetrance not associated with HLA. These genes could be located using systematic genome-screening methods in extended families. The single published study showed a significant link in 4q13-q21 (lod score of 3.09) in eight small multigenerational families of narcoleptics, which favors the implication of other genes such as the *CLOCK* gene and the GABA β -1 receptor gene in these families (Nakayama et al., 2000). The candidate gene strategy has also been used. Along this line, it has been reported that the tumor necrosis factor- α gene with thymine residue at position -857 in its promoter region (TNF- α [-857T]) are associated with human HLA-DRB1*1501-positive (Hohjoh et al., 2001) and -negative narcolepsy (Wieczorek et al., 2003). In addition, a different distribution of the catechol-O-methyl transferase genotype, a key enzyme in dopaminergic and noradrenergic degradation, was found as well as a correlation between this phenotype and the severity of narcolepsy in female narcoleptic subjects (Dauvilliers et al., 2001a).

13.5.3. Narcolepsy and the immune system

The strong association between HLA and narcolepsy raises the possibility that narcolepsy is an autoimmune disease (Mignot et al., 1992). There is, however, no evidence of inflammatory processes or immune abnormalities associated with narcolepsy (Mignot et al., 1992). Studies have found no classical auto-antibodies and no increase in oligoclonal CSF bands in narcoleptics (Frederickson et al., 1990). Typical autoimmune pathologies (erythrocyte sedimentation rates, serum immunoglobulin levels, C-reactive protein levels, complement levels and lymphocyte subset ratios), are apparently normal in narcoleptic patients (Matsuki et al., 1988). A variety of serological tests performed in narcoleptics, along with age- and sex-matched controls, showed a higher level of antistreptolysine O and of anti-DNAse antibodies in narcoleptics than in controls (Billiard et al., 1989;

Montplaisir et al., 1989). Such studies are preliminary but deserve to be further developed, in order to strive towards prevention of the disease.

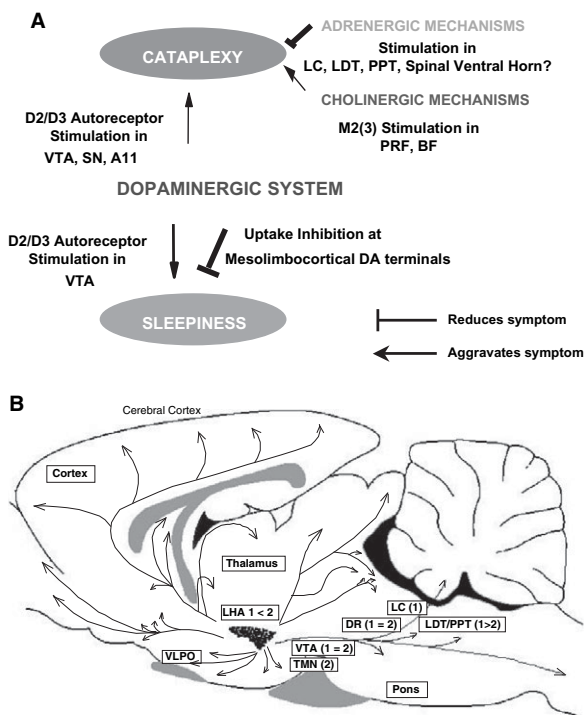
13.5.4. Pharmacological control of symptoms of narcolepsy

Systematic pharmacological studies were also conducted in canine narcolepsy. Pharmacological studies performed in these animals suggest that both the cholinergic and monoaminergic systems are critically involved. The administration of cholinomimetic drugs known to increase REM sleep exacerbates cataplexy in narcoleptic dogs, while the administration of anticholinergic substances decreases cataplexy (Delashaw et al., 1979). These results are similar to the facilitation of REM sleep obtained in animals after pharmacological increase of the central cholinergic transmission (Gillin et al., 1993). On the other hand, drugs that block the reuptake of noradrenaline (norepinephrine) have a powerful anticataplectic effect (Mignot et al., 1993; Nishino et al., 1993a) as opposed to dopamine reuptake inhibitors, which seem to have little effect on canine cataplexy (Figure 13.3).

Results obtained in dogs are similar to those reported in narcoleptic patients where selective noradrenaline (norepinephrine) reuptake inhibitors (protryptiline, desimipramine and viloxazine) were found to be effective in treating cataplexy. Animal studies also looked at the pharmacology of alpha and beta adrenergic receptors. Alpha-1 adrenergic antagonists (prazosine, phenoxybenzamine) facilitate whereas alpha-1 adrenergic agonists (methoxamine, cirazoline) suppress cataplexy (Mignot et al., 1989; Nishino et al., 1993b). Serotonin reuptake inhibitors were also found to be effective in treating cataplexy in canine narcolepsy although this effect seems to be less potent than in human narcoleptic patients. As mentioned above, dopamine reuptake inhibitors have little effect on cataplexy but exert a strong alerting effect (Nishino et al., 1996, 1998). In fact, these compounds have little influence on REM sleep, but do produce a reduction in slow-wave sleep and total sleep time (Nishino et al., 1996, 1998) (Figure 13.3).

13.5.5. Deficiency in hypocretin (orexin) transmission in canine and human narcolepsy

Narcolepsy has been described in several animal species including dogs, and most recently in genetically engineered mice models (Table 13.1). Canine narcolepsy is a naturally occurring model, with both spo-



radic (17 breed) and familial forms (Doberman, Labrador and Dachshund). In Doberman pinschers and Labrador retrievers, the disease is transmitted as a recessive autosomal trait with complete penetrance (Mignot et al., 1991).

In 1999, using positional cloning and gene-targeting strategies, two groups independently revealed the pathogenesis of narcolepsy in animals. The lack of the hypothalamic neuropeptide hypocretin/orexin ligand (preprohypocretin/orexin gene knockout mice) (Chemelli et al., 1999) or mutations in one of the two hypocretin/orexin receptor genes (hypocretin receptor 2 [*hcrtr 2*]) in autosomal recessive canine narcolepsy (Lin et al., 1999) was observed to result in narcolepsy (Table 13.1). After extensive screening (especially in familial and early-onset human narcolepsy), it was demonstrated that mutations in hypocretin-related genes are rare: only a single case with early-onset (6 months of age) was found to be associated with a single point mutation in the preprohypocretin gene (Peyron et al., 2000) (Table 13.1).

Despite the lack of genetic abnormalities in the hypocretin system, the large majority (85–90%) of patients with narcolepsy-cataplexy have low or undetectable hypocretin-1 ligand in their cerebrospinal fluid (CSF) (Nishino et al., 2000a, 2001b) (Figure 13.4). This hypocretin deficiency is tightly associated with occurrence of cataplexy and HLA-DQ1*0602

Fig. 13.3. Monoaminergic and cholinergic control of sleepiness and cataplexy in relation to hypocretin input: a schematic perspective. (B) Projections of hypocretin neurons in the rat brain and relative abundances of hypocretin receptor 1 and 2. (A) The stimulation of adrenergic transmission by adrenergic uptake inhibitors potentially reduces cataplexy; this pharmacological property is likely involved in the mode of action of currently used anticataplectic agents (e.g. tricyclic antidepressants). The fact that both presynaptic α -2 autoreceptor stimulation and postsynaptic α -1 blockade aggravate cataplexy is consistent with an inhibitory role of adrenergic transmission in the control of REM sleep atonia. Dopaminergic uptake inhibitors have no effect on cataplexy, although these compounds strongly induce electrocortical arousal. In contrast, D2/3 autoreceptor stimulation aggravates both cataplexy and sleepiness. Since DA uptake inhibitors are reported to be mostly active at the level of mesocortical and mesolimbic DA terminals, DA projections to these regions may be more involved in mediating EEG arousal. Muscarinic M2 stimulation induces behavioral wakefulness and cortical desynchrony in control dogs, while it induces cataplexy in narcoleptic dogs. Although muscarinic antagonists reduce cataplexy in the canine model, attempts to use this class of compounds in humans have not been successful mainly due to the side effects. (B) It was recently revealed that hypocretin-containing neurons project to these previously identified monoaminergic and cholinergic and cholinceptive regions where hypocretin receptors are enriched. Impairments of hypocretin input may thus result in cholinergic and monoaminergic imbalance and generation of narcoleptic symptoms. VTA, ventral tegmental area; SN, substantia nigra; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; PPT, pedunculopontine tegmental nucleus; PRF, pontine reticular formation; BF, basal forebrain; VLPO, ventrolateral preoptic nucleus; LHA, lateral hypothalamic area; TMN; tubero mamillary nucleus; DR, dorsal raphe.

positivity (Kanbayashi et al., 2002a; Krahn et al., 2002; Mignot et al., 2002). Postmortem human studies, although using few brains, have confirmed hypocretin ligand deficiency (both hypocretin 1 and 2) in the narcoleptic brain (Peyron et al., 2000; Thannickal et al., 2000) (Figure 13.4). Hypocretin deficiency has also been observed in sporadic cases of canine narcolepsy (seven of seven currently studied; the result of four cases are reported in Ripley et al. (2001a)), suggesting that the pathophysiology in these animals mirrors most human cases (Table 13.1).

Low CSF hypocretin 1 levels are very specific for narcolepsy when compared to other sleep or neurological disorders (Ripley et al., 2001b; Kanbayashi et al., 2002a; Mignot et al., 2002). The establishment of CSF hypocretin measurement as a new diagnostic

*Table 13.1***Characteristics of narcolepsy in human, dogs and mice.**

		Onset	Symptoms/ phenotype	Transmission	Association with HLA/DLA	Abnormality in hypocretin system
Human	Sporadic	Adolescent	EDS, cataplexy, SP, HH SOREMPs, sleep fragmentation obesity (+)	?	DQB1*0602 (+) (90–95%)	Hypocretin ligand deficiency (~90%)
	Familial	Earlier onset than sporadic cases	EDS, cataplexy, SP, HH SOREMPs, sleep fragmentation obesity (+)	?	DQB1*0602 (+) (75–80%)	Hypocretin ligand Deficiency (~75%)
	Hypocretin mutant (the only one case is identified)	Extremely early onset (6 mo)	EDS severe cataplexy	DeNovo mutant (?) dominant	DQB1*0602 (–)	Mutation in preprohypocretin gene Hypocretin ligand deficiency
Dog	Sporadic (17 breeds)	7 wks–7 yrs	Cataplexy, short sleep latency, SOREMPs	?	(–)	Hypocretin ligand deficiency
	Familial Dobermans, Labradors, Dachshund	Earlier than 6 months	Cataplexy, short sleep latency, SOREMPs	Autosomal recessive 100% of penetrance	(–)	Mutation in Hcrtr2 gene
Mice	Hypocretin KO	~4 wks	Cataplexy, SOREMPs, short sleep latency Obesity (?)	Autosomal recessive 100% of penetrance		Hypocretin ligand deficiency
	Hypocretin cell death Hypocretin/ ataxin-3 transgenic	~6 wks	Cataplexy, SOREMPs, short sleep latency, obesity (++)	Autosomal dominant 100% of penetrance		Hypocretin/dynorphin deficiency
	Hcrtr1 KO		Fragmented sleep obesity (?)	Autosomal recessive 100% of penetrance		Absence of Hcrtr1
	Hcrtr2 KO		Cataplexy, SOREMPs, short sleep latency, obesity (?)	Autosomal recessive 100% of penetrance		Absence of Hcrtr2
	Double receptor KO		Same sleep phenotype as that of preprohypocretin, KOMice, obesity (?)	Recessive for each receptor gene		Absence of Hcrtr1 and 2

EDS, excessive daytime sleepiness; SP, sleep paralysis; HH, hypnagogic hallucination; SOREMPs, sleep onset REM periods; KO, knockout; HLA, human leukocyte antigen; DLA, dog leukocyte antigen.

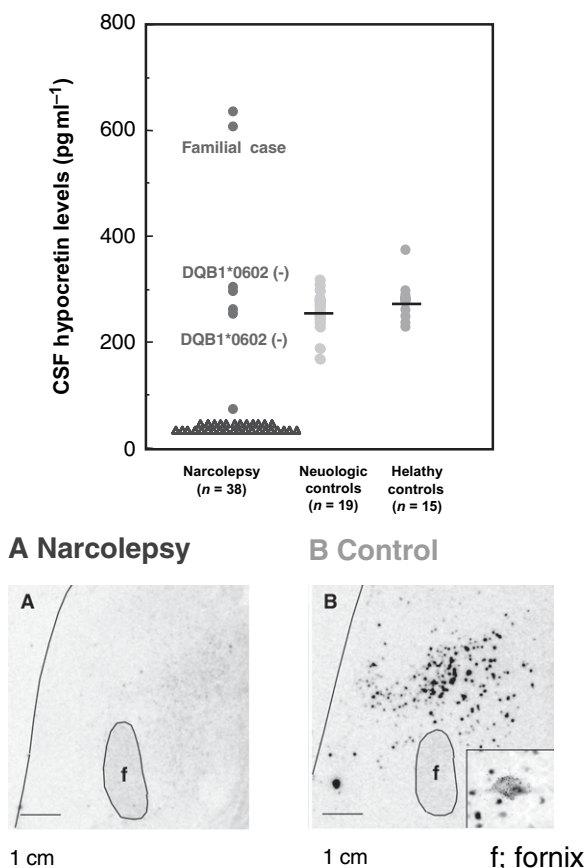


Fig. 13.4. CSF hypocretin levels in narcoleptic and control subjects. Hypocretin mRNA in situ hybridization in the hypothalamus of control and narcoleptic subjects. (A) CSF hypocretin levels are undetectably low in most narcoleptic subjects (84.2%). (B) Preprohypocretin transcripts are detected in the hypothalamus of control (B) but not narcoleptic (Haas et al.) subjects. While melanin concentrating hormone (MCH) transcripts are detected in the same region in both control and narcoleptic sections (data not shown), modified from (Peyron et al., 2000). Note that two HLA DQB1*0602 negative and one familial cases have normal or high CSF hypocretin levels.

tool for human narcolepsy is therefore encouraging. Previously, no specific and sensitive diagnostic test for narcolepsy based on the pathophysiology of the disease was available, and the final diagnosis was often delayed for several years after the disease onset, typically adolescence (Alaila, 1992). Many patients with narcolepsy and related EDS disorders are therefore likely to obtain immediate benefit from this new specific diagnostic test. Also, hypocretin agonists may be promising in the treatment of narcolepsy (see the section for the future directions).

13.5.6. Hypocretin/orexin system and sleep regulation

Hypocretins/orexins were only recently identified (in 1998, only 1 year prior to the cloning of the canine narcolepsy gene). Two independent research groups made this discovery. One group called the peptides 'hypocretin' because of their primary hypothalamic localization and similarities with the hormone secretin (De Lecea et al., 1998). The other group called the molecules 'orexin' after observing that central administration of these peptides increased appetite in rats (Sakurai et al., 1998). Hypocretins-1 and -2 are produced exclusively by a well-defined group of neurons localized in the lateral hypothalamus. The neurons project to the olfactory bulb, cerebral cortex, thalamus, hypothalamus and brainstem, particularly the locus coeruleus (LC), raphe nucleus and to cholinergic nuclei and cholinergic site (such as pontine reticular formation), thought to be important for the sleep regulation (Peyron et al., 1998) (see Figure 13.3).

A series of studies have now shown that the hypocretin system is a major excitatory system that controls the activity of monoaminergic (dopamine, noradrenaline (norepinephrine), serotonin and histamine) and cholinergic systems with major effects on vigilance states (Willie et al., 2001; Taheri et al., 2002). It is thus likely that a deficiency in hypocretin neurotransmission induces an imbalance between these classical neurotransmitter systems, with primary effects on sleep-state organization and vigilance. Indeed, dopamine and/or noradrenaline (norepinephrine) contents have been reported to be high in several brain structures in narcoleptic Dobermans, and in human narcolepsy postmortem brains (Nishino et al., 1997). These changes are possibly due to the compensatory mechanisms, since drugs that enhance dopaminergic neurotransmission, (such as amphetamine-like stimulants and modafinil (for EDS)), and noradrenaline (norepinephrine) neurotransmission, (such as noradrenaline uptake blockers (for cataplexy)), are commonly used to treat symptoms of narcolepsy (Nishino et al., 1997). Histamine is another monoamine implicated in the control of vigilance, and the histaminergic system is also likely to indirectly mediate the wake-promoting effects of hypocretin (Eriksson et al., 2001; Huang et al., 2001; Yamanaka et al., 2002). Interestingly, brain histamine contents both in *hcrtr-2* mutated and ligand-deficient narcoleptic dogs are dramatically reduced (Nishino et al., 2001a) and the involvement of the histaminergic

system for the pathophysiology of narcolepsy and therapeutic applications of histaminergic compounds (Tedford et al., 1999) should be further studied.

How hypocretin tone changes with zeitgeber time was assessed by measuring extracellular hypocretin-1 levels in the rat brain across 24 hours in the CSF and using in vivo dialysis (Fujiki et al., 2001b; Yoshida et al., 2001; Zeitzer et al., 2003). The results demonstrate the involvement of a slow diurnal pattern of hypocretin neurotransmission regulation (as in the homeostatic and/or circadian regulation of sleep). Hypocretin levels increase during the active periods and are highest at the end of the active period, and the levels decline with the onset of sleep. Furthermore, sleep deprivation increases hypocretin levels (Fujiki et al., 2001b; Yoshida et al., 2001; Zeitzer et al., 2003).

How hypocretin neuronal activity varies across different sleep stages is still unknown. Regardless of the firing pattern of the hypocretin neurons, however, our results suggest that basic hypocretin neurotransmission fluctuates across the 24 hours, and slowly builds up during the active period. Adrenergic LC neurons are typical wake-active neurons involved in the vigilance control, and it has been recently demonstrated that basic firing activity of wake-active LC neurons also significantly fluctuate among different circadian times (Aston-Jones et al., 2001).

Several acute manipulations such as exercise, low glucose utilization in the brain, as well as forced wakefulness, increase hypocretin levels (Willie et al., 2001; Yoshida et al., 2001; Wu et al., 2002). It is therefore hypothesized that a build-up/acute increase of hypocretin levels may counteract sleep propensity that typically builds up during the daytime and during forced wakefulness (Yoshida et al., 2001). Due to the lack of the build-up of hypocretin tone, narcoleptic subjects may not be able to stay awake for a prolonged period and do not respond to various alerting stimuli. Conversely, the release of the hypocretin tone at sleep onset may contribute to the profound deep sleep that normally inhibits REM sleep at sleep onset, and the lack of this system in narcolepsy may release REM sleep at sleep onset.

13.6. Treatments of narcolepsy

Non-pharmacological treatments (i.e., by behavioral modification), are often reported to be useful additions to the clinical management of narcoleptic patients (Rogers, 1984; Roehrs et al., 1986; Thorpy and Goswami, 1990; Mullington and Broughton, 1993). Regular napping usually relieves sleepiness for 1–2

hours (Roehrs et al., 1986) and is the treatment of choice for some patients, but has often negative social and professional consequences. Exercising to avoid obesity, keeping a regular sleep–wake schedule, having a supportive social environment (e.g., patient group organizations and support groups) are also helpful. In almost all cases, however, pharmacological treatment is needed; indeed, 94% of patients reported using medications in a recent survey by a patient group organization (American Narcolepsy Association, 1992).

13.6.1. Pharmacological treatment of EDS with amphetamine-like compounds

EDS is usually treated using amphetamine-like CNS stimulants or modafinil, a novel wake-promoting compound unrelated to amphetamines (Table 13.2). The most commonly used amphetamine-like compounds are methamphetamine, d-amphetamine, methylphenidate, pemoline and mazindol. The most important pharmacological property of these compounds is to release catecholamines, namely dopamine and norepinephrine (noradrenaline). Amphetamine-like compounds also share the property of blocking the reuptake and the degradation of these monoamines (monoamine oxidase (MAO) inhibition at high doses). All these properties presynaptically enhance dopamine transmission, which are likely to contribute to the EEG arousal effects of amphetamines.

The clinical use of stimulants in narcolepsy has been the subject of a recent American Sleep Disorders Association (ASDA) Standards of Practice publication (American Sleep Disorders Association, 1994). Typically, the patient is started at a low dose, which is then increased progressively to obtain satisfactory results (Table 13.2). This final dose varies widely from patient to patient (American Sleep Disorders Association, 1992). Minor side effects such as headaches, irritability, nervousness, tremors, anorexia, palpitations, sweating and gastric discomfort are common (Table 13.2).

Amphetamine was used for the first time to treat narcolepsy in 1935 (Prinzmetal and Bloomberg, 1935), only 8 years after Alles found its stimulant effect (Alles, 1933). Both the l- and d- isomers and the racemic mixture (dl-amphetamine) have been used for the treatment of narcolepsy, but the d- isomer was found to be a more potent stimulant compound (Parkes and Fenton, 1973; Parkes, 1985; Kanbayashi et al., 1997). D-amphetamine is the second most

Table 13.2

Current pharmacological treatment for human narcolepsy.

Compound	Usual daily doses	Side effects/notes
Wake-promoting compounds for EDS		
Sympathomimetic stimulants		
Non- D-amphetamine sulfate	5–60 mg	Irritability, mood changes, headaches, palpitations, tremors, excessive sweating, insomnia
Methylphenidate HCl	10–60 mg	Same as amphetamines, less reduction of appetite or increase in blood pressure
Pemoline	20–115 mg	Less sympathomimetic effect, milder stimulant slower onset of action, occasionally produces liver toxicity
Amphetamine wake-promoting compounds		
Modafinil	100–400 mg	No peripheral sympathomimetic action. headaches, nausea
Antidepressant compounds for cataplexy		
Imipramine	10–100 mg	Dry mouth, anorexia, sweating, constipation, drowsiness
Desipramine	25–200 mg	Effects and side effects similar to those of imipramine
Clomipramine	10–150 mg	Digestive problem, dry mouth, sweating, tiredness, impotence
Fluoxetine*	40–75 mg	Long half life (60 hour), no anticholinergic or antihistaminergic effects, fewer side effects, nausea, dry mouth

* Selective serotonin reuptake inhibitors (SSRIs). Clinical trial results using these compounds (Schachter and Parkes, 1980; Langdon et al., 1986; Montplaisir and Godbout, 1986; Schrader et al., 1986) suggests that SSRIs are effective for the treatment of cataplexy or other REM-related symptoms with less side effects than classical tricyclic antidepressants. It is however, still not conclusive whether SSRIs can be recommended as the first line of treatment, since SSRIs are usually less potent than tricyclic antidepressants (Schrader et al., 1986).

frequently prescribed stimulant in the USA for the treatment of EDS associated with narcolepsy (methylphenidate is the most common) (American Sleep Disorders Association, 1992).

L-amphetamine is also used for the treatment of narcolepsy in some European countries (dose range 20–60 mg) but is not available in the USA. However, l-amphetamine probably has no advantage over d-amphetamine in the treatment of narcolepsy as it is a slightly weaker stimulant (Parkes, 1976).

Methamphetamine is the most efficacious and most potent amphetamine derivative available. The addition of a methyl group makes this derivative more lipophilic, thus increasing CNS penetration and providing a better central over peripheral profile. The widespread misuse of methamphetamine has led to severe legal restriction on its manufacture, sale and prescription in many countries (Parkes, 1976).

Methylphenidate was introduced for the treatment of narcolepsy by Yoss and Daly almost 50 years ago (Yoss and Daly, 1959). It is now the most commonly prescribed stimulant medication in the US, with 46% of narcoleptic patients using the compound on a regular basis (American Sleep Disorders Association, 1992). Part of its popularity is due to its relatively

short duration of action (approximately 3–4 hours). This property allows narcoleptic patients to use the compound on an 'as needed' basis while still keeping open the possibility of napping. The compound is also reported to produce fewer psychotic complications at high doses (Pawluk et al., 1995).

Pemoline is usually better tolerated than methamphetamine or d-amphetamine in terms of side effects, but it is also less efficacious and less potent, and occasionally produces liver toxicity. The half-life of pemoline is 16–18 hours, and the long duration of action of pemoline may be associated with better compliance in narcoleptic patients (Rogers et al., 1997). Pemoline most selectively blocks dopamine reuptake and only weakly stimulates dopamine release. Pemoline has recently been withdrawn from the market in most countries because it produces hepatic failure on rare occasions. Pemoline is often prescribed in Japan, and it may still be considered when other treatments fail.

Mazindol is less frequently used due to its weak CNS stimulant activity (Iijima et al., 1986). It is a weak releasing agent for dopamine, but it also blocks dopamine and noradrenaline (norepinephrine) reuptake with high affinity (Nishino et al., 1998). Mazindol is effective for both excessive daytime sleepiness

and cataplexy (Iijima et al., 1986). Mazindol has also been taken off the market in most countries as a consequence of reported severe side effects in related appetite-suppressant substances, in particular fenfluramines: pulmonal hypertension and valvular regurgitation (Ryan et al., 1999; Rich et al., 2000). However, there are patients experiencing a better therapeutic response on mazindol compared to any other drug. For this reason closely monitored treatment seems warranted in selected cases.

Modafinil (200–400 g), 2-diphenyl-methyl-sulfinyl-acetamide, is a newly available long-acting wake-promoting drug. An alpha-1 agonistic action was presumed initially (Lin et al., 1992), but questioned later (Mignot et al., 1994a; Shelton et al., 1995). Two recent studies have outlined its action on dopamine. A first study (Nishino et al., 1998) conducted in narcoleptic dogs compared the activity of dopamine, noradrenaline (norepinephrine) reuptake inhibitors, d-amphetamine and modafinil on wakefulness and showed that the *in vivo* efficiency of the dopamine reuptake inhibitor, d-amphetamine and modafinil on wakefulness, was significantly correlated to their *in vivo* affinity for the dopamine transporter (DAT), whereas noradrenaline (norepinephrine) reuptake inhibitors had little effect on wakefulness. A second study (Wisor et al., 2001) has shown that dopamine transporter knock-out mice did not respond to the awakening action of modafinil, methamphetamine and of a selective blocker of the dopamine transporter called GBR 12909, thereby indicating the key role played by the dopamine transporter in the stimulant action of amphetamine and of modafinil. In contrast, a direct action on hypocretin-release (Chemelli et al., 1999) is unlikely, because hypocretin-deficient narcoleptic patients do improve using modafinil. The efficacy of modafinil has been studied in large randomized placebo-controlled studies and is probably comparable to that of other stimulants, although direct comparisons are lacking and some patients prefer amphetamines (Broughton et al., 1997; US Modafinil in Narcolepsy Multicenter Study Group 1998, 2000). The main advantage is the lower frequency and severity of side effects compared with stimulants (Bastuji and Jouvet, 1988; Billiard 1990; Broughton et al., 1997; Fry, 1998; US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000). Most notably, patients feel less irritable and agitated (Bastuji and Jouvet, 1988). Modafinil may lower plasma estrogen concentration in women using oral contraceptives (Robertson et al., 2000). Therefore, dose adjustment of the contraceptives is advised.

13.6.2. Pharmacological treatment of cataplexy

In contrast to their vigilance-enhancing effect, stimulants have little effect on cataplexy. Since the 1960s, it has been known that imipramine is very effective for reducing cataplexy (Akimoto et al., 1960). Together with protryptiline and clomipramine, these tricyclic antidepressants are now the most commonly used anticataplectic agents (American Sleep Disorders Association, 1992) (Table 13.2). Other antidepressant compounds of the tricyclic family have also been used with some success (Table 13.2).

The use of tricyclic antidepressants in the treatment of cataplexy is hampered by a number of problems. The first is the relatively poor side effect profile of most tricyclic compounds. These are mostly due to their anticholinergic properties, thus leading to dry mouth (and associated dental problems), tachycardia, urinary retention, constipation and blurred vision (see Table 13.2). Additional side effects are weight gain, sexual dysfunction (impotence and/or delayed orgasm), tremors, antihistaminic effects leading to sedation and occasionally orthostatic hypotension due to the alpha-1 adrenergic blockade of some compounds. In this respect, protryptiline is often preferred, due to its previously reported mild stimulant effect (Henry et al., 1988). Night-time sleep might also become more disturbed due to increased muscle tone and leg movements (Raynal, 1976; Thorpy and Goswami, 1990).

The cardinal pharmacological property of tricyclic antidepressants is their ability to inhibit the reuptake of norepinephrine (noradrenaline) (and epinephrine (adrenaline)) and serotonin (Baldessarini, 1983). The degree of uptake inhibition of norepinephrine (norepinephrine) and serotonin is quite variable depending on the compound and on the existence of active metabolites (mostly active on adrenergic uptake) (Baldessarini, 1983). Additionally, some tricyclic compounds (such as protryptiline), are also weak dopamine reuptake inhibitors (Baldessarini, 1983). The introduction of newer antidepressants with selective serotonergic uptake inhibition properties and no anticholinergic effects (such as fluoxetine, fluvoxamine, paroxetine, sertraline, femoxamine, zimelidine and trazodone), has raised hope that the control of cataplexy can be achieved with fewer side effects, but in general clinicians have been less impressed with the anticataplectic effects of the serotonergic compounds (Langdon et al., 1986; Montplaisir and Godbout, 1986; Schrader et al., 1986). Among these compounds, fluoxetine at the 40–75 mg dose is a viable

alternative to tricyclic compounds (Langdon et al., 1986). Fluoxetine has a good side effect profile and induces anorexia rather than weight gain, a significant advantage for some patients.

In addition to the antidepressants listed in Table 13.2, MAOIs (monoamine oxidase inhibitors) are known to potently reduce REM sleep, and are therefore candidate anticataplectic agents. However, these compounds are less often used due to their poor safety profile. Selective or reversible MAOIs have recently become available, but clinical trials of these compounds at a large scale are still not available (Nishino and Mignot, 1997).

Finally, gamma-hydroxybutyrate (GHB) or sodium oxybate, taken in the evening and once again during the night, reduces cataplectic attacks and other manifestations of REM sleep (Broughton and Mamelak, 1979). Its elimination half-life is 1–2 hours. GHB increases NREM sleep stages 3 and 4, decreases night-time awakenings and consolidates fragmented REM sleep (Broughton and Mamelak, 1980). Recent studies have demonstrated a measurable improvement in patient's reported daytime sleepiness. GHB given at bedtime and with a second dosage upon awakening during the night at least 3 hours before the rising time may also consolidate nocturnal sleep. If the patient wakes up during the night, he may experience dizziness and confusional states. Some patients also experience depressive mood while treated with GHB. One problem with GHB is the non-medical use of this compound to elicit altered state of consciousness with important social and legal implications. Its use has recently been approved by the FDA in the USA.

13.6.3. Treatment of sleep paralysis and hypnagogic hallucinations

The treatment of these two symptoms is much less well codified. Hypnagogic hallucinations can be quite bothersome, and often occur in patients who also suffer from frequent nightmares. As they are a manifestation of sleep-onset REM sleep, the compounds that suppress REM sleep are usually helpful in alleviating this symptom, and tricyclic antidepressant treatment has been reported to have some beneficial effects (Takahashi, 1976). Sleep paralysis only rarely requires treatment, but tricyclic antidepressants are also very effective for preventing this symptom. Recently, high doses (60 mg qd) of fluoxetine have been advocated as a very active treatment for isolated sleep paralysis (Koran and Raghavan, 1993). Gamma-hydroxybu-

tyrate (GHB) is also effective in suppressing both hypnagogic hallucinations and sleep paralysis (Mamelak et al., 1986).

13.6.4. Treatment of disturbed nocturnal sleep

Insomnia is a major complaint in narcoleptic subjects. Several studies reported that benzodiazepine hypnotics are effective in consolidating night-time sleep in narcoleptic patients (Thorpy et al., 1992). GHB (a compound with REM- and SWS-inducing properties), has also been used for consolidating night-time sleep, an effect that leads to decreased EDS and cataplexy the following day (Mamelak et al., 1986). Alternatively, this short half-life sedative hypnotic may induce rebound insomnia-like status the following day and produce alertness during daytime. Due to its positive effects on libido, and its SWS-enhancing properties and the reported connection between SWS and growth hormone release, the drug is, unfortunately, widely abused by athletes and other populations (Chin et al., 1992). The compound has also been reported to increase periodic leg movements in narcoleptic patients (Bédard et al., 1989).

13.7. Future Directions

- (1) The observation of low CSF hypocretin-1 levels is very specific for narcolepsy when compared to other sleep or neurological disorders. Measuring CSF hypocretin-1 is thus rapidly becoming a new diagnostic tool for the condition. The availability of this test is also challenging our view of the nosology of narcolepsy. As emphasized by Honda (1988), narcolepsy with cataplexy may be a more homogeneous etiological entity, as reflected by low CSF hypocretin, to be differentiated from narcolepsy without cataplexy or the related syndrome of idiopathic hypersomnia, with generally normal hypocretin levels. In the 2nd revision of International Classification of Sleep Disorders, narcolepsy with cataplexy and narcolepsy without cataplexy will be coded separately. Low CSF hypocretin-1 will also be considered as a positive diagnostic result for narcolepsy-cataplexy. Although a recent study reported that plasma hypocretin-1 levels in narcolepsy were significantly lower than those of control subjects (Higuchi et al., 2002), there has been considerable debate about the origin and nature of the hypocretin signal in the blood and whether the blood

hypocretins could reliably be measured. It is thus uncertain whether CSF measures will be replaced with plasma hypocretin measures in the future (Nishino and Mignot, 2002).

- (2) Even when a very strict criteria for cataplexy is applied, about 10% of narcolepsy-cataplexy patients have normal CSF hypocretin-1 (Nishino et al., 2001b; Krahn et al., 2002; Mignot et al., 2002). Whether or not hypocretin neurotransmission is abnormal in these rarer cases is unknown. Considering the fact that hypocretin production and hypocretin neurons appeared to be normal in *hcrtn* 2-mutated narcoleptic Dobermans (Ripley et al., 2001a), it is possible that deficiencies in hypocretin receptors and a downstream pathway may exist in some of these patients. However, this can not be tested currently. Similarly, it is not known whether narcoleptic subjects without cataplexy simply have milder neuropathology. Narcoleptic subjects without cataplexy may have sufficient hypocretin production to maintain normal CSF levels and stave off cataplexy, but the partial loss may still be great enough to produce sleepiness. Hypocretin levels as measured in lumbar CSF may imperfectly reflect central hypocretin status (Fujiki et al., 2001b; Salomon et al., 2003; Zeitzer et al., 2003), in contrast to cisternal CSF levels. It is also possible that some hypocretin non-deficient hypersomnia patients would show altered responses after various manipulations that normally increase hypocretin levels (i.e. exercise, sleep deprivation, food restrictions), if this was testable in humans.
- (3) Since most narcolepsy-cataplexy subjects (about 90% of idiopathic cases), are hypocretin ligand deficient, hypocretin agonists may be promising in the treatment of narcolepsy. In this respect, the development of small-molecular and centrally penetrant (i.e. non-peptide) hypocretin agonists is likely to be necessary (Fujiki et al., 2001a). A consideration is the possible absence of functional hypocretin receptors many years after the disease onset. Cell transplantation, using embryonic hypothalamic cells or neural stem cells, and gene therapy (preprohypocretin/orexin gene transfer using various vectors) might also be used to cure the disease in the future.
- (4) Although cataplexy is now known to be tightly associated with hypocretin deficiency in narcolepsy, the pathophysiological mechanisms underlying the occurrence of cataplexy are largely unknown. The observation that prepubertal narcolepsy-cataplexy cases are almost always hypocretin deficient suggests that hypocretin deficiency occurs at cataplexy onset (Kanbayashi et al., 2002b). Considering the fact that acute ablation of hypocretin ligands by focal hypothalamic lesions associated with immune-related inflammatory encephalopathies, such as in multiple sclerosis and acute disseminated encephalomyelitis (ADEM), do rarely induce cataplexy (Kubota et al., 2002; Kanbayashi, personal communication), chronic and selective loss of hypocretin ligand may be required to exhibit cataplexy. The mechanisms of emotional induction of cataplexy remain to be studied.
- (5) The causes/mechanisms of the ligand deficiency in human narcolepsy remain unknown, but are believed to be due to an acquired cell death of hypocretin neurons (Thannickal et al., 2000). This is likely because: (1) the onset of most sporadic cases of human narcolepsy is around puberty, later than those for the genetic animal models; (2) the only known human hypocretin gene mutation had a very early onset at 6 months of age; and (3) postnatal ablation of hypocretin neurons in mice (Hara et al., 2001) induces a phenotype that most resembles human narcolepsy. The mechanisms of the hypocretin cell death, especially in relation to HLA positivity, should therefore be determined to prevent and/or rescue the disease. The current hypothesis, that narcolepsy is an autoimmune disease, is still unsubstantiated.
- (6) Hypocretins are involved in various other hypothalamic functions such as feeding, energy homeostasis and neuroendocrine regulation (Willie et al., 2001; Taheri et al., 2002). Narcolepsy now appears to be a more complex condition than simply a sleep disorder (Nishino, 2003). The disease is likely to be associated with various hypothalamic dysfunctions due to hypocretin deficiency. Narcolepsy is thus an important model to study the fundamental hypothalamic mechanisms linking sleep regulation, energy homeostasis and/or feeding (Nishino, 2003).

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CHAPTER 14

The syndromes of excessive daytime somnolence (excluding narcolepsy and sleep-related breathing disorders)

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14.1. Introduction

‘Somnolence’ (or the synonymous terms ‘sleepiness’ or ‘drowsiness’) may be defined in several ways. Kleitman (1963) characterized sleepiness as ‘a succession of intermediate states, part wakefulness, part sleep, in varying proportions’. Other definitions of sleepiness include, ‘a manifestation of a physiological drive for sleep (having) objective and subjective components’ (Aldrich, 2000) and ‘the subjective feeling state of sleep need’ (Broughton, 1989b). Broughton has suggested that, in fact, there may be three types of sleepiness: NREM sleepiness, REM sleepiness and de-arousal sleepiness, arising, respectively from NREM sleep pressure, REM sleep pressure and impaired reticulocortical waking processes (Broughton 1982, 1992). For a detailed discussion of the concept that sleepiness represents a heterogeneous collection of brain states, see the excellent article by Pivik (1991). As a useful operational definition, sleepiness may be thought of as a physiologic state which promotes the onset of sleep under permissible conditions, and which is reversed or satiated (although not always) by the attainment of adequate sleep. While the state of somnolence may be defined along subjective or behavioral lines, it may also be characterized by several associated physiologic changes. Breathing slows and becomes more regular, heart rate, blood pressure and core body temperature tend to decrease, there is a trend toward decreased symp-

thetic and increased parasympathetic activity, and saccadic eye movements decrease as slow eye movements increase.

However we choose to denote it, somnolence is a complex state, which is impacted by multiple determinants. Such factors as quantity and quality of prior sleep, circadian time, drugs, attention, motivation, environmental stimuli and various medical, neurological and psychiatric conditions may contribute to the somnolent state. Obviously, somnolence is welcomed when sleep is desired, but it often becomes an unwanted symptom at other times. The International Classification of Sleep Disorders, Revised (ASDA, 1997) classifies the severity of sleepiness as follows:

- (1) Mild sleepiness: sleep episodes are present only during times of rest or when little attention is required, such as riding as a passenger in a car, lying down in a quiet room, reading or watching television. Mild sleepiness may not be present every day. The symptoms of mild sleepiness produce a minor impairment of social or occupational function.
- (2) Moderate sleepiness: sleep episodes are present daily and occur during very mild physical activities requiring, at most, a moderate degree of attention, such as driving, attending concerts, movies, the theater or group meetings. The symptoms of moderate sleepiness produce a moderate impairment of social or occupational function.
- (3) Severe sleepiness: sleep episodes are present daily and at times of physical activities which require mild and moderate attention, such as eating, direct personal conversation, driving, walking and physical activities. The symptoms of severe sleepiness produce a marked impairment of social or occupational function.

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14.2. Somnolence and society

Excessive daytime somnolence (EDS) is a common symptom. According to the National Sleep Foundation (NSF) 2000 Omnibus Sleep in America Poll: 'A sizable proportion of adults (43%) report that they are so sleepy during the day that it interferes with their daily activities a few days *per month* or more; and, one out of five (20%) experience this level of daytime sleepiness at least a few days *per week* or more'. The actual prevalence of daytime somnolence may be even higher, since some individuals deny or fail to recognize the state, even though their performance may be impaired. EDS not only detracts from quality of life but also exacts a significant toll in terms of productivity at work. According to the same poll, 51% of the American workforce reports that sleepiness on the job interferes with the amount of work they get done, and 40% admit that the quality of their work suffers when they are sleepy. Two-thirds of adults say that sleepiness interferes with their concentration and makes handling stress on the job more difficult. EDS is also responsible for the occurrence of accidents. According to NSF's 2000 poll, 51% of adults report driving while drowsy during the prior year. Each year, in the United States, more than 50 000 motor vehicle accidents are attributed to driving while sleepy (Mahowald, 2000). A recent study showed that the decrease in driving performance due to sleepiness can be worse than that observed with driving while intoxicated with alcohol (Powell et al., 1999). In a recent study of professional truck drivers, 40% of long-haul drivers reported difficulties staying alert during at least 20% of their drives, and 20% admitted to dozing off at least twice while driving (Hakkanen and Summala, 2000).

14.3. Neurological substrates of somnolence

The neurophysiological underpinnings of the somnolent state are not well defined. It is unclear whether alertness and sleepiness are subserved by separate brain mechanisms or represent gradations of state within a single system. Likewise, it is not known whether the substrates of normal physiological sleepiness and pathological sleepiness are the same. Numerous areas of the brain are known to participate in the initiation and maintenance of sleep and alertness, including the brainstem reticular activating system, locus coeruleus, dorsal raphe and other brainstem nuclei, basal forebrain, thalamus, hypothalamic loci and cortex (McCarley, 1999). It remains to be deter-

mined whether and how these and other brain structures act and interact to produce EDS in various disorders.

Many neurotransmitters and peptides are also known to play significant roles in the expression of alertness and sleep, including noradrenaline (norepinephrine), serotonin, dopamine, GABA, acetylcholine, histamine, glutamate, adenosine, substance P, interleukin-1, neuropeptide Y and prostaglandins (Zoltoski et al., 1999), and the list continues to grow. The recently discovered hypocretins (de Lecea et al., 1998; Peyron et al., 1998) appear to have central importance in animal and human narcolepsy (see Chapter 13); as further work in this area proceeds, it will be interesting to see whether these substances are involved in other clinical disorders associated with EDS.

14.4. Evaluation of somnolence

The evaluation of EDS is problematic for at least two reasons. First of all, the description of the symptom by patients may be misleading, as they may use other terms, such as 'fatigue', 'tiredness' or even 'weakness' to describe sleepiness, thus leading to potential semantic confusion. It is important for the examiner to be precise in eliciting the medical history, since the pathways for evaluating and treating sleepiness may diverge considerably from those addressing other symptoms, such as physical fatigue or lack of strength. Such questions as: 'Do you take naps (or would you, if given the opportunity)?', 'Do you doze easily in passive or monotonous situations?', 'Do you sleep later on weekends and holidays than during the work week?' and 'How long does it take to fall asleep at night?' may help the physician to distinguish true sleepiness from other, less-specific complaints.

The second problem with evaluating EDS is that the physiologic state is not easily measured. Several methodological questions must be addressed. Which variables best define the state of sleepiness? Should we focus on behavior? Performance? Central or autonomic nervous system activity? Where should subjects be monitored? Under what conditions and for what duration? Despite these difficulties, several tools have been developed for the task, using introspective scales, tests of performance or behavior or measurements of physiological parameters.

14.4.1. Subjective measures

Subjective scales require individuals to rate their own degree of sleepiness. To do this well, subjects must have

insight into their symptom and the capacity to dissociate sleepiness from other problems with performance. The Stanford Sleepiness Scale (SSS) (Hoddes et al., 1972) and the Karolinska Sleepiness Scale (Akerstedt, 1996) assess the momentary degree of alertness/sleepiness. These scales are useful in tracking symptoms during a given time epoch; they are less helpful in examining more global feelings of sleepiness.

The Epworth Sleepiness Scale (ESS) (Johns, 1991) offers a more appropriate method for assessing 'overall' sleepiness. It consists of eight questions, each scored with a degree of severity ranging from 0 to 3, asking the subject to rate the likelihood of actually falling asleep in specific situations. Although useful in clinical practice, this test has several limitations. For one thing, it asks subjects to imagine themselves in situations, which they may actually experience rarely or never. Semantic issues also may lead to confusion. Circadian variations in alertness are not captured with this scale. The eight questions are equally weighted, despite obvious differences in significance (for example falling asleep while lying down in the afternoon carries the same weight as falling asleep while stopped in traffic). Finally, there may be individual variation of scores over time. Generally, the ESS is more reliable when scores are abnormally high. Many sleepy subjects may score in the normal range because they do not actually fall asleep, despite their drowsy state, either because of effective compensatory measures or lack of opportunity.

14.4.2. Performance tests

These tests have been widely used, but many of them demonstrate score changes with habituation to the task. Performance alone may not always be the best indication of sleepiness, as motivation may temporarily override a performance decrement. Compensatory strategies may also be invoked; for example, an increase in errors may be avoided at the expense of a slower pace. Individuals might also accept lower levels of achievement.

Reaction time tests, simple or complex, are less problematic, and they have been more extensively used to investigate sleepiness. The presence of 'lapses' during reaction time tests provides an index of sleepiness. Computerized systems have been developed that can give immediate results. One example of such a system is the 'psychomotor-vigilance-task' (Dinges and Powell, 1985). It is administered after 2 minutes of training, and each test itself lasts 10 minutes. A small

rectangle appears at irregular intervals on a screen, and the subject must press a button to cause this figure to disappear as fast as possible. The computer program calculates different values, such as the longest response, the ten longest responses, the variability in speed of response, the overall mean, etc. This test is easy to administer and can be repeated several times per day to investigate the effect of circadian rhythm on performance and its impairment.

14.4.3. Pupillography

More objective tests, relying on measurement of physiologic parameters, are widely available. Pupillography (Schmidt and Fortin, 1982), based on changes in pupil stability with level of alertness, has been used to assess sleepiness. A normal alert individual sitting quietly in total darkness can maintain a stable pupil diameter usually well above 7 mm for at least 10 minutes without pupillary oscillation. With increased sleepiness, marked changes in pupillary stability and extent of diameter oscillation occur. Special equipment is needed (the TV pupillometer), patients must stay in darkness for 15 minutes before beginning the test, and the test usually lasts 10 to (more commonly) 20 minutes, while flashes of light are administered. One of the major problems with pupillography, once autonomic nervous system dysfunction has been eliminated, is eyelid drooping, which covers the pupil. This is a significant problem, as sleepiness is associated with eyelid drooping (in fact, eyelid drooping observed in standardized conditions and monitored with a mini-camera centered on the pupil has also been suggested and investigated as a means of evaluation of daytime sleepiness).

14.4.4. Polygraphic monitoring

Several different polygraphic approaches have been proposed to measure sleepiness. The best known is the multiple sleep latency test (MSLT) (Carskadon et al., 1986), which is discussed in detail elsewhere in this volume. It consists of four or five 20-minute nap opportunities administered in standardized conditions every 2 hours starting at 09:00 hours. Subjects are monitored with EEG, EMG and electro-oculogram (EOG) in a quiet, darkened comfortable bedroom, lying on a bed with eyes closed and asked to not resist sleep. The time to sleep onset after lights out (the sleep latency) is measured. The mean sleep latency is calculated (normal in adults is longer than 10 minutes); pathology

is always present if the latency is 8 minutes or shorter. There is a gray zone between 8–10 minutes, and most investigators will consider results in that zone to be indicative of mild dysfunction. To be of optimal diagnostic value, the MSLT should be preceded by an overnight polysomnogram to assure adequate total sleep time during the prior night, and to rule out disruptions of nocturnal sleep as a cause of daytime sleepiness. If sleep onset occurs during a 20-minute nap, the subject is observed for an additional 15 minutes to see if REM sleep emerges. The presence or absence of sleep-onset REM periods (SOREMPS) is important in regard to etiologic diagnosis (particularly with narcolepsy). This is valid only if the nocturnal polysomnogram has eliminated the presence of another syndrome that may be responsible for the daytime sleepiness and if other causes for SOREMPS, such as delayed bedtime or recent withdrawal from REM sleep suppressing drugs, do not confound the picture.

The maintenance of wakefulness test (MWT), which is also discussed in detail in this volume, is closely related to the MSLT in its methodology (Doghramji et al., 1997). The MWT also consists of four or five tests performed during the daytime at 2-hour intervals and after a night of polysomnographic monitoring, but the instructions given to the subject are different from those given during the MSLT. The subject is asked to try to remain awake while semi-reclined with eyes closed in a quiet, darkened room. Accumulation of normative data has shown that normal subjects, with adequate amounts of sleep during the prior night, have long sleep latencies and daytime periods during which sleep is unlikely (forbidden zones) and others where sleep has a greater chance to occur due to the circadian propensity to sleep. The MWT naps usually last 20 minutes (40 minute naps have also been used, but most of the published data have been collected using a 20-minute protocol). One of the problems with the MSLT is the meager amount of normative data. It is recommended that 10 minutes be used as the demarcation between normal and abnormal. However, the MWT is often used to assess appropriateness of a treatment, and it is unknown, for example, if a score of 11 minutes on the MWT should be accepted as an indication that a sleepy airline pilot or a sleepy driver should be given a 'clean bill of health' and allowed to perform their usual activities. The MWT is often requested by bureaucratic bodies in an attempt to assess disability or fitness for certain occupations or activities.

It is also possible to monitor subjects for more prolonged periods (24 hours or longer). This approach offers the advantages of measuring fluctuations of

brain state across the circadian period during normal activities (Broughton, 1989a).

14.4.5. Measurements of brain activity

As computing power continues to become less expensive and more accessible, the measurement of brain states, such as sleepiness, will be possible using more complex tools. Spectral analysis of EEG (Ogilvie and Simons, 1992), event-related potentials (Broughton, 1982), cyclical alternating patterns (CAP) (Terzano et al., 2000) and analytical techniques derived from chaos theory (Kim et al., 2001), all offer exciting new windows for viewing and understanding patterns of brain electrical activity. Likewise, the field of brain imaging, using methods such as PET, SPECT and fMRI (Wu et al., 1991; Starbuck et al., 1998; Smith et al., 2002), will assume an increasingly important role in advancing our understanding of alertness and somnolence.

In summary, several methods are available for assessing somnolence. All of them have strengths and limitations, and more than one may be useful in evaluating a given subject.

14.5. Syndromes of sleepiness

14.5.1. Insufficient sleep

The most common cause of daytime sleepiness is insufficient sleep, which may reflect poor sleep hygiene (behaviors impacting sleep) or self-imposed or socially dictated sleep deprivation. Again citing the National Sleep Foundation 2000 Omnibus Sleep in America Poll: 'Only one-third (33%) of adults say they get at least the recommended 8 hours or more of sleep per night during the workweek; and one-third (33%) of adults say they get fewer than 6.5 hours of sleep per night during the workweek'. It should be noted that the proverbial 8-hour sleep requirement has been challenged; recent epidemiological evidence suggests that the actual sleep requirement in the general population may be closer to 7 hours (Ohayon et al., 1997). In any event, an individual who gets insufficient sleep will accumulate a sleep-debt over time. The price to be paid usually takes the form of daytime dysfunction and may include cognitive impairment, disordered mood, sub-optimal performance, physical fatigue or mental drowsiness (Pilcher and Huffcutt, 1996; Dinges et al., 1997).

It is important to recognize the variation in sleep need among individuals. A total of 7–8 hours of sleep

may be sufficient for most individuals but inadequate to prevent sleep deprivation in those who require more. Adolescents generally need more sleep than adults, but are even less likely to obtain adequate amounts (Carskadon, 1990; Mercer et al., 1998). 'Long sleepers' (ASDA, 1997) require more sleep than their peers, sometimes 10 or more hours per 24-hour period. Their sleep quality and structure are essentially normal, but they suffer from sleep deprivation if they obtain less sleep than is dictated by their physiologic requirement. Sleep diaries (detailed patient accounts detailing sleep timing and characteristics) are helpful in documenting patterns of insufficient sleep; naps and longer sleep times on weekends are important clues.

14.5.2. Fragmented sleep

Sleep quality is as important as sleep quantity. Continuity appears to be an essential feature of refreshing sleep, and EDS may result from sleep fragmentation (Stepanski, 2002). Sleep may be fragmented by periods of wakefulness, which are obvious to the patient or bed-partner, but more occult fragmentation results from brief arousals, which may be unrecognized. The causes of sleep fragmentation are various and will be addressed below. Sleep-related breathing disorders, a very prevalent cause of sleep fragmentation, are discussed elsewhere in this volume.

14.5.2.1. Periodic limb movements of sleep

Periodic limb movements of sleep (PLMS) represent a very common cause of sleep fragmentation. Originally termed 'nocturnal myoclonus' by Symonds (1953), these are repetitive involuntary movements (not true myoclonus) of the limbs (usually the legs but occasionally the arms), which occur during sleep. The pathogenesis of the movements is unclear; motor oscillators have been proposed in both brain (Bucher et al., 1997; Tergau et al., 1999) and spinal cord (Lee et al., 1996; Trenkwalder et al., 1996). PLMS appear predominately in light NREM sleep, are less common in slow-wave sleep (SWS) and are rarely seen in REM sleep. The movements may or may not be associated with brief EEG arousals. Traditionally, it has been felt that in sufficient quantity, PLMS fragments sleep and may give rise to either insomnia or hypersomnia. Patients with PLMS and hypersomnia (without another apparent cause) are said to have periodic limb movement disorder (PLMD). However, there is lack of correlation between the frequency of PLMS during

sleep and the mean sleep latency on MSLT (Mendelson, 1996), and Montplaisir et al. (2000) have questioned the validity of PLMD as a distinct entity. Many patients with PLMS are unaware of their leg movements, and the diagnosis may be suggested by the bed-partner. The exact prevalence of PLMS is unknown, but they increase with age and approach 30% by age 50. PLMS occurs in the great majority of individuals with restless legs syndrome (RLS, which has an estimated prevalence of around 5% (Chokroverty and Jankovic, 1999)), but most patients with PLMS do not have symptoms of RLS. PLMS and RLS are associated with several medical and neurological conditions, including iron deficiency (Sun et al., 1998), folate deficiency, renal disease (Winkelman et al., 1996), peripheral neuropathy (Ondo and Jankovic, 1996), Parkinsonism (Trenkwalder, 1998), spinal disorders (Lee et al., 1996), narcolepsy and REM-sleep behavior disorder (Montplaisir et al., 2000). PLMS tends to be exacerbated by caffeine, neuroleptics and antidepressants. The movements are usually responsive to pharmacologic treatment. Dopaminergic agonists are widely considered as first-line therapy, but several other classes of drugs have been found to have efficacy, including benzodiazepines, opioids, anti-convulsants and beta-blockers.

14.5.2.2. Other medical conditions

A variety of medical conditions may be associated with sleep fragmentation, including arthritis, fibromyalgia, spondylosis, chronic pain of any nature, nocturnal angina, epilepsy, asthma, COPD, alcoholism, urinary dysfunction and GI disorders, such as peptic ulcer disease, gastro-esophageal reflux and irritable bowel syndrome (Chokroverty, 1999). Depending on the degree of sleep disruption, EDS may be a prominent feature of the clinical picture.

14.5.3. Primary disorders of somnolence

Several entities may be regarded as primary disorders of somnolence. Narcolepsy, the best known and the most completely understood disorder of this group, is considered elsewhere in this volume.

14.5.3.1. Idiopathic hypersomnia

Idiopathic hypersomnia (previously denoted 'idiopathic CNS hypersomnia') is an incompletely defined disorder characterized by EDS. Traditionally, this diagnosis has been used as a nosologic haven for

individuals with excessive somnolence but lacking the classic features of narcolepsy or another disorder known to cause EDS (such as sleep apnea). Without doubt, many patients have been diagnosed with idiopathic hypersomnia, when, in fact, they suffered from other disorders, such as narcolepsy without cataplexy, delayed sleep phase syndrome or upper airway resistance syndrome (Guilleminault et al., 1993). Roth (1976) described monosymptomatic (EDS) and polysymptomatic (EDS, prolonged nocturnal sleep time, marked difficulty with awakening) forms of idiopathic hypersomnia. Others have suggested that the category of idiopathic hypersomnia is heterogeneous, including individuals with EDS but with or without one or more of the other features of Roth's polysymptomatic form (Aldrich, 1998). Idiopathic hypersomnia is believed to be less common than narcolepsy, but estimation of prevalence is obviously elusive, because strict diagnostic criteria are lacking, and no specific biological marker has been identified. Typically, onset of symptoms occurs in adolescence or early adulthood. As denoted, the etiology of the disorder is not known, but viral illnesses, including Guillain-Barre syndrome, hepatitis, mononucleosis and atypical viral pneumonia may herald the onset of sleepiness in a subset of patients. EDS may occur as part of the acute illness, but it persists after the other symptoms subside. Rarely, familial cases are known to occur, with increased frequency of HLA-Cw2 and HLA-DR11 (Montplaisir and Poirier, 1988). Some of these patients have associated symptoms suggesting autonomic nervous system dysfunction, including orthostatic hypotension, syncope, vascular-type headaches and peripheral vascular complaints. Most patients with idiopathic hypersomnia have neither a family history nor an obvious associated viral illness. Little is known about the pathophysiology of idiopathic hypersomnia. No animal model is available for study. Neurochemical studies using CSF have suggested that patients with idiopathic hypersomnia may have a derangement in the noradrenergic system (Montplaisir et al., 1982; Faull et al., 1983, 1986).

The clinical picture of idiopathic hypersomnia varies among individual patients. The disorder may be mistaken for narcolepsy, if a careful history is not taken. The two disorders share several common features, including similar age of onset, lifelong persistence after onset (although a few patients with idiopathic hypersomnia have improved over time or attained complete remission of symptoms (Bruck and Parkes, 1996; Bassetti and Aldrich, 1997; Billiard and

Dauvilliers, 2001), EDS as the primary symptom and familial clustering of some cases. However, essential differences between the disorders become apparent in the history and in diagnostic studies. Patients with idiopathic CNS hypersomnia present with EDS, but without cataplexy (although some patients have episodes of sleep paralysis or hypnagogic hallucinations) or significant nocturnal sleep disruption (Billiard and Dauvilliers, 2001). They complain of daytime sleepiness, which interferes with normal activities. Occupational and social functioning may be severely impacted by sleepiness. Nocturnal sleep time tends to be long, and patients are usually difficult to awaken in the morning – they may become irritable or even abusive in response to the efforts of others to rouse them. In some patients, this difficulty may assume striking proportions and include confusion, disorientation and poor motor co-ordination – a condition called 'sleep drunkenness' (Roth et al., 1972). These patients often take naps, which may be prolonged but are usually non-refreshing. No amount of sleep ameliorates the EDS. 'Microsleeps', with or without automatic behavior, may occur throughout the day.

Polysomnographic studies of patients with idiopathic CNS hypersomnia usually reveal shortened initial sleep latency, increased total sleep time and normal sleep architecture (in contrast to narcoleptic patients, who exhibit significant sleep fragmentation). Using spectral analysis, Sforza et al. (2000), found reduced sleep pressure, as evidenced by decreased slow-wave activity during the first two NREM episodes of nocturnal sleep in patients with idiopathic hypersomnia. Mean sleep latency on MSLT is usually reduced, often in the 8–10 minute range, but SOREMPs are not typically seen. A study measuring evoked potentials found that subjects with idiopathic hypersomnia or severe obstructive sleep apnea had prolonged visual P300 latency compared to normals or subjects with narcolepsy; subjects with idiopathic hypersomnia or obstructive sleep apnea had longer auditory P300 latency than normals; subjects with idiopathic hypersomnia had reduced auditory P300 amplitude compared to subjects with narcolepsy (Sangal and Sangal, 1995).

As with narcolepsy, other disorders producing EDS (such as sleep-disordered breathing, PLMD, psychiatric diseases or circadian rhythm disorders) must be ruled out before the diagnosis of idiopathic CNS hypersomnia is made.

Treatment of idiopathic CNS hypersomnia is often less than satisfactory. Lifestyle and behavioral modi-

fications, including good sleep hygiene, are appropriate, but treatment with stimulant medication or modafinil is usually necessary.

14.5.3.2. *Recurrent hypersomnias*

14.5.3.2.1. *Kleine–Levin syndrome.* This uncommon disorder is a form of recurrent hypersomnia, which occurs primarily in adolescents (Critchley, 1967). There is a male preponderance. It is characterized by the occurrence of episodes of EDS, usually, but not invariably, accompanied by hyperphagia, aggressiveness and hypersexuality, lasting days to weeks and separated by asymptomatic periods of weeks or months. During symptomatic periods, individuals sleep up to 18 hours per day and are usually drowsy (often to the degree of stupor), confused and irritable the remainder of the time. During symptomatic episodes, polysomnographic studies show long total sleep time with high sleep efficiency and decreased slow-wave sleep. MSLT studies demonstrate short sleep latencies and SOREMPs (Rosenow, 2000). The etiology of this syndrome remains obscure. Symptomatic cases of Klein–Levin syndrome associated with structural brain lesions have been reported, but most cases are idiopathic. SPECT studies have demonstrated hypoperfusion in the thalamus in one patient and in the non-dominant frontal lobe in another (Arias et al., 2003). Treatment with stimulant medication is usually only partially effective. Effects of treatment with lithium, valproic acid or carbamazepine have been variable, but generally unsatisfactory. Fortunately, in most cases, episodes become less frequent over time and eventually subside.

14.5.3.2.2. *Menstrual-related hypersomnia.* Another form of recurrent hypersomnia is menstrual-related periodic hypersomnia (Billiard et al., 1975; Sachs et al., 1982), in which EDS occurs during the several days prior to menstruation. The prevalence of this syndrome has not been well characterized. Likewise, the etiology is not known, but presumably the symptoms are related to hormonal changes. Some cases of menstrual-related hypersomnia have responded to the blocking of ovulation with estrogen and progesterone (birth control pills) (Bamford, 1993).

14.5.3.2.3. *Idiopathic recurring stupor.* Numerous cases have been reported in which individuals (predominately middle-aged males) are subject to

stuporous episodes lasting from hours to days, in the absence of obvious toxic, metabolic or structural cause. The individuals are normal between episodes, which occur unpredictably. During the symptomatic episodes, EEG was characterized by fast background activity in the 13–16 Hz range. Several of these patients have been shown to have elevated plasma and CSF levels of endozepine-4, an endogenous ligand with affinity for the benzodiazepine recognition site at the GABA_A receptor (Rothstein et al., 1992). Administration of flumazenil, a benzodiazepine antagonist, produced transient awakening with normalization of the EEG (Lugaresi et al., 1998). In some cases, the episodes resolved spontaneously after several years. Similar cases have been reported in children (Soriani et al., 1997).

14.5.4. *Circadian rhythm disorders*

The normal circadian cycle, regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus, is a major determinate of alertness or sleepiness across the 24-hour period (Turek, 2000). The cycle is entrained by factors such as physical activity and, especially, environmental light. If this physiologic cycle becomes desynchronized with the major sleep period or with the daily schedule, EDS often results.

Several models have been devised to explain the sleep/wake cycle and fluctuations of sleepiness/alertness across the circadian period. The two-process model (Borbely, 1982) offers a single oscillator concept, incorporating ‘process S’ (sleep homeostasis or pressure, which accumulates during wakefulness and discharges during sleep) and ‘process C’ (innate circadian variation). Kronauer et al. (1982) modeled the circadian system with two interacting oscillators (rest-activity and body temperature). A three-process model (Folkard and Akerstedt, 1992) extends the two-process model to include ‘process W’ to account for sleep inertia (the time period necessary for full alertness to emerge after awakening from sleep). The opponent process model of Edgar and Dement (Edgar et al., 1993), proposes that sleep homeostasis is opposed by an alerting rhythm arising from the SCN.

Delayed sleep phase, i.e. a circadian-driven tendency for the major sleep period to begin and end at later times, is common during puberty and may be associated with hormonal changes occurring at that time (Carskadon et al., 1993). Delayed sleep phase syndrome (DSPS) (Weitzman et al., 1981) is less common. In DSPS, the shifting of the major sleep

period causes disruption of 'normal' activities and often conflict within the family. School performance typically suffers, particularly in morning classes, when the individual is in a state of suboptimal alertness. Often, a psychological or psychiatric component (including disorders of personality) is part of the picture. Treatment programs may be doomed to failure unless this aspect is addressed. Another chronic circadian disorder, known as advanced sleep phase syndrome (ASPS) (Baker and Zee, 2000), involves the shift of the major sleep period to an earlier time; this condition often occurs in the elderly population. The sleep of patients with DSPS and ASPS is normal in quality and architecture, but it occurs at times which conflict with societal dictates and which the patients may find problematic. DSPS may be mistaken for insomnia, as the patient may simply complain of difficulty with sleep initiation. Likewise, the patient with ASPS may be diagnosed with depression because of a complaint of early awakening. A careful history, perhaps supplemented with sleep diaries or actigraphy (a portable method for monitoring motor activity over time) usually eliminates any diagnostic uncertainty. Circadian rhythm disorders, such as ASPS and DSPS can be treated with exposure to bright (5000–10000 lux) broad-spectrum (non-UV) light. The timing of the light exposure is critical to shift the phase of the sleep period in the desired direction. Exposure to light prior to the circadian nadir of the core body temperature (which typically occurs around 2–3 hours before habitual wake-up time) tends to delay the sleep phase; light exposure after the temperature nadir tends to advance the sleep phase.

EDS is a common problem for shift-workers, who tend to have reduced total sleep times per 24-hour period, in addition to their circadian disruptions (Akerstadt, 1996). Much less common are patients with a 'non-24-hour sleep–wake syndrome' (ASDA, 1997). Most of these individuals are blind and lack effective input to the SCN from the optic nerves (Leger et al., 1999). Therefore, they are unable to entrain the circadian clock with environmental light. Their circadian clock behaves as in 'free-running' conditions, and the major sleep period tends to be progressively delayed each day. Over time, the major sleep period will work its way around the 24-hour clock; the patient will, thus, experience symptoms, which vary according to the synchrony of the circadian clock and the 24-hour clock. This disorder may rarely occur in patients with structural abnormalities involving the hypothalamus. Another uncommon cir-

cadian disturbance is known as 'irregular sleep–wake pattern' (ASDA, 1997). These individuals do not exhibit a consistent major sleep period; rather they have irregular periods of sleep and wakefulness across the 24-hour epoch, behaving as if they do not have a circadian timekeeper. This condition may be induced by social or environmental factors or because of intrinsic brain pathology. The possibility of a structural lesion should be strongly considered if the disorder has an acute presentation.

14.5.5. Nervous system disorders and EDS

EDS is often associated with disorders of the central or peripheral nervous systems. It is a clinical feature of many toxic or metabolic encephalopathic processes. These disorders often present with other symptoms and signs, but EDS may dominate the picture, particularly in chronic cases. Structural brain lesions, including strokes, tumors, cysts, abscesses, hematomas, vascular malformations, hydrocephalus and multiple sclerosis plaques are known to produce EDS. Somnolence may result either from direct involvement of discrete brain regions (especially the brainstem reticular formation or midline diencephalic structures) or because of effects on sleep continuity (for example, nocturnal seizure activity or secondary SRBD).

EDS is a frequent sequela of encephalitis or head trauma. Victims of 'encephalitis lethargica', described by Von Economo in the early twentieth century were found to have lesions in the midbrain, subthalamus and hypothalamus. Even post-traumatic narcolepsy with cataplexy has been described (Francisco and Ivanhoe, 1996). Epileptic patients may suffer from EDS as a consequence of medication effects or less obviously due to nocturnal seizure activity (Manni and Tartara, 2000).

EDS may be associated with numerous infectious agents affecting the central nervous system, including bacteria, viruses, fungi and parasites. Perhaps the best known is trypanosomiasis, which is called 'sleeping sickness' because of the prominent hypersomnia.

Sleepiness may occur with acute infectious illness, even without direct invasion of the nervous system, and may be mediated by cytokines, including interferon, interleukins and tumor necrosis factor (Toth and Opp, 2002). EDS may also persist chronically after certain viral infections (Guilleminault and Mondini, 1986).

Sleep disruption and EDS are common in neurodegenerative disorders, including Parkinson's

disease, Alzheimer's disease and other dementias and multiple system atrophy (Askenasy, 1993; Chokroverty, 1996; Trenkwalder, 1998).

Patients with neuromuscular disorders or peripheral neuropathies may also develop EDS because of associated SRBD (central or obstructive apnea), pain or PLMS (George, 2000). Patients with myotonic dystrophy often suffer from EDS, even in the absence of sleep-disordered breathing (Gibbs et al., 2002).

14.5.6. Psychiatric disorders and EDS

Psychiatric disorders are often associated with disrupted sleep. This is especially true of depression. While the majority of depressed patients with sleep disruption suffer from insomnia, some of them have hypersomnia. This subset of patients is often diagnosed with 'atypical' depression or depression with the DSM-IV atypical features specifier (which includes mood reactivity, increased appetite, leaden 'paralysis' and rejection sensitivity along with hypersomnia) (American Psychiatric Association, 2000: Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR). These patients are thought to respond better to MAO inhibitors and possibly norepinephrine (norepinephrine) reuptake inhibitors than to other types of antidepressants.

There are also patients who might be said to have 'psychogenic hypersomnia' (Vgontzas et al., 2000). Generally, they are young adults who complain of EDS and have MSLT mean sleep latencies in the 7–10 minute range. Overnight studies demonstrate long times in bed and poor sleep efficiency (ratio of total sleep time to total time in bed). These patients often develop symptoms after a prolonged period of stress or following a period of disrupted sleep. They respond to stress management, to improved sleep hygiene, with reduction of time in bed, and to reduced sleep time. Exposure to bright light immediately after rising in the morning (using commercially available light boxes) has also been found to be useful.

14.5.7. Drugs and EDS

Obviously, numerous drugs can produce EDS, including sedatives, hypnotics, anxiolytics, antihistamines, antidepressants, antihypertensives, anticonvulsants and neuroleptics. There is considerable variation in individual susceptibility in this regard. It is also important to remember that drug–drug interactions or metabolic derangements (such as liver disease) may

lead to EDS with doses of drugs which would normally be non-toxic. Withdrawal from stimulant drugs usually produces some degree of transient rebound hypersomnia. During the past few years, it has been reported that dopamine agonists may contribute to EDS in Parkinsonian patients (Frucht et al., 1999; Olanow et al., 2000).

14.6. Conclusion

Excessive daytime somnolence is a prevalent problem in medical practice and in society in general. It exacts a great cost in terms of quality of life, personal and public safety and productivity. The causes of EDS are myriad, and a careful evaluation is needed to determine the cause in an individual case. Several methods have been developed to assess EDS, although each of them has limitations. Treatment is available for the great majority of cases.

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CHAPTER 15

Obstructive sleep apnea syndromes

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15.1. Introduction

The first description of an obstructive sleep apnea (OSA) sufferer is generally attributed to the novelist Charles Dickens, who described 'Joe' in *The Posthumous Papers of the Pickwick Club*, published in 1836. Joe was an excessively sleepy, obese boy who snored loudly and had possible right-sided heart failure that led to his being called 'young dropsy' (but he may have been more a 'Prader-Willi syndrome' than a 'Pickwickian syndrome') (Dickens, 1836; Dement, 2000). The first physician to describe the clinical features of the later-defined obstructive sleep apnea was Broadbent in 1877 (Thorpy, 2000). By treating upper airway obstruction, Wells reported cure of sleepiness in several patients in 1898 (Thorpy, 2000). Burwell et al. studied obese patients with somnolence attributable to hypercapnia, and coined the term 'Pickwickian' in 1956 (Burwell et al., 1956; Dement, 2000). In 1965, Gastaut, Tasinari and Duron in France and Jung and Kuhlo in Germany described sleep apnea and its associated polysomnographic findings (Gastaut et al., 1965; Jung and Kuhlo, 1965). In 1972, in Rimini, Italy, Lugaresi and Sadoul organized the first international symposium on 'Hypersomnia with Periodic Breathing', mostly devoted to the dismemberment of the Pickwickian Syndrome, and reports, particularly by Coccagna et al., on hemodynamics, emphasized changes associated with abnormal breathing during sleep. Guilleminault, Eldridge and Dement reported the presence of sleep apnea in narcolepsy and in insomnia at the Rimini meeting and characterized insomnia with sleep apnea as a new syndrome in 1973 (Guilleminault et al., 1973). Guilleminault et al. coined

the terms 'sleep apnea syndrome' and 'obstructive sleep apnea syndrome' in 1976 to emphasize the occurrence of this syndrome in non-Pickwickians. In the same year, these authors reported the existence of this syndrome in children. In 1982, Guilleminault and colleagues reported the presence in children of abnormal respiratory efforts without apneas during sleep. A similar pattern was later described in adults and, in 1993, was given the name 'upper airway resistance syndrome' (UARS), thus completing the loop of hypersomnolence and insomnia and extending the spectrum of sleep apnea syndromes (Guilleminault et al., 1993).

Treatment of sleep apnea advanced significantly when Kuhlo, Doll and Franck in 1969 and Lugaresi et al. in 1970 reported that tracheostomy was an effective treatment for OSA (Kuhlo et al., 1969; Lugaresi et al., 1970). In 1981, Guilleminault and colleagues demonstrated the long-term effectiveness of tracheostomy in 50 OSA patients, all of whom had complete resolution of clinical symptoms, return to full activity, and normal adaptation to social and family life (Guilleminault et al., 1981). Although Ikematsu popularized uvulopalatopharyngoplasty (UPPP) for the treatment of snoring in 1964, it was not until 1981 that Fujita performed the first UPPP as a treatment for OSA (Thorpy, 2000). In 1981, Sullivan and colleagues successfully used nasal continuous positive airway pressure (CPAP) in OSA patients and reported it as a new treatment option (Sullivan et al., 1981). Further down the road, Riley et al. developed maxillo-mandibular surgical procedures in the 1980s for subjects intolerant of nasal CPAP or unsuccessful after UPPP (Riley et al., 1986). More recently, distraction osteogenesis was used as another treatment approach (Guilleminault and Li, 2004).

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15.2. Epidemiology

OSA exists in all age groups. From the data derived from a large cohort study, the prevalence of OSA in

the United States was reported to be 4% in men and 2% in women between the ages of 30–60 years (Young et al., 1993). However, the actual prevalence may be higher. Young and colleagues estimated that among middle-aged adults, 93% of women and 82% of men with OSA have not been diagnosed (Young et al., 1997). The Wisconsin Sleep Cohort Study evaluated the association of pre-, peri- and post-menopausal states in 589 women with sleep-disordered breathing (SDB). After adjusting for age, body habitus, smoking and other potential confounding factors, the odds ratios (95% confidence interval) for OSA (defined as apnea–hypopnea index >5 events per hour of sleep) was calculated to be 1.2 (range 0.7–2.2) with perimenopause and 2.6 (range 1.4–4.8) with postmenopause (Young et al., 2003). These results suggest that the transition from pre- to post-menopause may be associated with an increased risk of SDB, independent of known confounding factors. After menopause, women develop OSA at a rate similar to that in men (Coleman et al., 1982; Tishler et al., 2003). The maximum incidence for OSA occurs between the fifth and seventh decades (Coleman et al., 1982). Obesity increases the risk of developing OSA, and race may be an additional risk factor. The incidence of OSA is reportedly increased in Pacific Islanders, Mexican-Americans and Blacks (Grunstein et al., 1989; Schmidt-Nowara et al., 1990; Redline et al., 1997). The higher prevalence of OSA among Blacks was found to be more pronounced in individuals less than 25 years of age and was not accounted for by differences in body mass index (BMI) or by differences in exposure to alcohol and tobacco (Redline et al., 1997). Variable age at puberty, speed of development of secondary characteristics, and mucosal enlargement associated with hormonal surge may have biased these findings (Robinson and Guilleminault, 2000). In contrast, a study in New Zealand comparing sleep apnea severity among Maori, Pacific Islanders and Europeans found that race was not an important predictor of severity when adjusted for factors such as neck size, BMI and age (Baldwin et al., 1998).

15.3. Clinical presentation

15.3.1. Sleep-disordered breathing (SDB)

Sleep-disordered breathing (SDB) encompasses the spectrum from upper airway resistance syndrome (UARS) to severe obstructive sleep apnea (OSA). The categorization of OSA and UARS into two different syndromes is still controversial; some have rejected

UARS as a distinct clinical entity or even doubted its existence (Douglas, 2000); others considered it as part of a spectrum that includes benign snoring, UARS, obstructive hypopnea, OSA and hypoventilation. Regardless of the clinical definition, important issues include recognizing the different clinical signs and symptoms, looking for breathing abnormalities in sleep, understanding and choosing the right polysomnographic measurements, and utilizing established criteria to make an appropriate diagnosis (American Academy of Sleep Medicine, 2000).

Daytime sleepiness is the most common complaint among adult patients with OSA. It can occur following meals, while sitting as a passenger in a car, watching television, attending a meeting or a lecture, eating, talking or even while driving. Patients may notice difficulty with attention, concentration, memory, judgment and/or impaired performance of tasks requiring dexterity. Approximately 50% of patients report generalized, dull, morning or nocturnal headaches (Bassiri and Guilleminault, 2000). About one third of patients at the Stanford Sleep Disorders Clinic reported sexual dysfunction either as decreased libido or impotence. In a prospective study of 25 OSA patients with AHI >10, Farfulla et al. reported abnormal bulbocavernosus reflex (either prolonged latency or reduced amplitude) in 68% of these patients. These abnormalities correlated with the severity of OSA and the severity of gas exchange problems, but did not vary with age (Farfulla et al., 2000).

Nocturnal symptoms in OSA are more specific than those during daytime. Loud snoring with brief gasps alternating with episodes of silence lasting for 20–30 seconds occurs frequently (Guilleminault et al., 1976; Kales et al., 1985; Bassiri and Guilleminault, 2000). Seventy-five percent of spouses report apneic episodes terminated by gasps, choking sounds, snorts, vocalizations or brief awakenings (Hoffstein and Szalai, 1993). Diaphoresis in the neck and upper chest area as well as restlessness manifested as tossing and turning, probably due to increased respiratory effort related to upper airway obstruction, has been described in about half of the patients. A total of 18–31% of patients with OSAS report a sensation of choking or dyspnea interrupting sleep (Guilleminault et al., 1976; Coverdale et al., 1980; Kales et al., 1985; Maislin et al., 1995; Bassiri and Guilleminault, 2000). Dyspnea may be caused by congested pulmonary vasculature as a consequence of increased venous return secondary to the large negative intrathoracic pressure during episodes of upper airway obstruction. Other nocturnal symptoms include nocturia (28%),



Fig. 15.1. Example of a subject with high and narrow hard palate. This is related to a narrow maxilla and can be helped by rapid maxillary distraction in children and distraction osteogenesis in adult. Note also the asymmetrical nostril: it has been present from birth and responsible for abnormal nasal resistance. This abnormal resistance is involved in the abnormal development of the maxilla.

esophageal reflux, dryness of the mouth (74%) and drooling (36%) (Guilleminault et al., 1977; Kales et al., 1985; Bassiri and Guilleminault, 2000).

Physical examination findings in OSA include obesity (BMI > 28 kg/m²), neck circumference >40 cm (with reported sensitivity of 61% and specificity of 93% for OSA regardless of gender), nasal turbinate hypertrophy, septal deviation, high and narrow hard palate (see Figure 15.1), elongated low-lying uvula, redundant and low-lying soft palate, crowding of the oropharynx with enlarged tonsils and adenoids, prominent tonsillar pillars, macroglossia, narrow maxilla, narrow mandible, overjet and retrognathia, cross-bite and dental malocclusion (Kushida et al., 1997).

15.3.2. Upper airway resistance syndrome

In a series of 400 UARS patients, it was reported that 56% were women, 32% were of East Asian origin, and the mean age was 38 ± 14 years (Guilleminault et al., 1995, 2000). This sex, race and age distribution varies from that typically seen in OSA. Unlike OSA patients, who usually complain of daytime sleepiness, UARS patients frequently complain of insomnia, sleep fragmentation and fatigue. Their psychological profile reveals high anxiety. Other clinical features of UARS patients include cold extremities, postural hypotension, history of fainting, low systemic arterial blood pressure, orthostasis on tilt table testing, myalgias and functional somatic complaints (Guilleminault and

Chowdhuri, 2000; Bao and Guilleminault, 2004). During sleep, the arousal threshold in UARS patients is lower than that in OSA patients, thereby causing the patient to wake up in response to small increases in respiratory effort. In contrast, OSA patients usually have a high arousal threshold and wake up on higher negative inspiratory pressures up to -40 to -80 cmH₂O and/or oxygen desaturation. During sleep, UARS patients demonstrate an increase in alpha rhythm and a relative increase in delta waves, while OSA patients show a predominance of stage 1 and 2 non-rapid eye movement (NREM) sleep with a decrease in delta sleep. UARS has been linked to many somatic, psychiatric or psychosomatic conditions, including parasomnias, attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD), fibromyalgia, as well as chronic insomnia. In children, parasomnias are more often reported. The most common parasomnia is sleepwalking with or without sleep terrors and associated confusional arousal (Guilleminault et al., 2003). These children have a high incidence of enuresis and sleep talking. The lack of restful sleep due to nocturnal breathing problems has been associated with daytime inattention, hyperactivity in those children (Chervin et al., 2002), and could be responsible for the poor performance at school (Gozal and Pope, 2001; Urschitz et al., 2003). Gold and colleagues recently emphasized that UARS patients have complaints much more related to functional somatic complaints such as headaches, sleep-onset insomnia and irritable bowel syndrome; the symptoms were correlated with polysomnographic findings for UARS (Gold et al., 2003). Those symptoms are easily misinterpreted as chronic fatigue syndrome, fibromyalgia (Gold et al., 2004) or as psychiatric disorders, such as ADD/ADHD (Lewin and Pinto, 2004). The difference between UARS and OSA patients is hypothesized to be due to genetically predetermined and environmentally altered pharyngeal receptors, particularly mechanoreceptors. Patients with UARS may have intact but sensitive pharyngeal sensory nerves, whereas OSA patients have peripheral neuropathy of the pharyngeal area (Guilleminault and Chowdhuri, 2000; Bao and Guilleminault, 2004).

15.3.3. OSA syndromes and insomnia

OSA or more often UARS patients may present with complaints of sleep-onset and maintenance insomnia, or being unable to fall back to sleep after awakening, sometimes similar to primary insomnia. However,

other SDB-associated manifestations, such as snoring, choking/gasping/snorting, or frank apneic episodes, nocturia, reflux, hypertension, together with objective findings suggestive of upper airway obstruction, provide clues to the presence of SDB as the underlying etiology. On the other hand, a history of trying too hard to sleep, conditioned hyperarousal to bed and bedroom, evidence of somatization of tension (agitation, muscle tension or increased vasoconstriction) or prolonged wake after sleep onset associated with racing thoughts and heightened arousal, together with a normal physical examination, suggests psychophysiologic insomnia. However, sleep-onset insomnia can be induced by SDB due to frustrations from chronically disrupted sleep and associated tension and anxiety at bedtime.

15.4. Syndrome diagnostic criteria and severity classification

SDB is characterized by transient upper airway resistance, repetitive reduction or cessation of airflow due to partial or complete occlusion of the upper airway during sleep, associated with fragmentation of sleep, arousals, brady- and tachycardia, and failure to maintain adequate oxygen saturation despite an increased respiratory effort.

Apnea is defined as cessation of airflow ≥ 10 seconds. Various criteria have been used to define hypopnea, including: (1) $>50\%$ reduction in airflow from baseline during sleep, or (2) $30\text{--}50\%$ reduction in airflow during sleep associated with either $>3\text{--}4\%$ oxygen desaturation or an arousal, plus (3) event duration ≥ 10 seconds (American Academy of Sleep Medicine Task Force, 1999). Respiratory effort-related arousals (RERAs) are airflow limitations measured by a nasal cannula/pressure transducer, or abnormal esophageal pressure (Pes) by an esophageal manometer. RERAs must have duration of at least 10 seconds and terminate in an arousal. The use of a pediatric feeding catheter instead of the esophageal balloon has made the procedure better tolerable in both adults (Virkkula et al., 2002) and children (Serebrisky et al., 2002). The nasal cannula/pressure transducer is more sensitive than thermistors in picking up respiratory abnormalities, and has been used to detect RERAs. It allows recognition of 'flow limitation', such as flattening of the normally rounded curves seen at end inspiration (see Figure 15.1). Flow limitation can also present as abrupt peak wave near end inspiration followed by a decrease in airflow and a plateau (see

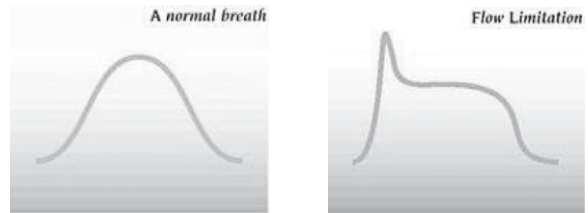


Fig. 15.2. A normal (left) and abnormal (right) respiratory curve measured by the nasal cannula/pressure transducer in polysomnography.

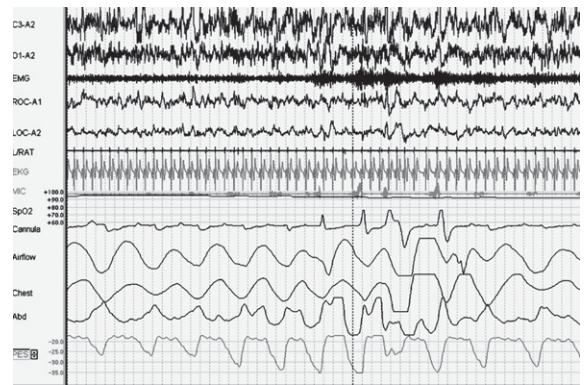


Fig. 15.3. Polysomnogram of a patient with obstructive sleep apnea. The cannula and airflow channels demonstrate reduction in oro-nasal airflow consistent with a hypopnea. Paradoxical respiration is noted on the chest and abdominal effort channels. Pes crescendo with pes reversal associated with an arousal is seen.

Figure 15.2). However, nasal cannula/pressure transducer has not demonstrated sensitivity comparable to that with the Pes measurement. Therefore, measurement of esophageal pressure (Pes) remains the gold standard for detection of increased respiratory effort. Three abnormalities have been described in the Pes measurement. (1) Pes crescendo: a progressive breath-by-breath more negative peak end inspiratory Pes terminating in an alpha wave EEG arousal, or a burst of delta wave, and not associated with oxygen desaturation (see Figure 15.3). (2) sustained continuous effort: a relatively stable and persistent more negative peak end inspiratory Pes lasting at least over four breaths. (3) Pes reversal: an abrupt drop in respiratory effort indicated by a less negative peak end inspiratory Pes after a sequence of variations in respiratory efforts independent of the EEG pattern seen (Guilleminault et al., 2001).

Although we believe UARS clearly represents a syndrome distinct from OSA, the American Academy

of Sleep Medicine (AASM) Task Force in 1999 included UARS in the obstructive sleep apnea–hypopnea syndrome and defined the syndrome as demonstration of five or more obstructive apneas–hypopneas or RERAs per hour of sleep (American Academy of Sleep Medicine Task Force, 1999; Guilleminault and Chowdhuri, 2000). OSA can be classified based on the AHI index (apneas + hypopneas per hour of sleep) or respiratory disturbance index (RDI; apneas + hypopneas + RERAs per hour of sleep) into mild ($5 \leq \text{AHI}$ or $\text{RDI} < 15$), moderate ($15 \leq \text{AHI}$ or $\text{RDI} < 30$) or severe (AHI or $\text{RDI} \geq 30$).

UARS has been defined as having an AHI < 5 and oxygen saturation $> 92\%$ (Bao and Guilleminault, 2004). With better understanding of respiratory events, more and more abnormal respiratory patterns have been included in the RDI definition, including presence of different Pes patterns as described above.

15.5. Polysomnography (PSG) and other tests

Overnight pulse oximetry has occasionally been used by some physicians as a screening test to identify patients with OSA, but it is not a substitute for PSG because of its inability to distinguish sleep from wakefulness as well as the two different sleep states. Furthermore, overnight pulse oximetry fails to detect UARS and apneas/hypopneas that are not associated with significant oxygen desaturation (Chesson et al., 1997; Lee-Chiong, 2002). Full-night PSG is routinely indicated for patients suspected of having sleep-disordered breathing (Chesson et al., 1997; Standards of Practice Committee of the American Sleep Disorders Association 1997; Lee-Chiong, 2002). Esophageal pressure (Pes) monitoring during PSG recording is the reference standard in detecting respiratory effort (American Academy of Sleep Medicine Task Force, 1999; Lee-Chiong, 2002). Pulse transit time (PTT) is a measure to describe the transmission time of the arterial pulse pressure wave from the aorta to the peripheral artery. PTT increases with the fall in blood pressure (BP) during inspiration and decreases during arousal-induced increases in BP. It has been used to help distinguish between central and obstructive apnea–hypopnea if Pes monitoring is not available, despite the increased frequency of both false positives and false negatives (Poyares et al., 2002).

In adult patients with OSA, PSG monitoring demonstrates ≥ 5 obstructive apnea–hypopneas per hour of sleep, lasting at least 10 seconds and associated with one or more of the following: (1) frequent

arousals from sleep; (2) brady/tachycardia; (3) arterial oxygen desaturation (American Academy of Sleep Medicine, 2000). Figure 15.2 depicts typical polysomnographic findings in a patient with hypopnea.

In some circumstances, split-night PSG may be considered (Chesson et al., 1997; Standards of Practice Committee of the American Sleep Disorders Association, 1997; Loube et al., 1999; Lee-Chiong, 2002) during a split-night PSG recording, the first half of the purpose, with the second half for CPAP titration. A consensus statement recommended that night is for diagnostic split-night studies may be considered in patients with $\text{RDI} > 40$ during the first 2 hours of a diagnostic PSG, utilizing the remaining time to titrate CPAP. The consensus statement further recommended that patients with an RDI between 20–40 may undergo a split-night study based on the occurrence of obstructive respiratory events of prolonged duration or associated with severe oxygen desaturation. A minimum of 3 hours of sleep is recommended for adequate titration during a split-night study and requires the recording and analysis of the same parameters as a standard diagnostic PSG. An additional full-night CPAP titration may be required if the split-night study did not allow for abolishment of the majority of obstructive events or if the prescribed CPAP treatment does not control clinical symptoms (Loube et al., 1999). Because of the decreased amount of time spent on both diagnosis and CPAP titration, split-night studies may be problematic. Split-night studies can potentially underestimate the severity of OSA, since breathing abnormalities usually become worse during REM sleep, and the longest REM sleep periods are in the second half of the night. In addition, CPAP titration during split-night recordings may be suboptimal due to the shorter time spent on titration.

Limited-channel diagnostic PSG (cardiopulmonary sleep studies) may be adequate (Ferber et al., 1994; Standards of Practice Committee of the American Sleep Disorders Association, 1994; Loube et al., 1999) in patients who have a high pre-test probability of OSA based on validated screening algorithms (Maislin et al., 1995; Kushida et al., 1997). Minimum parameters recorded and measured in limited-channel PSG are nasal airflow, chest wall impedance, electrocardiogram and oxygen saturation (Ferber et al., 1994). However, these limited-sleep studies cannot effectively distinguish sleep from wake or determine sleep stage, are less accurate than standard PSG in determining the number of obstructive respiratory events, and are unable to detect co-existing non-OSA sleep disorders, such as

periodic limb movements of sleep (PLMS). In addition, they routinely miss UARS. Therefore, limited-channel PSG can only diagnose subjects with severe problems (Phillips et al., 1998; Loube et al., 1999). Multiple sleep-latency testing (MSLT), which consists of 4–5 daytime naps during which the sleep latency and REM are measured, provides an objective measure of sleepiness, that is, propensity to sleep. OSA patients may or may not demonstrate abnormal mean sleep latency of less than 10 minutes (American Academy of Sleep Medicine, 2000). Maintenance of wakefulness test (MWT) is preferred by some to evaluate propensity of subjects to stay alert.

15.6. Co-morbidity

15.6.1. Hypertension

OSA is an independent risk factor for hypertension, and hypertension is a frequent co-morbid condition with sleep apnea (Peppard et al., 2000; Pepperell et al., 2002; Dart et al., 2003; Lattimore et al., 2003). About 30% of patients with systemic hypertension have OSA, while 50% or more of patients with OSA have systemic hypertension (Bassiri and Guilleminault, 2000; Somers and Fletcher, 2002). Moller and colleagues performed 24-hour BP monitoring and measured plasma levels of vasoactive hormones (renin, angiotensin II, aldosterone, atrial natriuretic peptide, brain natriuretic peptide, vasopressin and endothelin-1) in 24 OSA patients and in 18 control subjects (Moller et al., 2003). Compared to controls, OSA patients had significantly higher BP and heart rate, and the sleep-related nocturnal nadir BP was higher. Moreover, angiotensin II and aldosterone levels were significantly higher in OSA subjects compared to controls, with angiotensin II correlating positively with daytime BP levels. After 14 months of CPAP therapy, 13 OSA patients demonstrated a reduction in BP that correlated with a decrease in plasma renin and angiotensin II concentrations (Moller et al., 2003).

Brachial artery diameter and brachial artery flow-mediated dilation, which are surrogates of endothelial dysfunction, were measured in elderly participants in the Wisconsin Sleep Heart Health/Cardiovascular Health Study cohort ($n = 1037$, age >68 years, 56% female). After adjustment for BMI and other confounders, a statistically significant linear correlation was found between hypoxemia index and the baseline diameter. This association was stronger among partic-

ipants who were younger than 80 years old and were hypertensives. The authors suggested that vascular dysfunction might partially explain the relationship between OSA, hypertension and cardiovascular disease (Nieto et al., 2004). In another study, it was found that 40% of 301 patients with congestive heart failure (CHF) had OSA and systemic hypertension. After controlling for other risk factors, including obesity, OSA patients were 2.89 times (95% confidence interval range 1.25–6.73) more likely to have systolic hypertension (systolic BP ≥ 140 mm Hg) than those without OSA, and the degree of systolic BP elevation was directly related to the frequency of obstructive apneas and hypopneas (Sin et al., 2003).

Hypertension associated with OSA may be generated by sympathetic overactivity triggered by intermittent hypoxemia, large negative fluctuations in intrathoracic pressure, and arousal from sleep (Richert et al., 2002; Fletcher, 2003). Several studies have demonstrated reversal of sustained daytime hypertension by effective treatment of OSA through surgery (Guilleminault et al., 1975; Shibata et al., 2003) or nasal CPAP (Mayer et al., 1991; Logan et al., 2003).

15.6.2. Cardiovascular disease

The Sleep Heart Health Study reported that OSA is associated with relative odds of 2.38 for heart failure, independent of other known risk factors (Shahar et al., 2001; Javaheri, 2003). OSA has also been implicated in the pathogenesis of pulmonary hypertension, nocturnal cardiac ischemia, nocturnal arrhythmias and atherosclerosis (Tilkian et al., 1976; Blida et al., 1981; Guilleminault et al., 1983; Weitzenblum et al., 1988; Chaouat et al., 1996; Marrone and Bonsignore, 2002; Somers and Fletcher, 2002; Lattimore et al., 2003; Roche et al., 2003; Wolk and Somers, 2003). OSA patients demonstrate transient fluctuations in pulmonary artery pressure and pulmonary wedge pressure concomitant with apneas, which may lead to a progressive increase in pulmonary artery pressure. Permanent precapillary pulmonary hypertension at rest has been observed in some OSA patients and is reported to be poorly reversible after OSA treatment (Marrone and Bonsignore, 2002). Various studies have demonstrated that OSA can precipitate nocturnal angina in patients with coronary artery disease (Koehler et al., 1991; Hanly et al., 1993; Philip and Guilleminault, 1993; Franklin et al., 1995; Moore et al., 2000). Myocardial ischemia associated with OSA is postulated to result from a combination of increased

left ventricular afterload, sympathoadrenal stimulation and postapneic tachycardia (Somers and Fletcher, 2002). In a study of 400 OSA patients, 193 (48%) of the subjects experienced cardiac arrhythmias. Some serious arrhythmias include: non-sustained ventricular tachycardia ($n = 8$); sinus arrest lasting 2.5–3 seconds ($n = 43$); second-degree AV conduction block ($n = 31$); and premature ventricular contractions ($n = 75$). A relationship between low oxygen saturation ($<75\%$) and presence of severe arrhythmias was also shown (Guilleminault et al., 1983). A prospective study of 147 consecutive patients demonstrated significantly higher prevalence of nocturnal paroxysmal asystole in OSA patients and increased episodes of bradycardia and pauses that correlated with the severity of the sleep apnea (Phillips and Somers, 2002). OSA has been linked to other biochemical markers for cardiovascular disease, including leptin, C-reactive protein, homocysteine and insulin resistance syndrome (Phillips and Somers, 2002). The independent role of OSA in these overweight/obese subjects is unclear at this time.

15.6.3. Cerebrovascular disease

The relationship between OSA and cerebrovascular disease is bi-directional. Habitual snoring increases the risk of cerebrovascular disease with odds ratios ranging from 2.1–3.3 (Palomaki et al., 1992; Neau et al., 1995; Partinen, 1995; Bassetti and Chervin, 2000). A total of 69–95% of patients with acute strokes or transient ischemic attacks have OSA (Bassetti et al., 1996; Dyken et al., 1996). One hundred and fourteen male snorers, 40–65 years of age, with complaints of disturbed sleep underwent ultrasonographic examination of both carotid arteries to evaluate intima-media thickness (IMT) and the presence of plaque. The study revealed significantly higher IMT values in OSA patients compared to habitual snorers. Age and body mass index were significantly associated with IMT, while age and RDI were most predictive for plaque. It suggests that sleep-disordered breathing may be a predisposing factor for atherosclerosis and may precipitate plaque formation (Kaynak et al., 2003). Proposed mechanisms underlying increased risk of stroke in OSA patients are multifactorial and include hypertension, reduction in cerebral blood flow, altered cerebral autoregulation, impaired endothelial function, accelerated atherogenesis, thrombosis and paradoxical embolism (Yaggi and Mohsenin, 2003).

15.6.4. Obesity/metabolic syndrome

Approximately 60–90% of OSA patients are obese (Benumof, 2002). Obesity is the most common metabolic abnormality seen with sleep apnea and is predominantly central in pattern. BMI, body weight and the sum of fat skin folds are good predictors for the degree of OSA (Benumof, 2002; Schafer et al., 2002). The percentage of body fat and BMI are good predictors of AHI >10 , with high sensitivity (95.5%) but low specificity (46.2%) (Schafer et al., 2002). A review of magnetic resonance imaging (MRI) scans demonstrated a significant correlation between AHI and intra-abdominal and subcutaneous abdominal fat, but no correlation was established with subcutaneous fat in the neck region or parapharyngeal fat in the airway vicinity. Leptin concentrations correlate with AHI and with biochemical markers of the metabolic syndrome (lipoproteins, glucose). It has been demonstrated in OSA patients that, independent of obesity, various cytokines or mediators, such as IL-6, TNF alpha, leptin, and insulin levels are elevated (Vgontzas et al., 2003). Upper body obesity is linked to increased risk of diabetes, hyperlipidemia, insulin resistance and hyperinsulinemia, hyperuricemia, hypertension and cardiovascular/cerebrovascular disease (Grunstein, 2002; Ip et al., 2002). OSA has been implicated as an independent risk factor for insulin resistance, a known risk factor for atherogenesis, but this statement has been challenged by other data (Stoohs et al., 1996). The controversy lies in whether OSA is associated with reported metabolic markers and therefore is an independent risk factor for cardiovascular complications. Some of the publications involved a majority of subjects with a BMI $>25\text{ kg/m}^2$, and the statistical analysis to adjust for BMI may not be valid because of inadequate sample size (Guilleminault et al., 2004c).

15.7. Treatment

Treatment of OSA is influenced by severity of disease, effectiveness of proposed treatment, presence of co-morbid conditions and patient and physician preference. Non-surgical options include (1) weight loss, (2) avoidance of alcohol, nicotine and benzodiazepines, (3) positional therapy (avoidance of the supine posture) and (4) treatment of co-morbid conditions, such as hypothyroidism. Pharmacologic treatment of sleep apnea has not been very successful (Hudgel and

Thanakitcharu, 1998; Veasey, 2002). However, the use of stimulants, such as modafinil 200–400 mg day⁻¹, may be useful as adjunctive therapy for residual daytime sleepiness despite optimization of CPAP and other treatments. Oral appliances are useful for mild OSA and for patients with moderate or severe OSA who are unable or unwilling to use CPAP and who have failed surgery or are not surgical candidates. Oral appliances work by increasing airway space, providing a stable anterior position of the mandible, advancing the tongue or soft palate and possibly by changing genioglossus muscle activity (Lowe, 2000; Lowe and Schmidt-Nowara, 2002). These devices are not well tolerated by patients with significant temporomandibular joint symptoms.

15.7.1. Positive airway pressure therapy (continuous, bi-level and autotitrating)

CPAP therapy can be utilized for all categories of OSA and represents a first-line therapy for moderate to severe OSA, or symptomatic mild form and UARS. Based on the risk of increased hypertension documented in the Wisconsin Sleep Cohort Study, CPAP therapy has been recommended for all OSA patients with RDI of 30 (Loube et al., 1999). Similarly, based upon documented improvement in symptoms and daytime function in CPAP-treated patients, the same therapy is also recommended for patients with RDI of 5–30 associated with symptoms of excessive daytime sleepiness, impaired cognition, mood disorders (including insomnia, documented cardiovascular diseases (including hypertension and ischemic heart disease) or stroke. However, according to this consensus, treatment with CPAP is not indicated for asymptomatic, mild OSA patients without evidence of cardiovascular disease.

Effective CPAP therapy reduces nocturnal respiratory disturbances and improves nocturnal oxygenation, sleep architecture, daytime sleepiness, neurocognitive performance, driving performance and perceived health status (Weaver, 2002; Roux and Hilbert, 2003). Cardiovascular endpoints, such as hypertension, cardiac arrhythmia, nocturnal ischemia, left ventricular function and mortality, may also improve with CPAP therapy (Roux and Hilbert, 2003). Health care utilization is also reduced in OSA patients on CPAP therapy compared with untreated patients.

Seventy-six percent of OSA patients who were offered a trial of CPAP took their machines home (Pieters et al., 1996). In addition to patients declining

CPAP, patient compliance and adherence remain major concerns. Compliance refers to the proportion of patients using CPAP machines that are delivering a preset level of pressure, while adherence refers to the proportion of patients prescribed CPAP who report continued usage (Grunstein and Sullivan, 2000). Compliance rates assessed through patient self-reported usage of CPAP nightly range from 63–90% (Grunstein and Sullivan, 2000; Weaver, 2002). In one study when compared with objective measures, patients overestimated number of hours of use by 69 minutes $\pm$ 110 minutes, and 14% of subjects erroneously reported nightly usage of CPAP (Kribbs et al., 1993). The authors defined CPAP failure as usage of CPAP <4 hours per night on 70% of the nights and/or lack of symptomatic improvement. Objectively measured CPAP usage adjusted to reflecting mask-on time demonstrated average nightly use to be only 4.97 hours (range 2.8–6.9). The hallmark for eventual non-adherence and rejection of CPAP is use of CPAP <4 hours per night (Weaver, 2002). Reasons for non-adherence cited by our patients at the Stanford Sleep Disorders Clinic are similar to those reported by others: (1) nuisance factors (noise, partner intolerance, inconvenience); (2) mask problems (leaking mask, mask rubbing, skin rash/abrasion, conjunctivitis); (3) side effects (nasal congestion, rhinorrhea, epistaxis, sinus discomfort, oronasal dryness, chest discomfort, aerophagia, claustrophobia, difficulty exhaling, pneumothorax (exceptional), pneumocephaly (exceptional)); and (4) incomplete resolution of symptoms (frequent awakening, persistent fatigue or sleepiness). CPAP pressure has not been found to be a determinant of long-term use (Roux and Hilbert, 2003). Interventions to improve CPAP use are based on patient education and positive reinforcement with cognitive and behavioral therapy. These include providing literature addressing sleep apnea and good sleep habits; disseminating information on CPAP use, benefits and potential side-effects; organizing group educational sessions and support groups (e.g., AWAKE groups); teaching adaptation skills to the patient and bed partner; scheduling regular clinic follow-up to check the CPAP device for adequate pressures and to address patient's concerns; and implementing regular follow-up phone calls (initially weekly, then monthly). Most importantly, one should spend the time with the patient for optimal mask refitting.

Bi-level positive airway pressure allows independent adjustment of inspiratory and expiratory pressures. Indications for a trial of bi-level PAP include: (1)

intolerance of CPAP due to persistent massive nasal mask air leakage or discomfort exhaling against positive pressure; (2) concomitant nocturnal breathing disorders such as restrictive thoracic disorders, COPD and nocturnal hypoventilation (Loube et al., 1999).

Autotitrating PAP (APAP) devices detect snoring, apneas, hypopneas, flow limitation and changes in airway resistance or impedance, which are then interpreted by a central processing unit based on specific diagnostic algorithms to determine the resultant voltage for the APAP blower in response to these signals (Berry et al., 2002; Roux and Hilbert, 2003). The 2002 AASM practice parameters on APAP indicate that: (1) the diagnosis of OSA must be established by an acceptable method; (2) APAP may be used during attended titration to identify a single effective pressure for use with standard CPAP; (3) APAP may be used in self-adjusting mode for unattended treatment of OSA after an initial successful attended CPAP or APAP titration; (4) patients being treated with fixed CPAP on the basis of an APAP titration or being treated with APAP require follow-up to determine treatment effectiveness and safety; and (5) if symptoms do not resolve or if APAP therapy is ineffective, re-evaluation should be performed, and if needed, a standard CPAP titration should be done (Berry et al., 2002). APAP devices are not currently recommended for split-night studies or for patients with congestive heart failure, significant lung disease (COPD), daytime hypoxemia, respiratory failure or prominent nocturnal oxygen desaturation other than from OSA. APAP devices that rely on vibration or sound in the device's algorithm should not be used in patients who snore.

Recent studies have demonstrated that adding cognitive behavioral therapy (CBT) to CPAP treatment is beneficial for patients with chronic insomnia or psychosomatic symptoms secondary to SDB. In a randomized study conducted on postmenopausal women with UARS and chronic insomnia, radiofrequency reduction of nasal turbinates or turbinectomy, or a trial of CPAP showed better relief in daytime fatigue than behavioral treatment alone at 6 months (Guilleminault et al., 2002). Another study reported that one night CPAP titration improved objective measures of insomnia, arousal and sleep in patients with chronic insomnia and SDB (Krakow et al., 2004); and in the retrospective study of a small sample, validated measures of insomnia, sleep quality and sleep impairment achieved clinical cures or near-cures after combined CBT and SDB therapies. Septoplasty and radiofre-

quency reduction of enlarged nasal inferior turbinates can be successful, especially for improvement in nasal airflow and therefore enhance the effectiveness of CPAP therapy or compliance.

15.7.2. Surgery

Surgical therapy of OSA is directed towards site-specific obstruction in the upper airway. The three major anatomic regions of obstruction for OSA are the nose, palate (oropharynx) and base of the tongue (hypopharynx). Fujita classified the sites of obstruction as follows: Fujita type I – palate obstruction with normal base of the tongue; Fujita type II – palate and base of the tongue obstruction; and Fujita type III – base of the tongue obstruction with normal palate.

Surgical techniques involve either extirpation of soft tissue, secondary soft tissue repositioning through primary skeletal mobilization, or bypass of the pharyngeal airway (Riley et al., 2000; Sher and Goldberg, 2002; Guilleminault et al., 2004a). Procedures resulting in extirpation of soft tissue include tonsillectomy and adenoidectomy (T&A), a first-line therapy for children; uvulopalatopharyngoplasty (UPPP) or modified UPPP-extended uvulopalatal flap (discussed under the Stanford protocol); uvulopalatopharyngoglossoplasty (UPPGP); laser midline glossectomy (LMG); and lingualoplasty (Sher and Goldberg, 2002). UPPP, the most commonly used technique in adult OSA patients, enlarges the retropalatal airway through tonsillectomy (if present), trimming and reorientation of the posterior and anterior tonsillar pillars, and excision of the uvula and the posterior portion of the palate (Sher and Goldberg, 2002). UPPP has reported success rates (defined as 50% reduction in AHI or RDI and a RDI below 20) ranging from 43–67% (Gozal, 1998; Sher and Goldberg, 2002). Analyzing 37 papers with a total of 640 patients, Sher and Goldberg reported the following complications of UPPP: velopharyngeal insufficiency >1 month (14/640), postoperative bleeding (7/640), nasopharyngeal stenosis (5/640), voice change (4/640), vague foreign body sensation (1/640), successfully managed airway obstruction (2/640) and death secondary to upper airway obstruction (1/640) (Sher and Goldberg, 2002). A modified UPPP, called uvulo-flap, was described with less trauma or complications but at least similar success rate (Powell et al., 1996).

Surgical techniques involving primary skeletal mobilization include transpalatal advancement pharyngoplasty (TPAP), mandibular advancement

(MA), maxillo-mandibular advancement (MMA), genioglossal advancement (GA) and hyoid myotomy and suspension (Sher and Goldberg, 2002). TPAP involves resection of the posterior hard palate with anterior advancement of the soft palate into the bony defect, thereby enlarging the retropalatal airway; it is utilized for persistent retropalatal obstruction after UPPP, but its role in the surgical armamentarium is still vague (Sher and Goldberg, 2002). MA utilizes sagittal mandibular osteotomies to mobilize the tongue anteriorly and advance its insertion at the genioioid tubercle; this procedure is beneficial for a small group of patients with class II dental occlusion and significant mandibular deficiency (Riley et al., 2000, Sher and Goldberg, 2002). MMA involves LeFort I maxillary and sagittal-split mandibular osteotomies with simultaneous advancement of both maxilla and mandible, thereby producing maximal enlargement of the retrolingual airway and some enlargement of the retropalatal airway (Riley et al., 2000; Sher and Goldberg, 2002).

Tracheostomy may be used to bypass the pharyngeal airway in OSA patients with morbid obesity, severe facial skeletal deformity (mandibular deficiency) with excessive daytime hypersomnolence, severe hypoxemia ($\text{SaO}_2 < 70\%$), or significant cardiac arrhythmias (Riley et al., 2000; Sher and Goldberg, 2002; Li, 2003). The tracheostomy tube is plugged when the patient is awake to allow speech and swallowing. Although tracheostomy is easy to perform and is very effective for OSA, this procedure is only rarely performed due to inconvenience and hygiene issues.

The Stanford Protocol (Riley et al., 2000; Sher and Goldberg, 2002; Li, 2003) surgical approach consists of a two-phased approach to direct surgical treatment of suspected regions of obstruction. In conjunction with the clinical evaluation, patients undergo lateral cephalometry and fiberoptic nasopharyngoscopy with Müller maneuver. Phase I surgical intervention includes nasal reconstruction, UPPP or uvulo-flap, and limited mandibular osteotomy with genioglossus advancement. Nasal reconstruction is performed for patients with significant obstruction of the nasal airway (deviated septum, collapsed ala or enlarged turbinates) (Riley et al., 2000). In a series of 33 patients who underwent modified UPPP-extended uvulo-flap surgery, the reported success rate was 81.8% (Li, 2003) compared to the overall reported success rate of 60% for phase I surgery. Phase II surgery involves MMA osteotomy to treat refractory hypopharyngeal (base of the tongue) obstruction by

advancing the mandible forward at least 10 mm. The reported success rate for phase II surgery in 350 patients was 90% (Riley et al., 2000; Li, 2003). In a subgroup of 175 patients who underwent MMA between 1998–1995, the mean age was 43.5 years, the cure rate was 97%, the mean hospital stay was 2.4 days, and the mean post-operative RDI was 7.2 compared to 72.3 preoperatively (Li, 2003). Radiofrequency (RF) volumetric tissue reduction has been utilized for the treatment of turbinate hypertrophy as well as to reduce the base of the tongue (Li, 2003; Riley et al., 2003). In 18 patients treated with RF tongue-base reduction under local anesthesia with a mean of 5.5 sessions, mean RDI improved from 39.5 ± 32.7 to 17.8 ± 15.6 at 2.6 ± 0.7 months postoperatively (Li, 2003). Long-term follow-up (mean 28 ± 4 months) showed increase of RDI to 28.7 ± 29.4 , with persistent improvement of the mean apnea index but with worsening hypopnea index and with mean weight increase of 3.1 ± 7.9 kg (Li 2003), performance of extra sessions improved results. Although maxillary expansion has been routinely applied by the orthodontist for patients with a narrow maxilla and posterior cross-bite, it is rarely helpful in OSA patients with a narrowed airway due to limitation of the commonly co-existing mandible deficiency (Cistulli, 1998). Using distraction osteogenesis through midline osteotomy of the maxilla and mandible followed by gradual separation of the bone segments over 3–4 weeks and use of orthodontic techniques up to 12–18 months, it becomes feasible to expand maxilla and mandible simultaneously and generate enough airway space. Recently, Guilleminault and Li (2004) reported that distraction osteogenesis resulted in clinical and polysomnographic improvements in all six patients with no complications. The ideal candidate for this treatment may be adolescents or young adults with SDB who are already in need of orthodontic treatment and less likely committed to a life-long CPAP treatment.

Surgery is also a viable alternative to nasal CPAP in UARS patients. Since UARS patients often present with anatomical abnormalities involving soft tissues in the soft palate as well as the maxilla and mandible, absence of correction of the primary cause of abnormal breathing, such as crowded airway and narrow jaw, will leave patients with worsening functional somatic symptoms, and potentially may lead to development of local polyneuropathy and occurrence of OSA.

Before recommending surgical options, the indication, risks and potential complications of surgery, the

possibility of multiple and staged procedures, as well as other treatment options need to be discussed with the patient. The selection of surgical procedures should be based on the site of obstruction, anatomy of the airway, patient's medical condition, severity of the disease, age, patient preference, effectiveness of the surgery and the surgeon's experience and skill.

15.8. SDB in children

Although adolescent patients present with symptoms similar to those in adults with SDB, prepubertal children can have only non-specific and subtle symptoms. It is important to search for the following symptoms and syndromes that suggest presence of SDB: tiredness, fatigue, sleepiness, hyperactivity, attention deficit, poor school performance, aggressive behavior, extreme shyness, increased anxiety, depressed mood, sleepwalking, sleep terrors, confusional arousals, enuresis, morning headaches, unexplained morning nausea and vomiting, gastro-esophageal reflux, chronic allergies, crowded mouth, overlapping teeth, tongue thrust, recurrent upper airway infections or earaches. Nocturnal symptoms and signs include presence of regular snoring, agitated sleep, many awakenings from sleep with or without cry or confusion, mouth breathing asleep and awake, drooling during sleep, as well as unexplained night sweats (Guilleminault et al., 2004b).

Physical examination often reveals a long and narrowed face, nasal turbinate hypertrophy, septal deviation, high and narrowing hard palate, elongated low-lying uvula, redundant and low-lying soft palate, crowding of the oropharynx with enlarged tonsils and adenoids, prominent tonsillar pillars, macroglossia, narrow maxilla and mandible, overjet and retrognathia, cross-bite and dental malocclusion. Enlargement of tonsils and adenoids as well as hypertrophy of nasal turbinates is quite frequent, but one needs to understand in the context of a relatively small upper airway as a consequence of the above-listed abnormalities. The lymphoid tissues may not look as large as is seen in children with recurrent tonsillitis, but the relative size of those tissues can be large enough to compromise airflow in the upper airway, especially when a concomitant abnormality of the cranio-facial bony structure is present.

Major PSG findings in prepubertal children with OSA are snoring, flow limitation, hypopnea and apnea. The PSG is performed similarly as in adults, but the scoring criteria are different in many aspects:

for many years it has been accepted that in children, apnea index ≥ 1 was diagnostic for OSA. As respiratory rate varies with age during infancy and early childhood, it was also accepted that an apnea over two breaths was enough other than 10 s. By 2 years of age 98% of the children in control group monitored at Stanford had a respiratory rate <20 breaths min^{-1} ($16\text{--}17$ min^{-1} in NREM sleep and $17\text{--}19$ min^{-1} in REM sleep), with the upper normal limit similar to that in adults (Guilleminault and Lee, 2004). Recent data based on clinical outcome and repeat polysomnography have shown that SDB can exist in children without the presence of sleep apnea or hypopnea (Guilleminault et al., 2004a, 2004b). These findings were based on usage of the nasal cannula/pressure transducer system and esophageal pressure monitoring that helped determine SDB as much as apneas and hypopneas did. Other findings include presence of tachypnea, often the first indicator of abnormal breathing during sleep (a compensatory mechanism in maintaining minute ventilation, = tidal volume $\times$ respiratory rate); persistently elevated or progressively increased respiratory effort, measured by Pes with Pes crescendos or continuous sustained efforts, and discrete flattening of nasal airflow in the nasal cannula signals (Guilleminault et al., 2004b). Mouth breathing is always abnormal in a child and has detrimental consequences on the cranio-facial development of a young child, as 60% of the facial growth is completed by 4 years of age.

15.8.1. Treatment of SDB in children

Nasal CPAP has been used in infants and children with success. The key issue is to train and support parents at the beginning for their child's mask fitting and headgear usage during sleep. But the standard therapy for SDB in children is tonsillectomy and adenoidectomy, with simultaneous (unfortunately often overlooked by ENT specialists) treatment of enlarged nasal turbinates if present, preferably use of radio-frequency technology with temperature-controlled equipment. Suturing anterior and posterior layers of the tonsillectomy wound and attaching it laterally to pillars may gain additional airway space, further improving airway condition (Guilleminault et al., 2004a). Delaying T&A surgery in children with SDB will only prolong the suffering of those children and likely affect their physical and mental development as well as school performance (Gozal, 1998; Guilleminault et al., 2004d). Studies on post T&A outcomes demon-

strated improvement of nocturnal symptoms, such as bruxism (DiFrancesco et al., 2004), neurocognitive functions (Friedman et al., 2003), as well as quality of life in children (Mitchell et al., 2004). Recently, rapid maxillary expansion followed by orthodontic treatment has been applied in children with SDB and showed encouraging outcomes (Pirelli et al., 2004).

15.9. Summary

Obstructive sleep apnea syndromes afflict various age groups. OSA is reported to be more prevalent in middle-aged men (4%) compared to women (2%) in the United States, but the true prevalence may be higher. This paper reviews the history of sleep apnea, discusses the clinical presentation of OSA and UARS in adults and children, and presents the pertinent physical examination and polysomnography findings. Associated co-morbid conditions (hypertension, cardiovascular and cerebrovascular disease, obesity/metabolic syndrome) are addressed accordingly. Various treatment options, both non-surgical and surgical, are discussed.

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CHAPTER 16

Central sleep apnea

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16.1. Introduction

Jean Giradoux's 1939 play *Ondine* recounted a German mythical legend about the sea nymph Ondine, who married an unfaithful knight, Hans, and cursed him with the necessity of voluntary control over his breathing. Hans explained to Ondine how difficult it was to live with his curse: 'A single moment of inattention, and I forget to breathe. He died, they will say, because it was a nuisance to breathe...' Based on Giradoux's play, the term Ondine's curse has been applied to congenital central hypoventilation syndrome (CCHS), a form of central sleep apnea (Severinghaus and Mitchell, 1962).

Central sleep apnea syndrome (CSAS) consists of recurrent apneic/hypopneic episodes during sleep with reduction in esophageal pressure without associated upper airway obstruction. Figure 16.1 illustrates the polysomnographic findings associated with central sleep apnea. Absence or reduction of respiratory effort during sleep results in recurrent arousals, oxygen desaturation and daytime somnolence.

Central sleep apnea may be categorized into three types: hypercapnic, normocapnic and hypocapnic. Hypercapnic central sleep apnea is part of the sleep hypoventilation syndrome, whereas the normocapnic or hypocapnic types encompass idiopathic central sleep apnea syndrome (CSAS), Cheyne–Stokes breathing (CSB), and high-altitude sleep apnea (AASM Taskforce, 1999). The American Academy of Sleep Medicine (AASM) Taskforce has listed the following diagnostic characteristics for idiopathic central sleep apnea: excessive daytime sleepiness or frequent nocturnal arousal/awakenings unexplained by other

factors, ≥ 5 central apneas plus hypopneas per hour of sleep, and normocarbia while awake ($\text{PaCO}_2 < 45 \text{ mmHg}$) (AASM Taskforce, 1999; Lee-Chiong, 2003).

16.2. Physiology of respiration during wakefulness and sleep

Respiration is controlled by two independent and distinct systems located in the central nervous system: a behavioral system that is under cortical and forebrain control and an automatic, metabolic-dependent system that is under brainstem control. Supplementing the behavioral and automatic systems are additional cortical, hypothalamic and other regions of the brain that influence breathing but do not fit into either category (Sullivan, 1980). The automatic system controller consists of dorsal respiratory and ventral respiratory groups of neurons in the medulla and pons that regulate acid–base and oxygen homeostasis (Sullivan, 1980; Guilleminault and Robinson, 1998). Integration of sensory input from central chemoreceptors in the brainstem (CO_2 and pH-sensitive), peripheral receptors in the aortic (PaO_2) and carotid bodies (PaO_2 and PaCO_2), mechanoreceptors in the lung, chest wall, and upper airway, pressure receptors, and putative flow receptors provides an automatic neural drive to the respiratory pump (Sullivan, 1980; Guilleminault and Robinson, 1998; Chokroverty, 1999; Caruana-Montaldo et al., 2000). Central chemoreceptors increase the respiratory rate and the intensity and rate of rise of the inspiratory 'ramp signal' in response to increased $[\text{H}^+]$ concentration in the cerebrospinal fluid.

Sensory signals are received, analyzed and passed onto the 'executive' cells, which in turn mobilize the motor loop through ventrolateral pathways in the spinal cord conveying messages to the lower motor neurons. Messages to the respiratory neurons for coughing and hiccups utilize separate spinal pathways, while non-respiratory neurons in the medulla utilize the reticulospinal tracts. The voluntary system

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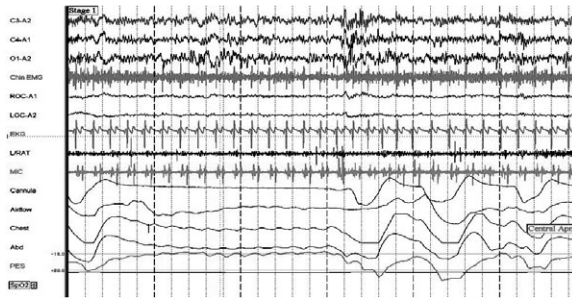


Fig. 16.1. Central sleep apnea. This 30-second epoch was recorded during sleep in a patient with neuromyopathy. Central apnea is demonstrated with absent airflow on the nasal cannula associated with absent respiratory effort on the chest and abdominal leads and reduction in esophageal pressure, followed by an arousal response. The oscillations seen in the airflow, chest and abdominal leads represent cardiac artifact.

conveys its commands through the corticospinal tract.

The spinal respiratory neurons integrate the phasic central respiratory drive with a variety of inhibitory and excitatory inputs from spinal respiratory motor neurons and interneurons, spinal segmental afferents (mainly muscle afferents), and descending non-phasic activity which sets the resting membrane potentials (Sullivan, 1980). Through a complex array of feedback loops and reflexes, tidal volume (V_T) normally varies with each breath in response to metabolic demands.

The metabolic and voluntary control systems are active during wakefulness. The brain anticipates metabolic rate demands through an involuntary excitation of breathing that Fink has called the wakefulness stimulus (Fink, 1961; Fink et al., 1963). This concept is supported by Hugelin and Cohen's demonstration of powerful excitatory connections from non-respiratory regions of the reticular activating system to medullary respiratory neurons (Hugelin and Cohen, 1963). The wakefulness stimulus is believed to be dependent on non-specific reticular excitation by visual, acoustic and somesthetic stimuli and is independent of metabolic and voluntary input.

During non-rapid eye movement (NREM) sleep, the metabolic controller is solely responsible for controlling respiration. At sleep onset, the wakefulness stimulus is significantly attenuated and the CO_2 chemoreceptor setpoint is reset (Dempsey and Skatrud, 1986). During unsteady NREM sleep (stage I and short periods of stage II interrupted by arousals),

periodic breathing at sleep onset occurs in 40–80% of normal subjects, lasts from 10–60 minutes and demonstrates either a Cheyne–Stokes pattern (decrecendo–crescendo amplitude of breathing before the apnea) or Biot's breathing pattern (progressive decrease in amplitude followed by apnea with brisk increase in amplitude on the first or second breath after the apnea). During steady NREM sleep (stable stage II and slow-wave sleep), the frequency and amplitude of breathing is regular (Krieger, 2000). The hypercapnic ventilatory response curve is shifted to the right during sleep onset and remains shifted throughout all stages of sleep (Dempsey and Skatrud, 1986). Ventilation and tidal volume progressively decrease from NREM stages I through IV, while alveolar and arterial pCO_2 increase by 3–7%, arterial pO_2 decreases by 3.5–9.4 mmHg and SaO_2 decreases by 2% or less (Krieger, 2000).

During rapid eye movement (REM) sleep, control of breathing is primarily through the automatic system, although parts of the behavioral system may be activated as well, since vocalization and intelligible speech can occur. Tonic (TREM) and phasic (PREM) REM sleep have different effects on breathing. During PREM sleep, the response of minute volume of ventilation to progressive hypercapnea is significantly less than in NREM sleep, and the duration of apnea elicited by sustained lung inflation is significantly shorter than during NREM sleep (Sullivan et al., 1979). The cumulative effect of different influences on the brainstem neurons during phasic REM sleep can result in hyperventilation, hypoventilation or apnea lasting one or two respiratory cycles (Phillipson, 1978; Orem, 1980). These positive or negative influences on phasic REM sleep affect the phrenic nerve neurons, thereby modulating the diaphragmatic effort during one or more respiratory cycles. During TREM sleep, the response of minute volume of ventilation and the duration of apnea elicited by sustained lung inflation are similar to that in NREM sleep (Sullivan et al., 1979). However, the major change in ventilatory control during REM sleep arises from the hypotonia and atonia that involves most skeletal muscles, including respiratory accessory muscles.

16.3. Disorders associated with central sleep apnea

Central sleep apnea can result from instability of the feedback loop of the automatic system – increased

arterial circulation time with delay in transmission of information from the lungs to the receptors, increased controller sensitivity with overcorrection of abrupt, physiologic fluctuations of gas tensions and reduced system damping (Sullivan, 1981). Other sites of dysfunction can include the motor loop, the sensori-motor loop, or the integrative and executive neuronal network.

These abnormalities can be produced by various neurological as well as non-neurological disorders (see Table 16.1). Neurological causes include lesions affecting the peripheral nervous system, the central nervous system, and the autonomic nervous system, as well as a combination of peripheral and central lesions. Non-neurological causes can arise from congestive heart failure, chronic obstructive pulmonary disease, chronic renal failure, upper airway resistance syndrome, high altitude exposure and iatrogenic CPAP titration.

16.3.1. Neurological causes of central sleep apnea

16.3.1.1. Peripheral nervous system

Lesions affecting the muscles, neuromuscular junction, nerve roots and nerves innervating the diaphragm, intercostal muscles and respiratory accessory muscles can produce respiratory abnormalities that are accentuated during sleep, with resultant apneas and hypopneas. Patients with myopathic weakness frequently complain of excessive daytime sleepiness and fatigability, particularly during exacerbations of their muscular weakness.

Howard et al. (1993) described a series of 84 patients with myopathies, including congenital myopathies, dystrophies (Becker, fascioscapulo-humeral, myotonic, Duchenne, limb-girdle), inflammatory disorders, and rigid spine syndromes, who presented with either progressive nocturnal hypoventilation with subsequent respiratory failure or arrest, recurrent respiratory tract infection or obstructive sleep apnea. Patients with inflammatory disorders had early onset of respiratory symptoms, while patients with limb-girdle and myotonic dystrophies and congenital myopathies had respiratory symptoms paralleling the development of limb weakness. Sixty-six of these 84 patients required ventilatory support, and 32 required tracheostomies. Patients with myotonic dystrophy evaluated at the Stanford University Sleep Disorders Clinic presented with daytime fatigue and sleepiness related to a combination of upper airway resistance during NREM sleep and a decrease in inspiratory muscle effort during REM sleep. Noctur-

nal polysomnograms demonstrated mild to moderate intermittent decreases in inspiratory esophageal pressure followed by transient alpha arousals lasting 2 seconds or longer. During REM sleep, transient apneas were seen, often associated with phasic events and transient arousals. Guilleminault and Robinson (1998) hypothesized that impairment of craniofacial muscle function early in life may impair mandibular growth in these patients, thereby predisposing to the development of upper airway resistance during sleep. After puberty, snoring as a manifestation of obstructive sleep apnea may develop in some patients and central diaphragmatic apneas in others.

In patients with metabolic myopathy due to acid maltase deficiency (AMD), diaphragmatic weakness usually precedes the onset of wasting of skeletal muscles. Mellies et al. (2001) reported a correlation between diaphragmatic dysfunction and degree of ventilatory restriction with sleep-disordered breathing in seven patients with acid maltase deficiency. AMD patients seen at the Stanford University Sleep Disorders Clinic complained of fragmented nocturnal sleep, tendency to fall asleep easily in quiet situations and daytime tiredness (Guilleminault et al. 1992). The underlying breathing disorder may be unmasked during sleep, since the respiratory accessory muscles that may initially compensate for slight diaphragmatic weakness during NREM sleep become atonic during REM sleep. Initially, the breathing problem in these patients is seen during phasic REM sleep, together with a higher number of transient alpha arousals. As the illness evolves, the number of central apneas increases, and hypopneas and apneas are noted during tonic REM sleep in addition to brief (2–10 seconds) alpha intrusions (Guilleminault et al., 1992).

All myopathies involving the thoracoabdominal and respiratory accessory muscles impair breathing during sleep by reducing tidal volume (V_T). The earliest and most prominent changes in arterial blood gas in these patients are significant and frequent episodes of nocturnal desaturation during REM sleep associated with hypoventilation (Smith et al., 1988; Krachman and Criner, 1998). The degree of nocturnal desaturation correlates with the severity of underlying diaphragm dysfunction (Bye et al., 1990). Mouth occlusion pressure ($P_{0.1}$) is maintained or increased in patients with neuromuscular disease with significant clinical weakness, suggesting intact central drive (Begin et al., 1980; Baydur, 1991).

Rogette et al. (2002) evaluated 42 patients with primary myopathies to determine patterns and

*Table 16.1***Disorders Associated With Central Sleep Apnea.**

Neurological Causes	Non-Neurological Causes
Peripheral Nervous System Myopathies Dystrophies (Becker, fascioscapulo-humeral, myotonic, Duchenne, limb-girdle) Inflammatory myopathies Metabolic myopathies (Acid maltase deficiency) Neuromuscular Junction Disorders Myasthenia gravis Neuropathies with phrenic nerve involvement Charcot-Marie-Tooth Diphtheria Varicella zoster Polyradiculoneuropathy Landry-Guillain-Barré-Strohl Central Nervous System Cervical cord lesions Cordotomy for cancer pain relief Lesions from trauma, neoplasm, infectious agents Syringomyelia Syringobulbia Arnold-Chiari malformations Basilar invagination Platybasia Vascular lesions—infarcts, angiomas Neoplasms—glioma, ganglioglioma Cerebellar lesions with brainstem compression—hematomas, subdural or epidural hematoma Cortical and subcortical lesions with brainstem compression Subdural or epidural hematomas Cerebral contusion Intracranial abscess Neoplasms Combined Lesions Leigh's encephalopathy and mitochondrial myopathy Poliomyelitis Amyotrophic lateral sclerosis Autonomic Nervous System Congenital central hypoventilation syndrome Acquired central hypoventilation syndrome Familial dysautonomia (Riley-Day) Shy-Drager Autonomic neuropathy associated with diabetes, chronic renal failure Obesity-Hypoventilation syndrome (Pickwickian syndrome)	Chronic obstructive pulmonary disease Congestive heart failure Metabolic diseases Uremia Hypothyroidism High altitude Medications Opiates Phenothiazines in infants Spinal anesthesia in pre-term infant

predictors for sleep disordered breathing. Three distinct patterns of sleep-disordered breathing (SDB) emerged: REM hypopneas, REM hypopneas with REM hypoventilation and REM/NREM continuous hypoventilation, which preceded daytime respiratory failure. They also showed that inspiratory vital capacity (IVC) and maximal inspiratory muscle pressure (P_{IMAX}) yielded highly predictive thresholds for SDB onset ($\text{IVC} < 60\%$, $P_{\text{IMAX}} < 4.5 \text{ kPa}$), SDB with continuous hypoventilation ($\text{IVC} < 40\%$, $P_{\text{IMAX}} < 4.0 \text{ kPa}$), and SDB with diurnal failure ($\text{IVC} < 25\%$, $P_{\text{IMAX}} < 3.5 \text{ kPa}$). Patients with $\text{IVC} > 60\%$ have good respiratory reserve with minimal risk of respiratory complications and are unlikely to have SDB. However, patients with $\text{IVC} < 60\%$ have reduced respiratory reserve, are predisposed to SDB, and should probably undergo polysomnography for assessment. At $\text{IVC} < 40\%$, capnometry is warranted to evaluate the need for non-invasive ventilation, since patients with continuous hypercapnic hypoventilation have barely compensated respiratory failure and are at high risk of acute respiratory deterioration (Rogette et al., 2002).

Twenty myasthenia patients studied by Quera-Salva et al. had daytime diaphragmatic weakness independent of functional capacity, autonomy and activity level reached. Older patients with abnormal daytime blood gas concentrations, abnormal total lung capacity, and increased body mass index were reported to be at higher risk of developing sleep-disordered breathing (SDB) (Quera-Salva et al., 1992). Of interest are Lu et al.'s findings of abnormal phrenic nerve conduction in patients with myasthenic crisis (Lu et al., 1998). Stepansky et al. (1997) reported central sleep apnea/hypopnea with oxygen desaturation to 60% during REM sleep in myasthenia patients and also noted memory dysfunction with normal vigilance performance in these patients compared to myasthenia patients without sleep apnea.

In addition to the myopathies and neuromuscular junction disorders, diaphragmatic weakness secondary to phrenic nerve involvement can result in sleep apnea. Phrenic neuropathy has been reported in association with hereditary motor-sensory neuropathy I (Charcot-Marie-Tooth) (Chan et al., 1987; Osanai et al., 1992; Akiba et al., 1996; Guilleminault and Robinson, 1998; Dematteis et al., 2001) as well as with infectious processes, such as diphtheria and varicella zoster (Chokroverty et al., 1999). Landry-Guillain-Barré-Strohl polyradiculoneuropathy can result in severe respiratory involvement during the

first 3–4 weeks with associated sleep apnea and hypoventilation (Chokroverty, 1999).

16.3.1.2. Central nervous system

Lesions involving the spinal cord, brainstem and cerebral cortex, or a combination thereof, can also result in central sleep apnea. These lesions can impair either the behavioral (cortical and forebrain) or the metabolic/automatic pathways that control ventilation. Brainstem lesions can affect the automatic controller and its descending pathways, as well as the voluntary pathways. Spinal cord lesions can damage the ventrolateral tracts, corticospinal tracts, reticulospinal tracts, other descending pathways, and the spinal respiratory neurons and interneurons.

Lesions within the cervical spinal cord may result from trauma, neoplasm, infectious agents or surgical procedures. Bilateral lesions of the ventrolateral tracts of the cervical spinal cord associated with cordotomy for intractable cancer pain have occasionally caused sudden death during sleep, severe hypoventilation, CO_2 retention, sleep fragmentation and repetitive central apneas (Krieger and Rosomoff, 1974).

Various brainstem nuclei and pathways involved in respiration can be compressed and damaged by syringomyelia and syringobulbia. In addition, associated malformations, such as Chiari I (cerebellar tonsillar herniation) and Chiari II (cerebellar tonsillar herniation with caudal displacement of the hindbrain), basilar invagination and platybasia can affect respiratory control (Malow, 1999; Nogues et al., 1999). Syringomyelia and syringobulbia have been associated with both central and obstructive sleep apnea (Rodman et al., 1962; Bokinsky et al., 1973; Bullock et al., 1988; Omer et al., 1996; Nogues et al., 1999). Despite prolonged apneas with severe hypoxemia, respiratory symptoms were absent in many patients with syringobulbia and high cervical syringes described by Nogues et al. (1999). The sleep-related respiratory disturbances in these patients were not due to respiratory muscle weakness or to vocal cord paralysis. Furthermore, there was no correlation between the severity of the sleep-related respiratory abnormalities and the size of the syrinx. The respiratory abnormalities were attributed to involvement of respiratory rhythm-generating structures in the medulla, including the ventral and dorsal respiratory groups, interactions with the parabrachial/Kolliker-Fuse pontine respiratory group, effector respiratory motoneurons of the nucleus ambiguus, and the descending bulbospinal pathways regulating phrenic and intercostals motoneurons in the spinal cord.

Acquired central hypoventilation seen during sleep is classically attributable to bilateral medullary lesions from vascular pathologic lesions, such as infarcts or bulbar angiomas (Devereaux et al., 1973; Juan et al., 1999). Rarely, hemimedullary infarcts have been reported to cause respiratory insufficiency (Levin and Margolis, 1977; Takehara et al., 1992; Minami et al., 2000). Brainstem neoplasms have resulted in central apneas and alveolar hypoventilation syndrome (Valente et al., 1993; Hui et al., 2000; Nakajima et al., 2000; Manning and Leiter, 2000; Ios et al., 2001). Apnea due to medullary compression can also occur as a result of posterior fossa lesions (cerebellar hematoma, subdural hematoma or effusion, epidural hematoma) (Ohishi et al., 1983; Nishizaki et al., 1988). Cerebellar hematomas in neonates and low-birth-weight infants can present with severe progressive apnea and falling hematocrit (Martin et al., 1976; Rom et al., 1978). Supratentorial lesions, such as subdural or epidural hematoma, cerebral contusion, intracranial abscess and neoplasm can produce herniation with secondary bilateral brainstem lesions (Quera-Salva and Guilleminault, 1987; Kemp et al., 2003). Encephalitis can also lead to central alveolar hypoventilation with significant blunting of daytime hypoxic and hypercarbic responses.

16.3.1.3. Combined lesions of the central nervous system

Bilateral dysfunction of the medullary respiratory neuronal network can result from degenerative and metabolic diseases, such as Leigh's disease. The extent of the lesion determines the decrease in tidal volume and the degree of CO₂ retention during sleep, as well as the relative distribution of apneas and hypopneas. Patients with mitochondrial disease, particularly those with Leigh's encephalopathy, cytochrome *c* deficiency, or neurogenic muscle weakness, ataxia, and retinopathy (NARP), may present with apneic events, which are most commonly central, but occasionally are obstructive (Clay et al., 2001). Magnetic resonance imaging and autopsy have demonstrated medullary lesions involving predominantly the dorsal respiratory group of medullary neurons (Yasaki et al., 2001). Reduced ventilatory response has been postulated as the mechanism for central sleep apnea in patients with mitochondrial disease. Respiratory arrest during sleep has been reported in these patients, and treatment of sleep apnea with tracheostomy has resulted in improvement in cerebral apnea and general cerebral functioning.

Poliomyelitis affects the anterior horn cells, thereby producing atrophy of respiratory accessory and thoracoabdominal muscles. Kyphoscoliosis or restrictive lung disease ensues, causing ventilatory impairment present during the wakeful state and aggravated during sleep. In addition, poliomyelitis can produce cranial neuropathy affecting the motor root of the trigeminal nerve, the facial nerve and the hypoglossal nerve, resulting in tongue muscle dysfunction and maxillo-mandibular impairment. Defects in medullary control can also result from bulbar poliomyelitis. Both central and obstructive apneas can be seen with this disorder. Abnormal upper airway resistance leads to decreased inspiratory effort that varies with sleep state (NREM or REM). Tidal volume is reduced and CO₂ retention occurs in varying degrees. Apneas are worse during REM sleep due to a combination of REM sleep atonia and pathologic phrenic nerve output secondary to medullary impairment. Tidal volume is reduced with variable degrees of CO₂ retention. The respiratory status of post-poliomyelitis patients needs to be monitored, since acute respiratory infections can exacerbate their respiratory problems.

Amyotrophic lateral sclerosis is characterized by progressive loss of upper and lower motor neurons leading to respiratory failure and death. It is associated with severe diaphragmatic dysfunction and is a common cause of repetitive central apnea (Howard et al., 1989; Ferguson et al., 1996; Guilleminault and Robinson, 1998; Arnulf et al., 2000). ALS patients with bulbar involvement have more arousals per hour of sleep, more stage I sleep, and shorter total sleep time compared to age-matched normal controls (Ferguson et al., 1996). Diaphragmatic dysfunction in ALS patients is associated with a dramatic reduction in REM sleep and significant reduction in survival time (Arnulf, 2000). Nevertheless, in the absence of severe bulbar impairment, patients with diaphragmatic weakness and nocturnal apnea can experience symptomatic benefit from supportive ventilation (CPAP, cuirass, or intermittent positive pressure ventilation) (Howard et al., 1989).

16.3.1.4. Autonomic nervous system

Congenital central hypoventilation syndrome (Ondine's curse), a rare, life-threatening syndrome that usually presents shortly after birth, is characterized by failure of autonomic respiratory control with impaired ventilatory response to hypercarbia and hypoxemia (Guilleminault et al., 1982, 1986; Schulte et al., 1982; Oren et al., 1987; Verloes et al., 1993;

Gozal, 1998; Spengler et al., 2001; Redline et al., 2002). Marked developmental abnormalities of the brainstem or cerebral cortex have been reported in some of these patients, associated with hypotonia, delay in developmental milestones and epilepsy. These patients possess central chemoreceptor dysfunction, defective central integration, or a combination of both, resulting in profound blunting of the hypercapnic and hypoxic ventilatory responses to afferent chemosensory and metabolic inputs. Alveolar hypoventilation is particularly prominent during NREM sleep, with severe gas exchange disturbances, presumably since respiratory output is primarily controlled by metabolic inputs during these sleep stages (Gozal and Harper, 1999). Anesthetic care for children with CCHS requires special precautions to monitor for superimposed upper airway obstruction, cor pulmonale, autonomic dysfunction and seizures (Strauser et al., 1999). CCHS has been linked to sudden infant death syndrome, and familial occurrence of this combination has been reported. Complex segregation analysis, using either multifactorial threshold or major locus models, demonstrates familial incidence with recurrence risk of SIDS in CCHS families is likely to be <5% (Khalifa et al., 1988; Weese-Mayer et al., 1993; Kerbl et al., 1996).

CCHS has also been described in association with Hirschsprung's disease, a congenital intestinal dysmotility disorder. About 50% of CCHS patients are afflicted with Hirschsprung's disease, and 20% of CCHS/Hirschsprung patients develop neuroblastoma or ganglioneuroma (Minutillo et al., 1989; Bolk et al., 1996; Croaker et al., 1998; Rohrer et al., 2002; Silvestri et al., 2002; Shahar and Shinawi, 2003). The association of CCHS with these disorders has led to speculation that a shared genetic mechanism may underlie these neurocristopathies (a heterogeneous group of disorders that result from defective growth, differentiation and migration of neural crest cells). Screening mutations of the receptor tyrosine kinase RET and endothelin 3 have revealed that only occasional patients were affected by these mutations, leading Gozal and Harper (1999) to hypothesize that CCHS may result from disruption of more than a single gene. Segregation analysis suggested a complex model of inheritance with a major locus involved, and disruption of the RNX gene produced a phenotype similar to CCHS. However, Matera and colleagues (2002) were unable to demonstrate any alteration in RNX gene in 13 patients with CCHS/Hirschsprung disease. Amiel and colleagues (2003) found heterozy-

gous de novo polyalanine expansion mutations of the paired-like homeobox gene PHOX2B in 18 out of 29 CCHS patients and suggested that PHOX2B plays an essential role in the normal patterning of the autonomous ventilation system.

Familial dysautonomia (Riley-Day syndrome), another congenital autonomic disorder, may present with intercurrent lung infections accompanied by CO₂ retention during sleep. Apneas and hypopneas with reduction in tidal volume are seen in both NREM and REM sleep (Gadoth et al., 1983; Guilleminault and Robinson, 1998). Different levels of severity are observed, and CO₂ retention parallels the amount of sleep time. The CO₂ set point for arousal is always abnormal and remains constant, unless superimposed metabolic abnormalities disrupt the equilibrium and lead to further impairment of chemical sensitivity (Guilleminault and Robinson, 1998).

Autonomic neuropathies secondary to insulin-dependent diabetes mellitus, chronic renal failure, Shy-Drager syndrome, and other chronic neuropathies may present similarly to Riley-Day syndrome (Guilleminault et al., 1977, 1981, 1985; Lehrman et al., 1978; McNicholas et al., 1983). During NREM sleep in these disorders, irregular breathing pattern for one or two breaths has been noted on PSG, associated with decreased tidal volume, but without CO₂ retention. However, in most acquired autonomic neuropathies, apneas and hypercapneas are more frequently seen during REM sleep (Guilleminault and Robinson, 1998).

Obesity-hypoventilation syndrome (Pickwickian syndrome) is characterized by chronic alveolar hypoventilation (PaO₂ < 70 mmHg and PaCO₂ > 45 mmHg) in obese patients (body mass index > 30 kg/m²) in the absence of lung, neuromuscular, chest wall or metabolic disease that could explain the gas dysfunction. It is usually seen in males > 50 years of age with exercise-induced shortness of breath and is often associated with hypertension, diabetes and heart disease (Weitzenblum et al., 2002). The hypoventilation in these subjects may result from a combination of reduced hypoxic (one sixth of normal) and hypercapnic (one third of normal) ventilatory drives, abnormal chest wall mechanics, respiratory muscle fatigue, and repeated episodes of nocturnal obstructive apnea (Zwillich et al., 1975; Teichtahl, 2001; Weitzenblum et al., 2002). Leptin (the anti-obesity hormone which acts as a respiratory stimulant and an appetite suppressant) deficiency or resistance may play a role in the pathophysiology of obesity-hypoventilation syndrome (Fitzpatrick, 2002). Genetic determinants related to

the *ob* locus in genetically obese mice (*ob/ob*) influence hypercapnic ventilatory response prior to the emergence of obesity (Tankersly et al., 1996). Treating obese mice with leptin attenuates the respiratory complications of the obese phenotype and increases awake and asleep minute ventilation independent of food intake, weight or carbon dioxide production (Tankersly et al., 1998; O'Donnell et al., 1999). Phipps et al. (2001) reported that mean serum leptin levels in 12 hypercapnic obese subjects was twice as high as mean serum leptin levels in 44 eucapnic obese subjects, with both groups demonstrating severe mean apnea–hypopnea indices, suggesting leptin resistance in the first group. The potential role of leptin in respiratory modulation requires further elucidation.

16.3.2. Non-neurologic causes of CSA

16.3.2.1. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is associated with increased lower airway resistance during wakefulness and can potentially lead to sleep-related hypoventilation. The severity of sleep hypoventilation in COPD patients is best predicted by a combination of baseline arterial CO₂ tension (PaCO₂), body mass index and percent REM sleep. REM-related hypoventilation correlates significantly with the severity of inspiratory flow limitation in REM and with the apnea–hypopnea index. Sleep hypoventilation is associated with significant increases in arterial carbon dioxide tension from night to morning (O'Donoghue et al., 2003).

In patients with decreased pO₂ during wakefulness, slight hypoventilation at sleep onset can result in significant desaturation, as predicted from the change in the slope of the oxyhemoglobin dissociation curve. Central apneas and hypopneas can be observed during phasic REM sleep (Jonczak et al., 2001). During REM sleep, significant oxygen desaturation is noted, accompanied by increased pCO₂. The desaturation during REM sleep results from physiologic atonia of the respiratory accessory muscles and intercostal muscles, leading to further reduction in alveolar ventilation in patients who already have impaired breathing due to a flattened diaphragm (Guilleminault and Robinson, 1998; Fleetham, 2003).

16.3.2.2. Congestive heart failure

Central sleep apnea occurs in approximately 40–66% of patients with congestive heart failure (CHF) (Burgess, 1997, 1998; Andreas, 2000; Kohnlein,

2001; Topor, 2001; Javaheri, 2003). Low arterial pCO₂ (≤ 35 mmHg) in an awake state is a reliable predictor of central sleep apnea in patients with CHF. Several factors have been identified that lead to central sleep apnea in CHF patients. The difference in two pCO₂ setpoints (prevailing pCO₂ and pCO₂ at the apneic threshold) is narrow. As long as the prevailing pCO₂ is greater than the apneic threshold, central apnea does not occur. Patients with CHF and central sleep apnea are unable to increase their prevailing pCO₂ during the transition from wakefulness to sleep, so sleep unmasks the apneic threshold. In addition, increased arterial circulation time delays the transfer of information regarding pulmonary capillary PO₂ and PCO₂ to the controllers (the chemoreceptors). Prolonged circulation time may be due to low stroke volume, increased intrathoracic blood volume due to pulmonary congestion, or increased left atrial and left ventricular volumes. Moreover, low functional residual capacity due to pleural effusion, pulmonary edema or cardiomegaly can result in underdampening (Javaheri, 2003). Wilcox proposed that patients with CHF have an exaggerated ventilatory response to CO₂ that may play a role in the repetitive central apneas associated with CHF (Wilcox et al., 1993).

16.3.2.3. Metabolic diseases

Uremia, independent of any autonomic neuropathy, may be associated with repetitive central sleep apnea. Dialysis may also be associated with central apneic events with increased frequency the night after hemodialysis. Disturbances in acid–base or electrolyte balance have been postulated as causative factors. Hypothyroidism can also result in central sleep apnea.

16.3.2.4. Upper airway disorders

Between 1972–1973, Guilleminault et al. (1972, 1973) reported a group of subjects who complained of daytime fatigability, fragmented sleep with frequent awakenings, intermittent snoring and repetitive sleep apnea. These subjects were studied with electromyographic (EMG) monitoring using electrodes placed in the superior and middle pharyngeal constrictor muscles, geniohyoid and genioglossal muscles, combined with closed circuit video camera imaging of the velopharynx or oropharynx, and simultaneous monitoring of airflow on the polysomnogram. Changes that occurred before, during and after central sleep apnea were analyzed: narrowing of the upper airway occurred during the central apnea events in the absence of both pharyngeal constrictor muscle activ-

ity and negative inspiratory pressure (Guilleminault et al., 1995; Guilleminault and Robinson, 1998). This study, together with a similar study by Badr et al. (1995), suggests that nasal airway receptors may play a role in the development of central sleep apnea.

16.3.2.5. *High altitude*

Sleep disturbances occur frequently during acute ascent to high altitude. Subjects in several studies (Reite, 1975; Lahiri, 1983) reported frequent awakenings with a sensation of suffocation and were observed to have periodic breathing, normal total sleep time, significant increase in time spent awake, increase in stage I sleep, and decrease in slow-wave sleep (Weil, 2004). Periodic breathing seen at high altitude reflects respiratory oscillation in which the stimulatory effects of hypoxia are opposed by the inhibitory effects of hypocapnic alkalosis. The occurrence of apnea with lessening of ventilatory stimuli is seen during sleep. Sleep fragmentation with frequent arousals leads to poor subjective sleep quality.

16.3.2.6. *Medications*

Respiratory depressant medications can result in central sleep apnea. Farney et al. (2003) reported sleep-disordered breathing in three patients on long-term opioid therapy. During NREM sleep, PSG recordings in these patients demonstrated ataxic breathing, central apneas with sustained hypoxemia, and unusually prolonged obstructive hypopneas secondary to delayed arousal responses. Oxygen desaturation was worse during NREM sleep compared to REM sleep. Phenothiazine administered to four normal infants resulted in increased frequency of central and obstructive apneas and reduced frequency and duration of arousals (Kahn et al., 1985). Kahn and colleagues recommended avoiding CNS depressants in infants < 1 year of age. Using tetracaine in dextrose 10% solution, pre-operative spinal anesthesia administered at the T4–T6 level to two ‘former pre-term infants’ resulted in apnea and bradycardia (Tobias et al., 1998). Tobias and colleagues recommended that even with spinal anesthesia, appropriate monitoring for apnea should be performed, based on an infant’s post-conceptual age.

16.4. **Diagnosis and treatment**

For measuring respiratory effort, esophageal pressure monitoring is the reference standard. Other methods, including thermal sensors or expired CO₂ measure-

ments, piezo sensors and strain gauges, respiratory inductance plethysmography (RIP), and surface recording of diaphragm EMG are insensitive and may result in misclassification of respiratory events (AASM Taskforce, 1999; Lee-Chiong, 2003).

Titration pressures that are too low or too high can result in iatrogenic central sleep apnea. Low pressures result in incomplete elimination of low-level upper airway obstruction. Excessive nasal flow from high CPAP pressures leads to discomfort, increased arousals, fragmentation of sleep and hyperstimulation of upper airway receptors. Careful titration using esophageal manometry can improve these apneas.

Treatment is directed toward the underlying cause of the central sleep apnea. Table 16.2 lists the various treatment modalities. Pharmacologic agents have a limited role. Medroxyprogesterone, a respiratory stimulant which works on the hypothalamus and hippocampus through hormonal receptors, is reportedly beneficial in the treatment of obesity-hypoventilation syndrome, as well as in other conditions where respiratory drive is impaired. However, in the authors’ experience, this treatment, by itself, has not been very effective and should be viewed as adjunctive therapy. Protriptyline hydrochloride, other tricyclic agents, and selective serotonin reuptake inhibitors, which suppress REM sleep and increase tone of the genioglossus and geniohyoid muscles, have been utilized for both central and obstructive apnea with limited success. Acetazolamide, an agent that induces metabolic acidosis by inhibiting CO₂ transport, may be useful in cases of central sleep apnea due to hypocarbia secondary to hyperventilation at high altitude (Guilleminault and Robinson, 1998). For patients with congestive heart failure, optimizing treatment with diuretics, angiotensin-converting enzyme inhibitors and beta-blockers may normalize PCO₂ by decreasing pulmonary congestion and sympathetic activity, thereby improving central sleep apnea. Treatment of CHF may stabilize breathing during sleep by increasing stroke volume, shortening arterial circulation time due to reduction in cardiopulmonary blood volume, and increasing functional residual capacity through a decrease in cardiac size, pleural effusion, and intravascular and extravascular pulmonary fluid. Several open studies and a double-blind study have demonstrated the efficacy of theophylline in the treatment of central sleep apnea in heart failure, although the mechanism of action remains unclear (Javaheri, 2003).

Supplemental nasal oxygen eliminates desaturation, improves central sleep apnea, and may decrease

Table 16.2

Treatment Modalities for Central Sleep Apnea.

Treatment	Indications	Advantages	Disadvantages
Pharmacologic			
Acetazolamide	Central sleep apnea (CSA), high altitude sleep apnea	Decreases central apneas and reduces arousals	Paresthesias
Theophylline	Cheyne-Stokes respiration (CSR)	Improves cardiac function, decreases apnea-hypopnea index	Need to monitor levels and drug interactions
Medroxyprogesterone	Obesity-hypoventilation syndrome	Increases central respiratory drive	Not very effective
Protriptyline, other tricyclic medications	CSA	Reduces number of apneas	Cholinergic side-effects, minimal efficacy
SSRI agents	CSA	Reduces number of apneas	Minimal efficacy, cost
Positive Airway Pressure			
CPAP	CSA, CHF with CSR	Decreases central apneas, improves sleep quality and reduces mortality in CHF patients	Mask leaks, aerophagia, compliance issues
Bilevel-PAP	CSA, CHF with CSR, hypoventilation with neuromuscular disease	Decreases central apneas, improves sleep quality and reduces arousals, reduces mortality in CHF patients, slightly better patient compliance compared to CPAP	Mask leaks, more expensive than CPAP, more bulky equipment compared to CPAP
Mechanical Ventilation			
<i>Non-invasive negative-pressure ventilation</i>			
Tank ventilators	Severe symptomatic hypoventilation	Efficient, dependable, does not require airway intubation, simple to use	Cumbersome, immobile, can induce claustrophobia, potential for upper airway obstruction
Cuirass and pulmo-wrap ventilators	Severe symptomatic hypoventilation	More portable than the tank ventilators	Can induce upper airway obstruction, less efficient than the tank ventilators
<i>Non-invasive positive pressure ventilation</i>			
	CSA, CHF with CSA. Preferred modality for non-invasive ventilation	Improves sleep quality and quality of life while avoiding upper airway obstruction, better tolerated, simpler equipment, patient-triggered, leak compensated	Leaks from mask and mouth, aerophagia, skin breakdown
<i>Invasive Mechanical Ventilation</i>			
Tracheostomy and positive pressure ventilation	Stable neuromuscular disease or chest wall disorders, quadriplegia from cervical cord lesions	Reliable ventilation, ability to suction secretions, controls upper airway	Requires tracheostomy, expensive, limits speech and swallowing, requires nursing care

Table 16.2

Continued

Treatment	Indications	Advantages	Disadvantages
Diaphragm pacing	Congenital and acquired hypoventilation syndrome	Decreases ventilatory dependency	Expensive, may induce upper airway obstruction, diaphragm fatigue, equipment failure
Atrial pacing	CHF with CSA	Reduces central and obstructive apneas	Uncertain long-term efficacy, invasive therapy
Oxygen supplementation	CHF with CSA, obesity-hypoventilation, severe neuromuscular disease with hypoventilation	Reduces significant desaturation associated with hypoventilation	Cumbersome, requires regular tank changes

arousals. However, Haque and colleagues (1996) reported that oxygen had adverse hemodynamic effects in seven subjects with class III and class IV heart failure, wherein breathing supplemental oxygen (FIO₂ 24%, 40%, 100%, each for 5 minutes) resulted in progressive dose-dependent increase in systemic vascular resistance and pulmonary capillary pressure with decrease in stroke volume.

Studies using acute and chronic nasal continuous positive airway pressure (CPAP) to treat central sleep apnea in congestive heart failure have yielded variable results ranging from no benefit to significant benefit (Takasaki et al., 1989; Bradley et al., 1990; Buckle, 1992; Guilleminault et al., 1993; Naughton et al., 1994; Javaheri, 1996, 2000; Krachman et al., 1999; Sin et al., 2000; Yasuma, 2002). Proposed mechanisms for the beneficial effects of CPAP in CHF patients with Cheyne–Stokes respiration – central sleep apnea (CSR-CSA) include unloading of inspiratory muscles (acute effect) and chronic effects, such as elimination of upper airway occlusion, reduction of minute volume of ventilation, increase in PaCO₂ above the apnea threshold, improvement in nocturnal oxygenation, reduction in the frequency of central apneas, alleviation of symptoms of sleep apnea, and increase in inspiratory muscle strength (Tkacova and Bradley, 2000).

Nasal CPAP may improve survival in CHF patients by decreasing ventricular arrhythmias and improving ejection fraction. Randomized controlled trials have demonstrated significant reduction in 3-year-mortality cardiac transplantation (Javaheri, 2000). In a random-

ized controlled trial of 66 CHF patients (29 with and 37 without CSR-CSA) treated with CPAP followed over a mean of 2.2 years, Sin et al. (2000) reported significant improvement in left ventricular ejection fraction (LVEF) at 3 months and a relative risk reduction of 81% in the mortality–cardiac transplantation rate in the subgroup with CSR-CSA who used CPAP compared to controls. CPAP use did not affect these outcomes in non-CSR-CSA patients. Sin et al. (2000) did not establish sustained benefit in LVEF, since ejection fractions were not repeated after the third month, and the study did not include quality of life measures. The Canadian Positive Airway Pressure for Heart Failure (CANPAP trial), an on-going 5-year multicenter randomized trial of CPAP in heart failure patients, will assess cardiac transplant-free survival, compliance and quality of life measures and evaluate sustained benefit in LVEF.

Compliance with PAP therapy is a major issue in CHF patients. In a randomized controlled study performed at the Stanford Sleep Disorders Clinic, 56 patients with sleep-disordered breathing and CHF New York class III and IV were enrolled in a study to evaluate compliance with PAP therapy (Kreutzer et al., 2003). Twenty-three patients were randomized to therapy (CPAP = 11, bilevel = 12) and 33 patients to the control group (no PAP therapy). There were no significant differences in age and severity of cardiac failure between the two treatment groups. The majority of the patients in the treatment group were men (18 men, five women). Patients underwent PAP titration in the laboratory at entry, with repeat titration

after 3 months; patient–mask interface was optimized throughout the study, phone interviews were conducted every other day during week 1 and every 1–2 weeks thereafter. Compliance was measured at the patient–mask interface, and data stored on the patients' PAP machines were downloaded using Encore™ software at 3 and 6 months. Compliance was defined as > 5 hours average nightly use for five nights per week. Six out of 23 treated patients (26%) had poor compliance. Greater non-compliance was noted in the CPAP-treated group (36.4%) versus the bi-level-treated group (16.6%). Poor compliance was associated with lack of perceived change in daytime cardiac symptoms, higher scores on visual analog scale for physical impairment that did not change over time, frequent arousals during the night attributed to PAP equipment, lower Epworth Sleepiness Scores at entry into the study, and patient-perceived primary care physician's viewpoint of non-efficacy of PAP therapy. There was no relationship between the severity of cardiac failure indicated by ejection fraction at entry and compliance.

To improve compliance with CPAP therapy in CHF patients, Tkacova et al. (2000) have recommended a regimen of 2–3-day acclimatization to CPAP, wherein patients are started at low pressures while they are awake, before using it during sleep. CPAP pressure should be raised by 2–3 cmH₂O increments until 10–12 cmH₂O is reached. Polysomnography can be performed 4–6 weeks later, at which time the frequency of central events should be markedly reduced.

The role of CPAP versus bi-level ventilation in the treatment of CSA patients remains controversial. In the Heart-PAP study, a randomized controlled trial performed at the Stanford Sleep Disorders Clinic, 56 patients with congestive heart failure NY classes III and IV were enrolled in the study. Out of 23 patients with sleep-disordered breathing, 11 were randomized to CPAP and 12 received bi-level ventilation. LVEF was performed at baseline and after 3 months, and quality of life questionnaires compared daytime sleepiness and daytime energy at baseline and 3 months after therapy. Satisfaction scores with CPAP and bi-level usage were obtained at 3 months. The study showed reduced short-term mortality (at 3 months) in the treated group (0 mortality) versus the control group (9%). Unlike the findings of Sin et al., (2000) there was no difference in LVEF at 3 months compared with baseline in either treated group. Patients in the CPAP group had higher non-compliance (36.4%) compared with the bi-level group

(16.7%). CPAP non-compliance was defined as <5 hours average nightly use for at least five days per week. Quality of life indicators showed improvement in daytime sleepiness and daytime energy scores in both treated groups, with no difference in two-way ANOVA between CPAP and bi-level ventilation. A strong trend towards higher satisfaction scores was seen with bi-level versus CPAP. Considering the difficult patient population, the great chance of non-acceptance of positive airway pressure treatment on the first night of equipment calibration, and the perception of a better quality of life with bi-level than with CPAP, Afifi et al. (2003) suggested that bi-level treatment should be considered as a first line of prescription for this indication. Kohnlein and colleagues (2002) reported significant and equal improvements for CPAP and bi-level ventilation in the parameters of sleep quality, daytime fatigue, circulation time, and New York Heart Association class in CHF patients treated with two 14-day cycles of CPAP or bilevel ventilation.

Atrial pacing has been reported to be beneficial in reducing the apnea–hypopnea index in patients with central and obstructive sleep apnea (Garrigue et al., 2002). The patient population reported in this study was poorly defined and the benefit reported could have represented an acute effect. The long-term efficacy of this modality cannot be assumed based on the results of one night's study.

Patients with both neuromuscular disease and sleep-disordered breathing may also benefit from use of bi-level ventilation. Guilleminault et al. (1998) reported 20 patients with neuromuscular disease followed over a mean of 3.5 years who were treated with bi-level positive airway pressure (mean inspiratory positive pressure was 11.5, range of 9–14, and mean expiratory pressure was 4.5, range 4–5 cmH₂O) and eight control patients with neuromuscular disease. Three patients had low flow (0.5 L min⁻¹) 100% oxygen bled into their masks. Using bi-level PAP, the respiratory disturbance index was significantly decreased, and there was a significant decline in Epworth Sleepiness Scale (ESS) scores.

Diaphragm pacing by electrical stimulation of the phrenic nerve has been utilized successfully in patients with congenital and acquired central hypoventilation syndrome (Weese-Mayer et al., 1989; Flageole et al., 1995; Eleftheriades and Quin, 1998; DiMarco, 2001; Eleftheriades and Quin, 2002). Careful patient evaluation regarding intact phrenic nerve function, motivation, adequate psychosocial support, and

close medical follow-up are critical for successful pacing (Chervin and Guilleminault, 1997; Eleftheriades and Quin, 1998). Problems include the need for surgical implantation or thoracoscopy; high cost (approximately \$20 000); need to replace component parts due to receiver failure, electrical wire or wire insulation breakage; infection requiring diaphragm pacer system removal; mechanical nerve injury; the development of upper airway obstruction; and diaphragmatic fatigue and the need for gradual conditioning to obviate this problem (Weese-Mayer et al., 1989; Chervin and Guilleminault, 1997; Krachman and Criner, 1998). Although a select group of patients may benefit from this modality, less-invasive and less-costly therapies, such as nasal bi-level PAP, or intermittent positive pressure ventilation may be more useful for most patients.

Mechanical ventilation may be needed to augment spontaneous breathing in patients with severe hypoventilation (Krachman and Criner, 1998). Non-invasive mechanical ventilation (negative-pressure ventilation and non-invasive positive-pressure ventilation) is generally preferred, although patients with cervical cord injuries and severe neuromuscular disease with excessive airway secretions may require invasive mechanical ventilation (tracheostomy with positive-pressure ventilation). Krachman and Criner recommend the following indications for mechanical ventilation: symptomatic nocturnal hypoventilation (morning headaches, nightmares, enuresis, decreased energy), dyspnea at rest or increased work of breathing during sleep, hypoventilation that could predispose to cor pulmonale ($\text{PCO}_2 > 45 \text{ mmHg}$, $\text{pH} < 7.32$ after treating reversible causes), and nocturnal hypoventilation ($\text{SaO}_2 < 88\%$) despite supplemental oxygen therapy.

In summary, central sleep apnea has diverse causes, both neurological and non-neurological, and management strategies need to be tailored to the underlying pathologic process. Quality of life can be improved with appropriate therapy. For the treatment of central sleep apnea, the primary modality of therapy is PAP therapy, although a minority of patients may benefit from medications, atrial or diaphragm pacing or mechanical ventilation. Controversial issues that require further investigation include comparison of CPAP versus bi-level therapy on various outcome measures (short term and long term), such as mortality, hospital admission rates and length of stay, general quality of life measures, quality of sleep measures, patient satisfaction measures and compliance with

therapy. Additional research is needed to clarify the role of leptin in the respiratory modulation of central sleep apnea.

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CHAPTER 17

Sleep and neuromuscular disorders

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17.1. Introduction

There has been an increasing awareness in the medical community regarding sleep-disordered breathing (SDB) in patients with neuromuscular disorders since its initial recognition in bulbar poliomyelitis by Sarnoff and colleagues (1951) and in myotonic dystrophy by Benaim and Worster-Drought (1954). Most of the sleep disturbances in neuromuscular disorders are secondary to sleep-related respiratory dysfunction. However, other factors (e.g. pain, muscle cramps, muscle immobility, joint pains, contractures, kyphoscoliosis, obesity due to sedentary lifestyle, craniofacial abnormalities, anxiety and depression) may further contribute to sleep dysfunction. SDB may be present even at a time when daytime arterial oxygenation is unaffected as respiratory homeostasis is especially compromised in sleep and in particular REM sleep. A high prevalence of SDB has been reported in neuromuscular disorders by Labanowski and colleagues (1996), who demonstrated respiratory distress index of 15 or more in 42% of patients with neuromuscular disorders as compared to 4% in the general population. Over 90% of the respiratory events were scored as hypopneas; only 1.5% of all events were apneas of which 60% were central apneas. Despite its high incidence in neuromuscular disorders, SDB frequently remains underdiagnosed and untreated, particularly in its early stages. Labanowski and colleagues (1996) reported further that only one out of 60 patients attending a neuromuscular clinic had

been investigated for SDB. A common complication and consequence of undiagnosed, untreated sleep-disordered breathing is development of chronic respiratory failure. Certain neuromuscular disorders can even present initially with acute respiratory failure (e.g., acid maltase deficiency, myasthenia gravis). It is important to understand the clinical findings and laboratory investigations that help early detection of nocturnal SDB, so that appropriate treatment may be initiated to improve quality of life and possibly longevity. A knowledge of breathing physiology in sleep is first required to understand its alterations and effects on neuromuscular diseases.

17.2. Physiology of sleep and respiration

Breathing is controlled during wakefulness and sleep by two independent and separate systems—the metabolic or automatic and the voluntary or behavioral systems (Chokroverty, 1999a). During wakefulness both systems operate but during sleep breathing is entirely dependent on the metabolic or automatic control system in the medulla. Respiratory rhythmogenesis depends on tonic input from the peripheral and central structures converging on medullary neurons. The parasympathetic vagal afferents, the carotid and aortic body peripheral chemoreceptors, the central medullary chemoreceptors, supramedullary and reticular activating systems all influence the medullary respiratory neurons in maintaining respiratory homeostasis.

The voluntary control system for breathing originates in the cerebral cortex and terminates partly on the automatic medullary respiratory control system but primarily descends to the spinal respiratory motor neurons where they integrate with the reticulospinal fibers originating from the medullary respiratory neurons.

During sleep, alveolar hypoventilation occurs due to a combination of factors: reduction in tidal volume, slowing of metabolism (i.e., reduction of CO₂ pro-

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duction (VCO_2) or O_2 consumption (VO_2)), absence of tonic influence from brain stem reticular activating system, decreased chemosensitivity and increased upper airway resistance to air flow. The upper airway resistance increases during sleep as a result of hypotonia of upper airway dilating and the intercostal muscles, and decreased output from sleep-related medullary respiratory neurons. Further, during rapid eye movement (REM) sleep there is a marked generalized reduction in the tone of skeletal muscles with the exception of diaphragm and extraocular muscles. Thus there is a further fall in tidal volume (due to decreased rib cage contribution), minute ventilation and mean inspiratory flow from non-rapid eye movement (NREM) to REM sleep. Therefore, the sleep-related hypoventilation is more marked in REM sleep as compared with NREM sleep. Additionally, although the diaphragm maintains phasic activity, the tonic activity is reduced in REM sleep. REM sleep is not a homogeneous state but comprises tonic and phasic states. Phasic REM is associated with smaller tidal volume, higher respiratory rate, and lower minute ventilation. Thus breathing is more compromised during phasic as compared with tonic REM state. The functional residual capacity (FRC) decreases in sleep, particularly so in REM sleep. Position-dependent changes in vital capacity (VC) further cause a worsening of symptoms in the supine position.

As a result of alveolar hypoventilation in sleep the PCO_2 rises by 2–8 mm and PO_2 decreases by 3–10 mmHg, and oxygen saturation decreases by less than 2% during sleep (despite reductions of VO_2 and VCO_2 during sleep). Also, the decrease in hypoxic and hypercapnic ventilatory drives during sleep is more marked during REM sleep as compared with NREM sleep. Thus respiratory homeostasis is relatively unprotected during sleep, particularly during REM sleep. Nonetheless these sleep-related changes do not have any significant effects in normal individuals. However, in patients with neuromuscular disorders weakness of the respiratory muscles including diaphragm appears to cause a loss in the safety factor. Thus physiological sleep-related hypoventilation might transform into pathologic alveolar hypoventilation resulting in hypoxemia, abnormal breathing patterns and respiratory failure.

17.2.1. Breathing patterns

The term SDB has been used synonymously with the term obstructive sleep apnea syndrome (OSAS) and is

commonly measured in terms of the apnea–hypopnea index (AHI). In a broader sense it includes all the disorders of breathing during sleep. This encompasses a wide and varying range of diagnostic etiologies, pathophysiologies and symptomatic severity. In its mildest form it may present as snoring. The other presentations include: upper airway resistance syndrome, OSAS, alveolar hypoventilation, paradoxical breathing, periodic respiration including Cheyne–Stokes breathing, apneustic breathing or dysrhythmic breathing. These conditions can be differentiated based on the analysis of breathing patterns in sleep (Chokroverty, 1999b). Sleep-related apneas are recognized in three forms: central, obstructive and mixed apneas. When measured by polysomnography (PSG), obstructive apneas are defined as complete cessation of airflow at nose and mouth lasting at least 10 seconds with persistence of thoracic and abdominal efforts. Cessation of airflow with no respiratory effort constitutes central apnea. In mixed apnea, initially airflow and respiratory effort cease followed by a period of upper airway obstructive sleep apnea. Hypopnea is defined as greater than 50% decrease in airflow and effort as compared with preceding or following respiratory cycles, lasting at least 10 seconds accompanied by arousals or $\geq 4\%$ oxygen desaturation. Apneas and hypopneas are usually accompanied by oxygen desaturation and terminated by an arousal. Thus recurrent apnea, hypopnea, arousal and oxygen desaturation result in sleep disruption and fragmentation with subsequent changes in systemic and pulmonary hemodynamics. Recurrent arousals related to increasing upper airway resistance but without accompanying apnea, hypopnea or oxygen desaturation are believed to constitute the upper airway resistance syndrome. Paradoxical breathing (movements of thorax and abdomen in opposite directions) may occur in patients with upper airway resistance syndrome or OSAS while paradoxical inward movement of abdomen is seen with diaphragmatic paralysis. Alveolar hypoventilation, defined as a reduction in alveolar ventilation resulting in hypoxemia and hypercapnia, is the most common sleep-disordered breathing in patients with neuromuscular disorders. In the initial stage of neuromuscular disease this is primarily seen as nocturnal alveolar hypoventilation, particularly so during REM sleep. During wakefulness both voluntary and metabolic respiratory systems are intact. In order to drive the weak respiratory muscles in neuromuscular disease the central respiratory neurons increase the firing rate or recruit additional

respiratory neurons during wakefulness to maintain adequate ventilation. During sleep this voluntary control is entirely lacking, aggravating the existing ventilatory problems. Thus, multiple factors are responsible for SDB in neuromuscular disorders resulting in sleep-related hypoventilation and eventual respiratory failure. An additional factor is kyphoscoliosis secondary to neuromuscular disorders causing extrapulmonary restriction of the lungs with impairment of pulmonary functions, breathlessness, sleep apnea and hypoventilation. In the advanced stage of the illness, respiratory failure may be present during daytime as a result of alveolar hypoventilation, ventilation–perfusion mismatching, hypoxemia and hypercapnia. The nocturnal alveolar hypoventilation may later persist during daytime as well and lead to chronic respiratory failure. Respiratory failure is defined as an inability of the lungs to effectively exchange gas and maintain normal acid–base balance (Moxham, 1996), resulting in an arterial oxygen tension (PaO_2) of less than 8.0 kPa (60 mmHg) or a carbon dioxide tension (PaCO_2) greater than 6.7 kPa (50 mmHg).

17.3. Clinical approach to diagnosis

Alveolar hypoventilation associated with neuromuscular disease may present acutely or insidiously. The acute form presents with progressive rapid reduction in vital capacity (VC) followed by respiratory failure. Symptoms and signs of acute respiratory failure are characterized by dyspnea, irregular, rapid, shallow or periodic breathing, cyanosis and tachycardia. This has been seen in myasthenia gravis, poliomyelitis, acute inflammatory demyelinating polyneuropathy (Guillain–Barré syndrome). However, nocturnal hypoventilation and chronic respiratory failure in neuromuscular disease may present insidiously and remain asymptomatic. Thus a high index of suspicion is necessary. The important clinical clues (Chokroverty, 1999b, 2001; Attarian, 2000) include nocturnal restlessness, frequent unexplained arousal, excessive daytime sleepiness, daytime fatigue, shortness of breath, orthopnea, morning headaches, intellectual deterioration, and failure to thrive and declining school performance in children. Signs of impending cor pulmonale include severe insomnia, morning lethargy, headaches and unexplained dependent edema. The evaluation of SDB begins with a detailed sleep history, which must specifically include clues suggestive of sleep-disordered breathing as described above. Clinical approach must also include

a history of present and past illnesses, family, social and medication histories. Physical examination including a detailed medical and neurologic examination is aimed at assessing the underlying cause of SDB. Particular attention should be paid to uncovering bulbar weakness and respiratory muscle weakness, use of accessory muscle of respiration and paradoxical respiration. Patients with neuromuscular disorders showing these clinical symptoms or findings must be investigated further to evaluate for nocturnal hypoventilation in order to prevent serious consequences of chronic respiratory failure, such as pulmonary hypertension, congestive cardiac failure and cardiac arrhythmia.

Neuromuscular disorders causing SDB (Chokroverty, 1999b; Attarian, 2000) include poliomyelitis and post-polio syndrome, amyotrophic lateral sclerosis, muscular dystrophy, myotonic dystrophy, acid maltase deficiency, congenital or acquired myopathies, myasthenia gravis and myasthenic syndrome, polyneuropathies including Guillain–Barre syndrome.

17.3.1. *Sleep and poliomyelitis and post-polio syndrome*

Respiratory disturbances have been reported in acute and convalescent stages of bulbar poliomyelitis and some patients have sequelae of respiratory dysrhythmia, particularly sleep-related hypoventilation or apnea requiring ventilatory support. The poliovirus infection directly affects the medullary respiratory and hypnogenic neurons and this explains the patients' respiratory difficulties. Post-polio syndrome is manifested by increasing weakness in previously affected or unaffected muscles of a subject with poliomyelitis. Sleep disturbances are common in patients with post-polio syndrome and in one series were reported in 31% of patients (Cosgrove et al., 1987).

17.3.2. *Sleep and amyotrophic lateral sclerosis*

Amyotrophic lateral sclerosis (ALS) is the most common degenerative motor neuron disease in adults affecting the spinal cord, brain stem, motor cortex and corticospinal tracts. It is characterized by degeneration of both upper and lower motor neurons manifesting as a varying combination of weakness, wasting, fasciculation, dysarthria, dysphagia and gait dysfunction. Symptomatic respiratory muscle weakness is usually noted late in the course of progression. ALS can be associated with profound sleep

disturbances secondary to sleep-disordered breathing and other factors, e.g., decreased mobility, muscle cramps, anxiety and swallowing difficulty. No significant relation between bulbar involvement and the severity of SDB or the type of respiratory event has been reported (Kimura et al., 1999; Arnulf et al., 2000). Sleep disruption in ALS therefore appears to be due mainly to diaphragmatic weakness and hypoventilation rather than to obstructive events due to bulbar weakness (Kimura et al., 1999; Arnulf et al., 2000). SDB has also been reported at an early stage ALS (Kimura et al., 1999; Barthlen and Lange, 2000; Takekawa et al., 2001).

17.3.3. Sleep and peripheral neuropathy

SDB occurs in diffuse polyneuropathy due to involvement of nerves supplying the intercostals, diaphragm and accessory muscles of respiration. Neuropathic pain and immobility may further contribute to sleep disturbances. Unilateral phrenic nerve paralysis may be asymptomatic but bilateral paralysis may become life threatening and is the main cause of sleep-disordered breathing in polyneuropathy. The most common cause of phrenic nerve involvement and respiratory dysfunction is acute inflammatory demyelinating polyneuropathy (Guillain–Barre syndrome). Other causes of polyneuropathy with phrenic nerve dysfunction may include diphtheria, Charcot–Marie–Tooth disease, varicella zoster infection, brachial plexopathies, paraneoplastic syndromes and diabetic neuropathy. Dematteis and colleagues (2001) reported sleep apnea syndrome in patients with Charcot–Marie–Tooth 1A, reportedly attributed to pharyngeal neuropathy. Diaphragm weakness is suspected in the presence of paradoxical respiration and a significant fall in VC from standing to supine posture. Respiratory disturbances in sleep including OSAS have also been described in patients with diabetic autonomic neuropathy (Bottini et al., 2000).

17.3.4. Sleep and neuromuscular junctional disorders

Myasthenia gravis is an autoimmune disorder characterized by impaired neuromuscular junctional transmission of nerve impulses due to a reduced number of functional acetylcholine receptors in postjunctional region. It manifests as easy muscle fatigability. Sleep-disordered breathing is common in myasthenia gravis associated with respiratory muscle weakness particu-

larly diaphragmatic weakness. Nocturnal desaturation is most pronounced in REM sleep and the presence of central apneas is a common manifestation of SDB. Quera-Salva and colleagues (1992) reported that older patients with moderately increased body mass index (BMI), abnormal total lung capacity and abnormal daytime blood gas concentrations were the primary candidates for development of sleep apneas and hypopneas and oxygen desaturation of less than 90% during sleep. Sleep-disordered breathing and nocturnal desaturation may improve following treatment with thymectomy or prednisone. SDB has also been described in Eaton–Lambert myasthenic syndrome (Chokroverty, 1999b).

17.3.5. Sleep and myopathies

Myopathies are a primary muscle disease characterized by weakness of muscles resulting from a defect in the muscle membrane or contractile elements, which is not due to a dysfunction of the lower or upper motor neurons. The patients develop restrictive lung disease as respiratory muscle weakness progresses. In addition, respiratory center abnormalities have also been documented in Duchenne’s muscular dystrophy (DMD) (Takasugi et al., 1995). SDB is commonly seen in patients with DMD and limb-girdle muscular dystrophies and myopathies associated with acid maltase deficiency (Martin et al., 1983; Mellies et al., 2001) but may also occur in congenital, inflammatory, metabolic or mitochondrial myopathies. In comparison to subjects with ALS, sleep architecture appears to be better preserved in DMD.

17.3.6. Sleep and myotonic dystrophy

Myotonic dystrophy (MD) is an autosomal dominant muscular dystrophy of adult onset associated with myotonia. Sleep-related problems in MD are due to two factors: SDB and primary hypersomnia. SDB is due to alveolar hypoventilation secondary to weakness and myotonia of respiratory and upper airway muscles, and an abnormality in central control of ventilation likely related to a membrane abnormality of muscles and other tissues including brainstem neurons that regulate breathing and sleep (Guilleminault et al., 1978). Some authors have also shown central, mixed and upper airway obstructive sleep apneas in patients with MD (Labanowski et al. 1996). Sleep-disordered breathing has been reported in both early and late stages of the illness. SDB is, however, not the only cause of hypersomnia in patients with MD (Park and Radtke,

1995) and therefore correction of hypoventilation does not always lead to improvement in excessive daytime sleepiness. Additionally, there is suggestion of malfunction of circadian and ultradian systems involving neuroendocrine abnormality in sleep contributing to excessive daytime sleepiness (Culebras et al., 1977). Park and Radtke (1995) demonstrated the presence of sleep-onset REMs in patients with MD without associated evidence of SDB suggesting other causes for hypersomnia. Thus, it is very important to evaluate patients with MD with overnight PSG and MSLT, as excessive daytime sleepiness may not be related to SDB.

Sleep disturbances have also been reported in proximal myotonic myopathy (PROMM) (Chokroverty et al., 1997). PROMM is a hereditary myotonic disorder differentiated from MD by absence of chromosome 19 CTG trinucleotide repeat that is associated with MD. In PROMM there is mutation of the gene encoding for zinc finger 9 on chromosome 3q21. The sleep disturbances in these patients include snoring, excessive daytime sleepiness, frequent awakenings and sleep-onset insomnia that may be related to involvement of REM–NREM-generating neurons as part of a generalized membrane disorder.

17.4. Laboratory investigations

Laboratory investigations are mere extensions of history and physical examination, which have been addressed above. The definitive test for alveolar hypoventilation is an analysis of arterial blood gases (ABG) showing evidence of hypoxemia and hypercapnia. An indwelling arterial catheter would be required to measure nocturnal arterial blood gases, which is both invasive and impractical. Also, it does not monitor the ABG continuously throughout the night. ABG during daytime may remain normal in early neuromuscular disorders and it may become abnormal only as the disease advances.

The single most important laboratory test in patients with sleep complaints secondary to neuromuscular disease is polysomnographic recording (Chokroverty, 1999b). PSG findings include increased numbers of awakenings, sleep fragmentation, reduced total sleep time, central, mixed or upper airway obstructive sleep apneas/hypopneas associated with oxygen desaturation and non-apneic oxygen desaturation, worse in REM sleep.

Finger oxymetry is always included in overnight PSG recordings. Finger oxymetry reflects reduced arterial oxygen tension but does not necessarily cor-

relate with the severity. For example, finger oxymetry may display only mild oxygen desaturation in the presence of significant hypoventilation and decreased arterial oxygen tension on account of the hyperbolic shape of the oxyhemoglobin dissociation curve.

CO₂ concentration can also be measured in expired air at the nose. Under optimal conditions end-tidal PaCO₂ reflects alveolar CO₂ and thus arterial PaCO₂. However, because of dilution of sampled expired air with room air, the PaCO₂ measurement is reduced. Several laboratories use transcutaneous monitoring of PaCO₂ but this is unreliable and correlates poorly and unpredictably with PaCO₂.

The multiple sleep latency test (MSLT) may be performed to document the presence and severity of daytime sleepiness in patients with sleep-disordered breathing. A mean sleep-onset latency of less than 5 minutes is consistent with pathologic sleepiness. Additionally, the presence of two or more sleep-onset REMs out of 4–5 nap recordings is suggestive of associated narcolepsy.

Phrenic nerve conduction studies and needle electromyographic examination of the diaphragm may be performed to evaluate diaphragm function (Saadeh et al., 1993). Electromyography and nerve conduction studies may assist in diagnosing the primary condition causing SDB and sleep dysfunction.

The pulmonary function test (PFT) assesses respiratory and ventilatory muscle functions (Chokroverty, 1999b). The tests include spirometry with flow volume loops, lung volumes and gas distribution and transfer. Spirometry with flow volume loops assess the mechanical properties of respiratory system by measuring expiratory volumes and flow rates, e.g., forced expiratory volume 1 (FEV 1), vital capacity, forced vital capacity (FVC), peak expiratory flow rate (PEFR) and maximum voluntary ventilation (MVV). The lung volumes permit detection of restrictive lung disease, e.g., total lung capacity (TLC), residual volume (RV) and functional residual capacity (FRC). Gas distribution and gas transfer measure the diffusion capacity of the lung volume. Respiratory muscle strength must be severely reduced before significant reduction in lung volumes is appreciated, as pressure/volume characteristics of the respiratory system are not linear. Thus, static respiratory pressure measurements are often used to assess respiratory muscle strength, e.g., maximal inspiratory pressure (PI max) and maximal expiratory pressure (PE max). These measurements require cooperation of patients and the normal values have large ranges and variability, which may be related to factors such as lung volume,

type of mouthpiece, variable effort and learning. In order to reduce the effect of these variables in the measurement of PI max, investigators have used respiratory pressures during maximal sniff maneuvers. The maximal sniff pressure (SNP) may be measured, using transdiaphragmatic (Pdi), esophageal (Pes) or nasal (Pn) methods. Pn is often measured rather than Pes because it is much less invasive. Non-invasive sniff pressure is reported to be more sensitive than VC and PI max in predicting respiratory muscle strength and risk of ventilatory failure in ALS patients (Lyal et al., 2001a).

Vital capacity provides a global assessment of respiratory muscle function and is the quickest and simplest way to determine respiratory muscle weakness. Additionally, a significant fall in VC from upright to supine position has been used to assess diaphragmatic weakness. In patients with suspected diaphragmatic paralysis, transdiaphragmatic pressure measurement may be necessary. This is, however, invasive, requiring placement of esophageal and gastric catheters and is difficult to perform. The chest radiograph is non-invasive and permits visualization of the diaphragm dome but provides little information regarding diaphragm function. Diaphragm fluoroscopy provides real-time examination of the start of diaphragm dome motion but carries the disadvantage of exposure to ionizing radiation and poor sensitivity and specificity.

Since nocturnal desaturation is likely to precede daytime respiratory failure more sensitive predictors of nocturnal desaturation have been sought. It is important to note that indices of daytime lung function (VC and PI max) have been quoted to be better predictors of survival than overnight oxygen saturation (Phillips et al., 1999; Mellies et al., 2003).

17.5. Treatment

Treatment should be first directed toward treatment of the primary neurological condition. However, in many neuromuscular disorders specific treatment is unavailable and only supportive or symptomatic measures are available. The objective of treatment of SDB in patients with neuromuscular disorders is to improve arterial oxygenation, prevent serious consequences of chronic respiratory failure, eliminate daytime symptoms and improve quality of life.

17.5.1. Interventional treatment

Respiratory failure must be treated with external devices, either invasively or non-invasively. In the

past the mainstay of treatment was invasive ventilation through a tracheostomy. This has, however, been largely replaced by non-invasive methods of ventilation. Tracheostomy may still be the only effective emergency measure for patients with marked respiratory failure or acute respiratory arrest after resuscitation by intubation. The decision for tracheostomy must, however, be weighed in the light of the nature, progression and prognosis of the primary neuromuscular disorder. Non-invasive ventilation may be applied round the clock in severely affected patients but generally nocturnal assisted ventilation is sufficient to keep the patient in a stable state as alveolar hypoventilation is most pronounced in sleep.

There are two types of ventilatory support available for patients with SDB (Martin et al., 1983; Chokroverty, 1999b, 2001): negative- and positive-pressure ventilators. In the early 1950s mechanical-assisted ventilation through negative-pressure devices was introduced to treat victims of poliomyelitis with respiratory failure in the intensive care setting. Negative pressure ventilators include the 'iron lung' or tank respirator, 'the raincoat' or 'Pneumo ventilator' and the cuirass or 'tortoise shell'. The tank respirator is the most effective negative-pressure ventilator but is bulky and limits the patients' acceptance. Negative-pressure ventilation has been shown to improve oxygenation, particularly during REM sleep. However, sleep arousals, fragmentation of sleep architecture and severe desaturation may continue to occur during sleep. It can induce upper airway obstructive apneas during REM sleep causing severe hypoxemia and hypercapnia (Ellis et al., 1987). Positive-pressure ventilation is available in three types of delivery systems: continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) and intermittent positive-pressure ventilation (IPPV). CPAP is ideal for the treatment of patients with upper airway obstructive sleep apneas. Some patients, however, feel more comfortable using BiPAP where the expiratory pressure (EPAP) is lower than the inspiratory pressure (IPAP). IPPV uses no expiratory positive airway pressure and is the current standard of care for treatment of SDB in neuromuscular disorders. This may be provided using nasal mask or prongs. Either pressure-cycled or volume-cycled ventilators may be used to deliver IPPV. Improvement of respiratory muscle fatigue and pulmonary gas exchange, prevention of pulmonary atelectasis, decrease in respiratory work of breathing and restoration of the sensitivity of the respiratory center to CO₂ are important mechanisms

believed responsible for improvement in sleep-disordered breathing following non-invasive IPPV in neuromuscular disorders (Martin et al., 1983; Chokroverty, 1999b; Langevin et al., 2000). Changes in pulmonary mechanics may additionally contribute towards improvement in symptoms (Kramer et al., 1996). Several studies have shown the benefit of non-invasive nocturnal ventilation during sleep in patients with neuromuscular disorders (Leger et al., 1994; Barbe et al., 1996; Aboussouan et al., 1997; Simonds et al., 1998; Annane et al., 1999; Langevin et al., 2000; Lyaal et al., 2001b; Newsom-Davis et al., 2001; Bourke et al., 2003). IPPV improves nocturnal oxygen saturation, sleep efficiency, sleep architecture and prevents obstructive sleep apnea-hypopnea by supporting the upper airway. Other benefits of IPPV include improvement of daytime oxygen saturation and hypercapnia, increased survival and reduction of repeated hospitalizations and overall cost.

Although randomized controlled trials are lacking noninvasive IPPV is recommended in neuromuscular disorders based on the evidence of improvements in quality of life, survival and daytime oxygenation. A recent consensus conference report (Consensus report, 1999) listed the criteria for non-invasive positive-pressure ventilation for patients with neuromuscular disorders. The diagnosis must be established by history and physical examination followed by appropriate laboratory tests. The patient should also receive treatment for associated or underlying conditions. In addition to clinical symptoms the suggested indications include one of the following physiologic criteria: (1) $\text{PaCO}_2 \geq 45 \text{ mmHg}$; (2) nocturnal oxygen desaturation (by finger oxymetry) of $\leq 88 \text{ mmHg}$ for 5 consecutive min; and (3) in cases of progressive neuromuscular diseases, maximal inspiratory pressure of $< 60 \text{ cmH}_2\text{O}$ or FVC $< 50\%$ predicted. A follow-up in 1–3 months for assessment for compliance and monitoring awake arterial blood gases is also suggested. However, it must be remembered that different neuromuscular disorders evolve and progress at different and varying rates depending upon the etiology of the disease process and other associated variables. Thus, this set of guidelines may need further modifications depending upon the disease process involved, for example, Bourke and colleagues (2001a) stated that at least in ALS even before development of daytime hypercapnia, earlier intervention in the presence of orthopnea, sleep dysfunction and $\text{PI max} < 60\%$ predicted is associated with improved symptoms and quality of life.

Patients treated with IPPV need to be regularly followed clinically to evaluate changes in symptoms or signs that suggest disease progression or a decrease in treatment efficacy. Although there is no controlled study the simplest and most widely used parameter is nocturnal finger oxymetry to evaluate progression of disease and efficacy of treatment. In addition, transcutaneous or end-tidal CO_2 concentration can be added. Thermocouple to monitor airflow through the nose or mouth can also be helpful. EMG of an accessory respiratory muscle may help in indicating evidence of ventilatory failure. However, a repeat PSG remains the best test for evaluating quality of sleep and effectiveness of IPPV. Guilleminault and Shergill (2002) suggested that even if there is no change in clinical symptomatology a PSG is recommended at least once a year as respiratory changes can occur without accompanying clinical symptoms. However, further guidelines in this direction need to be established.

Comfort and compliance of the nasal mask can pose a limitation as it can cause claustrophobia, particularly in patients with breathing problems. Using a heated humidifier can increase comfort as can the use of nasal pillows instead of a nasal mask. Nasal stuffiness or rhinorrhea can be annoying and may be relieved by using a warm humidifier or nasal corticosteroids. Leaks are also a common problem with IPPV. Leaks lead to arousals, sleep fragmentation and a subsequent decrease in efficiency of IPPV. Correction of leaks increases efficiency of IPPV and improvement in sleep quality and architecture. Thus in order to optimize treatment the ideal situation would be to have polysomnography performed under IPPV. This is, however, not a common practice but needs to be a future consideration.

In young subjects, long-term use of a nasal mask can lead to maxillary hypoplasia. A child's face grows quickly during infancy and children with nasal ventilation should be seen monthly to adjust mask size, particularly in first two years of life. Airways develop and remodel during this time and frequent repetition of nocturnal PSG has been suggested approximately every 3 months (Guilleminault and Shergill, 2002).

17.5.2. Supplemental oxygenation

The role of supplemental oxygen therapy using low-flow oxygen ($1\text{--}2 \text{ L min}^{-1}$) in treatment of SDB in neuromuscular disorders is controversial. Most feel that besides being ineffective in these situations it can also

be dangerous as it can lead to marked CO₂ retention (Masa et al., 1997).

17.5.3. Lifestyle modifications

Weight reduction and improving BMI would be helpful if obesity, particularly abdominal obesity is an associated factor. Alcohol, sedative drugs and other drugs that can cause sleep disturbance or depression of breathing during sleep should be avoided. Strength training of the inspiratory or accessory muscles of respiration may be beneficial in some early cases.

17.5.4. Diaphragmatic pacing

Diaphragmatic pacing has very limited application in the treatment of SDB in neuromuscular disorders. It is indicated in central alveolar hypoventilation that persists during wakefulness despite appropriate ventilation during sleep (Chervin and Guilleminault, 1997; Guilleminault and Shergill, 2002). It necessitates surgery for placement of subcutaneous stimulator and phrenic nerve electrodes and careful follow-up. IPPV through tracheostomy or nasal mask may be used in association with diaphragmatic pacing. There are many potential complications of diaphragmatic pacing (e.g. nerve fibrosis, infection, unit malfunction, surgical complications).

17.5.5. Pharmacologic treatment

Patients with myotonic dystrophy may require additional treatment with stimulants for treatment of excessive daytime sleepiness as they may have hypersomnia unrelated to alveolar hypoventilation. Modafinil, a novel stimulant (Damian et al., 2001; Guilleminault and Shergill, 2002), may be initiated at 100 mg per day increasing to a maximum of 400 mg per day to be taken in two divided doses. Amphetamine and methylphenidate can also be used.

17.6. Conclusion

Sleep-disordered breathing is a common and serious consequence of neuromuscular disorders associated with respiratory muscle weakness. It frequently remains underdiagnosed or undiagnosed as it presents as nocturnal hypoventilation in its early stages. A high degree of suspicion and clinical awareness are necessary. In the presence of important clinical clues suggestive of SDB screening overnight PSG study is

recommended in patients with neuromuscular disorders for detection of frequent arousals, sleep architectural changes, nocturnal oxygen desaturation and exclusion of OSAS. However, nocturnal measurements are surprisingly weak predictors of sleep-disordered breathing in comparison with daytime lung function tests (Bourke et al., 2001b; Ragoette et al., 2002; Mellies et al., 2003). Thus there is need for development of optimal criteria for detection of sleep-disordered breathing and nocturnal hypoventilation in its early stages. Non-invasive nasal IPPV remains the mainstay of treatment of SDB in neuromuscular disorders. Improvement in daytime oxygenation, quality of life and survival have been reported with its use. Further studies are needed to answer additional critical questions regarding its use, e.g., definitive and sensitive markers for starting treatment in different etiologic subtypes, the long-term effects and outcomes, requirements of follow-up care.

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CHAPTER 18

Arousal parasomnias

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18.1. Introduction

Sleepwalking and sleep terrors have been described as 'disorders of arousal'. It is classically associated with a confusional arousal preceded by a burst of delta waves that most commonly occurs out of slow-wave sleep or stage 3–4 NREM sleep. Autonomic nervous system reactions of variable intensity are seen with the confusional arousal. These oscillate between a simple increase in heart and respiratory rate to significant autonomic discharge particularly in sleep terrors with prominent tachycardia, tachypnea, perspiration, distress and glassy staring. These events are accompanied by complex behaviors that vary from sitting in bed with or without utterance of words or sentences to driving a car. Sleep terrors may occur in isolation or lead to a sleepwalking event. Efforts to rouse the individual lead to agitation and do not result in an immediate awakening. Reactions may be violent. The individual, when awakened, is amnesic about the event, but may have vague memories of fright, fear and threat. If rare events seen in children have been considered of no consequence, sleepwalking in adults is always pathological. The succeeding discussion focuses on arousal parasomnias in the young adult.

18.2. Epidemiology

The prevalence of sleepwalking is 2% in the general population (Ohayon et al., 1999) and 1–2% for sleep terrors (Hublin et al., 1999; Ohayon et al., 1999; Kimble et al., 2002).

Epidemiologic studies have shown that features associated with sleepwalking in adults are: age 15–20

years, subjective sense of choking or blocked breathing at night, sleepwalking and a road accident in the past year (Ohayon et al., 1999). There is higher prevalence of sleep terrors in sleepwalkers (Kales et al., 1980a). In the 15–44-year age range of subjects with violent behavior during sleep, obstructive sleep apnea (OSA) is the most common association (Ohayon et al., 1997). Factors associated with sleep terrors are a subjective sense of choking or blocked breathing at night, OSA, alcohol consumption at bedtime, violent or injury-causing behaviors during sleep, hypnagogic hallucinations and nightmares at least once a month (Ohayon et al., 1999).

Sleepwalking is more frequently reported in men (Hublin et al., 1997) and male gender is significantly associated with violent somnambulism (Moldofsky et al., 1995; Ohayon et al., 1997). For sleep terrors, there is no gender difference in adults (Ohayon et al., 1999).

18.3. Pathophysiology

Several factors have been considered as predisposing despite the fact that the evidence presented is not necessarily strong. Familial incidence of sleepwalking has been noted by several authors specifically parent–child transmission (Abe et al., 1984) and presence in several family members (Kales et al., 1980a; Wise, 1997). Other indications of 'genetic transmission' described are: the proximity of the genetic relationship being directly related to the trait being transmitted (Bakwin, 1970); and presence of a higher concordance in monozygotic than dizygotic twins (Hublin et al., 1997) by as much as six times (Bakwin, 1970). Human leukocyte antigen (HLA) typing has shown a high association with HLA DQB1 in sleepwalkers particularly DQB1*05 and DQB1*04 (Lecendreux et al., 2003). Yet, as also indicated by Kales et al. (1980a), the relatively high frequency seen among near relatives indicates that environmental factors may precipitate expression of the trait.

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What has been mentioned as 'the trait' remains unclear. The unresolved question is whether or not the behavior necessarily points to a genetic origin. It may well be that several factors, genetic and otherwise, are involved in the expression of sleepwalking and sleep terrors. This familial trait may underlie the probability of its occurrence but perhaps, in itself, is not sufficient to bring about the abnormal behavior. For example, restless leg syndrome (RLS) and periodic limb movement syndrome (PLMS) are strongly suspected to have a genetic component and both fragment sleep (Montplaisir et al., 1997; Lazzarini et al., 1999; Ondo et al., 2000; Winkelmann et al., 2000, 2002; Hening, 2002; Trenkwalder, 2002). RLS with PLMS can be associated with sleepwalking (Guilleminault et al., 2003) with these expressed simultaneously in parents and their children. Treatment of RLS eliminates its symptoms as well as sleepwalking. Therefore, the genetic factor may be more related to RLS than to sleepwalking.

Other variables have been reported to aggravate the occurrence of sleepwalking and sleep terrors. There is increased incidence of sleepwalking in subjects with migraine headache (Pradlier et al., 1987). Alcohol and illicit drug intake, and sleep deprivation likewise increase its occurrence (Moldofsky et al., 1995).

The question of an underlying psychopathology is always raised in adult sleepwalking and sleep terrors (Sours et al., 1963; Lauerma, 1996). This element may come from early life experiences as 85–89% of adult sleepwalkers in the Finnish Sleep Cohort reported events in childhood (Hublin et al., 1997). It is also possible that an individual who is predisposed to developing parasomnias since childhood (such as one who experiences recurrent sleep disturbance due to another sleep disorder) experiences a traumatic psychological event in adulthood (rape, physical attack, crime, war event, accident, etc.) will subsequently develop both post-traumatic stress disorder (PTSD) and arousal parasomnias. The psychopathologic traits reported in literature are: mood disorders, substance abuse (Llorente et al., 1992), inhibition of outward expression of aggression and predominance of anxiety, depression, obsessive-compulsive tendencies and phobicness (Kales et al., 1980), hysteria and anxiety (Crisp et al., 1990). Patients with a history of psychological trauma scored high on anxiety, phobic and depression scales. The traumatic event usually dictates the content of dreams (Hartman et al., 2001). But even if 55% of sleep terrors report a 'life-event' and 92% report that 'mental stress' (Kales et al.,

1980b) or 'stress' at work or home (Guilleminault et al., 1995; Moldofsky et al., 1995), it does not necessarily increase the risk of sleepwalking and sleep terror events. It has been shown that PTSD and anxiety disorders exist without sleepwalking and sleep terrors and vice versa. Schenck et al. (1989) reports that over 50% of 100 patients with sleep-related injury had no psychiatric diagnosis and Hartman et al. (2001) showed that a history of psychological trauma exists only in a minority of adults. Furthermore, neither the onset nor progression of the arousal parasomnia were associated with the onset or progression of any axis I psychiatric disorder; and the successful treatment of an axis I disorder did not usually control the sleepwalking or sleep terrors (Schenck and Mahowald, 2000).

18.4. Clinical features

Broughton (1968) has described somnambulism as having the following characteristics: mental confusion and disorientation; automatic behavior; relative non-reactivity to external stimuli; poor response to efforts to provoke behavioral wakefulness; retrograde amnesia; and only fragmentary recall of apparent dreams or none at all. The patient may display an array of behaviors without full awakening. Oftentimes, they will sit up and appear to look around or rise and walk about uneventfully and return to bed with no incident. There are also more complex behaviors documented in the literature. People have gotten up and cleaned the house, prepared and eaten meals, driven a car and engaged in injurious behaviors to self and others (Luchins et al., 1978; Hartmann, 1983; Oswald and Evans, 1985; Ovuga, 1992; Morissette, 1995; Lauerma, 1996; Milliet and Ummenhofer, 1999; Shatkin et al., 2002). A famous case is that of an adult male who, during a somnambulist episode, drove to his in-laws' home and committed homicide and attempted homicide then drove to the police station afterwards confused with only fragmentary recollection of the events (Broughton et al., 1994).

A typical sleep terror episode occurs approximately 45–100 minutes after sleep onset (Fisher et al., 1973a; Kales et al., 1980b). The first sign is often a gasp followed by increase in respiratory amplitude and rate. The patient suddenly sits up and emits a fearful scream. There is a dramatic increase in heart rate, which may go from 64 to 152 in 15–45 seconds. The highest recorded was 176min^{-1} . This returns to normal in 1–3 minutes. There is also a marked

decrease in skin resistance evidenced by profuse sweating (Fisher et al., 1973a). Sleep terrors often cross over to sleepwalking when the agitated patient gets up to escape the terrifying subjective experience (Kavey et al., 1990).

Recall for the parasomnia is variable. Initially, it was thought that recollection was rare and often did not resemble the activity during the event (Jacobson et al., 1965; Kales et al., 1966a). Others have found that there can be substantial and elaborate dream-like recall (Schenck et al., 1989). Fisher et al. (1974) report 58% recall of sleep terrors. Others report that sleep terrors occur with frightening dreams to a greater extent than can be attributed to chance (Klackenberg, 1971).

18.5. Associated conditions

Sleep-disordered breathing has been identified as a trigger of parasomnias by several authors. As already indicated, Ohayon et al. (1997) have shown that OSA is the most common association in the 15–44-year old age group. In adults, a subjective sense of choking or blocked breathing at night, consistent with OSA, is a factor significantly associated with sleepwalking and sleep terrors (Ohayon et al., 1999). Espa et al. (2002) found that respiratory effort was responsible for the occurrence of a great number of arousal reactions in parasomniacs than controls. Consistent with this, Guilleminault et al. (2004) described that OSA and more commonly upper airway resistance syndrome (UARS) may trigger sleepwalking. Appropriate treatment of the breathing disorder completely resolved the events. Scott (1988) reports on a 44-year-old male who began to sleepwalk and have night terrors during a period of high stress and excessive weight gain with significant snoring. He was successfully treated with thioridazine and weight loss.

On the other hand, treatment of SDB may result in rebound deep sleep precipitating an acute episode of parasomnias. There are reports of arousal parasomnias occurring during CPAP titration – one resulted in sleepwalking and the other in sleep terrors during identified periods of delta sleep rebound (Millman et al., 1991; Pressman et al., 1995).

Febrile illness is also associated with parasomnias. There is rebound of slow-wave sleep after a febrile episode occasionally resulting in sleepwalking and sleep terrors. Events are differentiated from delirium by its occurrence early at night, short duration and persistence after febrile period (Kales et al., 1979).

Certain medications precipitate parasomnias. Drugs implicated are methaqualone, chlorprothixene, zolpidem, lithium, chlorpromazine, triazolam, midazolam, benztropine, paroxetine, amitriptyline, ciprofloxacin, phenothiazines and propranolol (Flemenbaum, 1976; Huapaya, 1976; Pilette, 1978; Huapaya, 1979; Glassman et al., 1986; Pradlier et al., 1987; Lauerma, 1991; Mendelson, 1994; Iruela, 1995; Landry and Montplaisir, 1998; Harazin and Berigan, 1999; Landry et al., 1999; Von Vigier et al., 1999; Ferrandiz-Santos and Mataix-Sanjuan, 2000; Koli-vakis et al., 2001; Kawashima and Yamada, 2003). The effect appears dose-related in some. Episodes ceased after discontinuation of the medications.

Some case reports relate sleepwalking and sleep terrors with menses and pregnancy (Snyder, 1986; Berlin, 1988; Schenck et al., 1995). Hedman et al. (2002) noted a decline in parasomnias during pregnancy until 3 months postpartum. This was more marked in primiparas.

Other conditions associated with sleepwalking are herpes simplex encephalitis (Hori et al., 1990), hypomagnesemia (Popoviciu et al., 1990) and Tourette syndrome (Barabas et al., 1984).

18.6. Diagnostic evaluation

It is likely that many patients with arousal parasomnias never seek medical help. The events may be minor, self-limiting, or might have gone unnoticed. Common reasons for consult are: the individual or others come to harm; other people are inconvenienced or threatened; there are endless sleep interruptions (if they recognize/remember); and secondary complications such as alcoholism occur (Crisp, 1996).

The clinical history should include a complete review of sleep complaints of the patient, preferably with a person who witnessed the events in question. Symptoms relating to other sleep disorders should be elicited, particularly sleep disordered breathing and RLS/PLM. It is not uncommon for other sleep irregularities to be ignored when dramatic parasomnias are the focus of the complaint.

A thorough physical and neurologic examination is mandatory. Attention should be placed on the anatomic features of the upper airway. This includes evaluation of the nose, oral cavity and pharynx.

The International Classification of Sleep Disorders (2001) states a minimal diagnostic criteria for sleepwalking as: (1) the patient exhibits ambulation that occurs in sleep; (2) onset typically occurs in

prepubertal children and; (3) associated features include: difficulty in arousing the patient during an episode and amnesia following an episode. The minimal diagnostic criteria for sleep terrors are: (1) the patient complains of a sudden episode of intense terror during sleep; (2) the episodes usually occur in the first third of the night and; (3) partial or total amnesia occurs for the events during the episode.

Some patients will not fit the criteria as stated, however, this should not preclude the clinician from making a diagnosis when all indications are consistent with a sleepwalking episode or sleep terrors. Distinctions between arousal parasomnias are often blurred in adults (Schenck et al., 1995) and these conditions frequently co-exist.

Polysomnography (PSG) should be performed systematically and should probably be repeated with different montages, locations and conditions of recording. Considering the association with other sleep disorders reported by many authors in the recent past, a general diagnostic PSG should be performed. The following variables are monitored: electroencephalogram (EEG) specifically C3/A2, C4/A1, Fpz/A1-A2, O1/A2, electro-oculogram (EOG), chin and leg electromyogram (EMG), electrocardiogram (EKG), and position sensors. Usage of more EEG leads with bipolar derivation montage: Fp1-T3, T3-O1, O1-C1, C1-Fp1, Fp2-T4, T4-O2, O1-C4, C4-Fp2, for example, is highly recommended. Respiration should be thoroughly checked as upper airway resistance syndrome (UARS) has been reported in association with the parasomnia (Guilleminault et al., 2004). This is done using a nasal cannula/pressure transducer system, mouth thermistor, thoracic and abdominal piezo-bands, pulse oximetry, neck microphone and, if possible, esophageal pressure (Pes). The recording should be all night with video monitoring and surveillance by the sleep technicians with annotation of all abnormal behavior (Aldrich and Jahnke, 1991). Often, parasomnia is least seen in the first night and another recording night should be scheduled. Sleep deprivation has been reported to enhance the chance of sleepwalking and sleep terrors (Joncas et al., 2002) and PSG may be obtained after 24 hours of sleep deprivation.

The existence of portable, computerized sleep systems with video-recording capability has led to the performance of such studies at home with system such as the SiestaTM (Compumedics, Australia). The computerized systems allow the raw data to be re-referenced to other electrodes post-test. Recording should only be performed if the subject does not live alone

and a family member or companion can take responsibility for noting abnormal behaviors. Otherwise a sleep technician will be needed to monitor the behavior of the patient during sleep.

Depending on the frequency of the events, actigraphy used for 15 days may be helpful in investigating the timing of the abnormal behavior. Bed partners or family members are asked to fill accompanying sleep logs with details on the types and frequency of any unusual event.

18.7. Results of monitoring

Sleep architecture is an inconsistent indicator of arousal parasomnias. It has been described that it generally remains normal (Schenck and Mahowald, 1995; Zucconi et al., 1995). However, in the presence of other sleep disorders, the sleep architecture may take on the morphology of the associated condition.

Sleepwalking and sleep terror events are normally seen out of stage 3–4 NREM sleep, particularly during the first third of the night at the time of the first sleep cycle, sometimes during the second. If one event occurs, a second one may take place in the next sleep cycle. It is rarely seen out of stage 2 NREM sleep except if an event had occurred in the previous cycle.

Early studies describe specific sleep patterns during slow wave sleep as an 'awakening response'. These are sudden rhythmical high-voltage bursts of delta waves that begin prior to the abnormal behavior that do not always result in waking (Jacobson et al., 1965; Kales et al., 1966b; Halasz et al., 1985; Blatt et al., 1991; Espa et al., 2000; Gaudreau et al., 2000) (Figures 18.1 and 18.2). Guilleminault et al. (2002) performed spectral analysis of the EEG from the central leads preceding the events and concluded that these were low (0.5–2 Hz) delta frequencies. The beginning of the event is obscured by EMG artifacts; however, many authors have shown that the EEG is not indicative of wakefulness. Patterns described are: diffuse non-reactive alpha and low-voltage beta and delta waves (Gastaut and Broughton, 1965; Broughton, 1968). The duration of these EEG patterns is unclear especially since EMG artifacts obscure the recording. But at least 60 seconds of slow-wave EEG frequencies have been well documented after the beginning of the abnormal behaviors. Though classically associated with an arousal, these patterns are believed to be reactions against 'activation' and help maintain sleep (Halasz et al., 1985; Guilleminault et al., 2001). Negative elements such as sharp transients

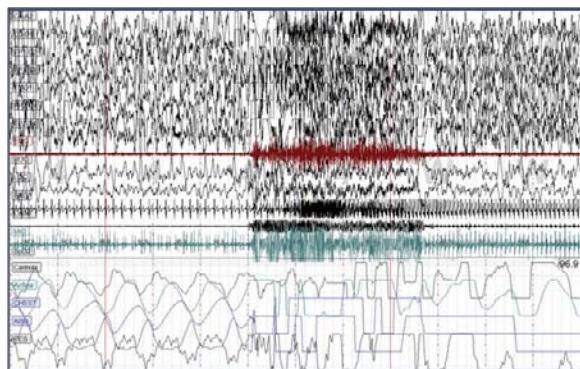


Fig. 18.1. This 18-year-old gentleman had recurrent sleepwalking and sleep terrors since childhood. He had sustained injury when he walked through a window during sleep necessitating 100 stitches. This diagnostic PSG demonstrates one of several episodes during the study wherein the patient sat up and went back to sleep with no recollection of the event. Subsequently it was shown that he had mild OSA with a respiratory disturbance index (RDI) of 6, minimum oxygen saturation of 89% and maximum negative esophageal pressure (Pes) of $-17\text{ cmH}_2\text{O}$. Note the hyper-synchronous delta wave pattern prior to the event. This trend continues during the behavior, although obscured by movement artifact, until after the event. After treatment of the OSA, the patient only had rare episodes when experiencing periods of great stress.

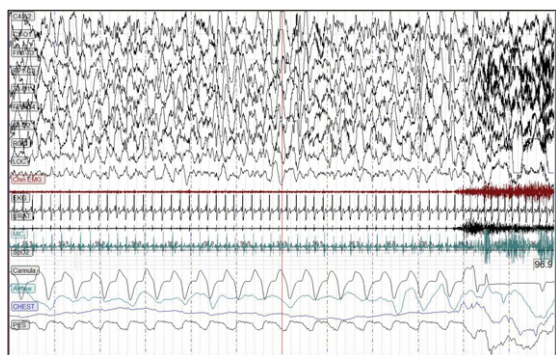


Fig. 18.2. This 33-year-old health worker had been experiencing parasomnias since childhood. Due to demands of shift work schedule and other stresses, the episodes became more alarming and potentially hazardous particularly when he was seen picking his baby up during a sleepwalking episode. As the patient entered slow-wave sleep, he sat up, tried to get out of bed and pulled out the esophageal pressure tube and went back to sleep. When questioned the following day, he did not recall doing so. Again, hypersynchronous delta waves preceded the abnormal behavior.

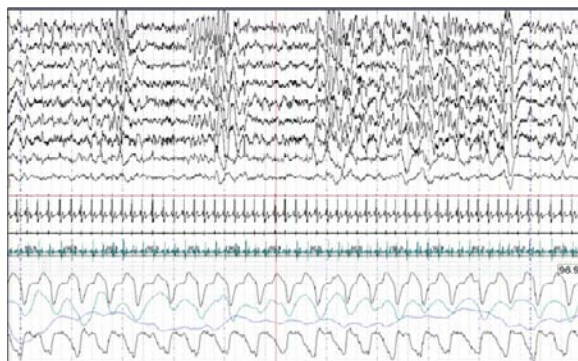


Fig. 18.3. The same patient as in Figure 18.2 demonstrated frequent cyclic alternating patterns (CAPs) representing arousal oscillation. There is a pattern of intermittent synchronized high-amplitude waves intervening with mixed frequency waves of lower amplitude.

and spike-slow-wave complexes are not seen preceding or at the beginning of events.

Post-arousal EEG is characterized by stage 2 sleep with spindles and slow waves or low-voltage theta, alpha and beta waves during longer sleepwalking events (Jacobson et al., 1965). Schenck et al. (1998) specifically illustrate three post-arousal patterns: diffuse rhythmic delta activity with a typical frequency of 2.2 Hz, amplitude of $85\mu\text{V}$ and duration of 20 seconds; diffuse delta and theta activity intermixed with alpha and beta activity; and prominent alpha and beta activity.

Repeated arousal oscillations known as cyclic alternating patterns (CAPs) were prominently noted in NREM sleep (Figure 18.3). These indicate that sleep instability and many behavioral events occurred during a CAP cycle (Zucconi et al., 1995).

Evidence of OSA or periodic limb movements (PLM), especially when associated with sleepwalking or sleep terror events, should be noted. These events may figure prominently on PSG and occur immediately prior to the arousal parasomnia.

If no abnormal behaviors occur, however, it does not negate the diagnosis. Behaviors may be brief and incomplete and are easily missed. As mentioned earlier, another study night may be necessary.

18.8. Differential diagnosis

Complex partial seizures occur anytime during the night. Events are very brief wherein the individual is awakened from sleep but has a blank stare and is unresponsive. Automatic behaviors such as fidgeting with

the sheets, hand wringing or lip smacking are common. There is post-ictal lethargy and confusion. Autonomic activation is extremely rare and the events may resemble confusional arousals or sleepwalking. Full EEG often does not demonstrate evidence of seizures or inter-ictal wave patterns. Treatment with anticonvulsants resolves the episodes (Provini et al., 2000).

Episodic nocturnal wandering is similar to parasomnias in that the patient rises from sleep and walks briskly. There may be complex, violent behaviors with incoherent speech. Events do not follow a particular time frame, occur any time during the night, and may be multiple. There is retrograde amnesia. A full EEG may show abnormalities but in some cases, it may not. These individuals also respond to anticonvulsant therapy (Pedley and Guilleminault, 1977; Maselli et al., 1988; Plazzi et al., 1995; Huang and Chu, 1998).

REM behavior disorder may be distinguished from sleep terrors and sleepwalking as it occurs predominantly in the third part of the night. Patients are often elderly, possibly with a concomitant neurologic complaint. The individual acts out a dream that is usually unpleasant. Punching, kicking and running often occur. However, there is a lesser degree of autonomic activation and the patient is easily roused from the event with vivid recall. PSG may not reveal a full episode but typically shows loss of REM atonia with movement in REM sleep (Masand et al., 1995).

Nocturnal panic attacks are associated with psychopathology and may be difficult to differentiate from sleep terrors that progress to sleepwalking. It is important to note that these individuals often display similar agitated episodes during daytime (Merritt-Davis and Balon, 2003).

Dissociative disorders result in longer events with behaviors that are complex and purposeful. There is an underlying psychopathology that manifests in sleep (Masand et al., 1995). Attention to information elicited during the interview may reveal the psychiatric condition that is the basis for the sleep condition.

Malingering should be considered especially if the behaviors are purposeful and directed towards a clear gain. PSG shows the patient is awake during the event (Masand et al., 1995).

18.9. Management

Arousal parasomnias in adults are never benign. Aside from morbidity due to other underlying conditions, it can potentially lead to injury to the affected individual and those nearby. Resolution of events dramati-

cally improves safety and quality of life of patients and families (Wills and Garcia, 2002). Therefore, all adults with sleep terrors and sleepwalking should be evaluated and treated as necessary.

Prior to a confirmed diagnosis, assuring environmental safety should be discussed (Guilleminault and Anders, 1976; Thiedke, 2001). Remove all dangerous objects from the room including mirrors, place heavy drapes in front of windows, put aside any obstruction that the patient may trip over and lock doors and windows. It may be necessary to relocate the patient to the ground floor (Wills and Garcia, 2002). A mattress or sleeping bag on the floor is the safest. In cases where the initiating factor is environmental noise, ear plugs may be used. Bystanders are advised to let the event run its course while assuring safety and guide the patient back to bed once calm.

Certain conditions that aggravate the occurrence of events are easily managed. Maintain a regular sleep/wake schedule, manage stress appropriately, avoid alcohol, discontinue certain medications and minimize environmental noise.

The best treatment approach is to address the underlying OSA or RLS once confirmed by polysomnography. Management with positive airway pressure, surgery or medications, as appropriate, will resolve episodes by eliminating initiating factors (Guilleminault et al., 2003).

There is no medication currently approved for arousal parasomnias although several have been used empirically. These include benzodiazepines (Glick et al., 1971; Fisher et al., 1973b; Guilleminault and Anders, 1976; Vela et al., 1982; Goldbloom and Chouinard, 1984; Kales et al., 1987; Schenck et al., 1989; Lillywhite et al., 1994; Schenck and Mahowald, 1996; Thiedke, 2001; Kimble et al., 2002), tricyclic antidepressants (Pesikoff and Davis, 1971; Marshall, 1975; Beitman and Carlin, 1979; Logan, 1979; Cooper, 1987) and serotonin selective reuptake inhibitors (SSRIs). Among these, clonazepam 0.5–1.0 mg is the most commonly prescribed medication especially when there is concern for the safety of the individual and others. However, medications must be used only as a temporary measure in order to avoid injury. It cannot be over emphasized that management of the underlying pathology is the best approach.

Other treatment modalities involving psychotherapy, behavioral modification and hypnosis have shown varying results and are rarely curative.

Psychotherapy has been reported as beneficial for patients with an identified psychosocial concern

(Clement, 1970). Hypnotherapy has had inconsistent results but may be helpful (Reid, 1975; Reid et al., 1981; Gutnik and Reid, 1982; Hurwitz et al., 1991). Results are often partial but aid the patients in managing the episodes to an acceptable level (Koe, 1989; Hurwitz et al., 1991; Sadigh and Mierzwa, 1995).

A behavioral technique called scheduled awakenings has gained attention in recent years (Frank et al., 1977; Lask, 1988; Tobin, 1993; Kuhn and Elliot, 2003). Patients are woken 15–30 minutes before the expected time of sleepwalking and are allowed to fall back asleep once full awakening was achieved. This was reported to have significantly decreased events in patients. The mechanism is unclear but may be related to altering sleep patterns to eliminate disruption of slow-wave sleep, conditioning the child to self-arousal before the event occurs and indirectly reducing events by increasing total sleep time (Kuhn and Elliot, 2003).

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CHAPTER 19

REM sleep behavior disorder

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Parasomnias are undesirable experiential or motor phenomena arising from the sleep period, and can conveniently be divided into two major categories: those representing abnormalities of sleep states per se, and those due to abnormalities of various organ systems taking advantage of the sleep state to declare themselves. The primary sleep parasomnias can be divided into three categories: those arising from non-rapid eye movement (NREM) sleep such as disorders of arousal (confusional arousals, sleepwalking or sleep terrors), those arising from REM sleep (REM sleep behavior disorder – RBD), and those not respecting sleep states such as head-banging, bruxism or enuresis. The secondary sleep parasomnias may be classified by the organ system involved such as central nervous system (nocturnal seizures) (Mahowald and Ettinger, 1990). The REM sleep behavior disorder (RBD) is one of the most common parasomnias and typically presents with violent and potentially injurious complex motor behaviors arising from the sleep period.

RBD was predicted by animal experiments in 1965: cats with bilateral perilocus ceruleus lesions demonstrated prominent motor activity during REM sleep (Jouvet and Delorme, 1965). The cat animal model has recently been extended to the rat (Sanford et al., 2001). This persistence of muscle tone during REM sleep was termed ‘REM sleep without atonia’ (RWA). Although various polysomnographic and clinical components of RBD have been identified by European, Japanese and American investigators since 1966, RBD was not formally recognized and named until the mid-1980s, and it was incorporated within

the International Classification of Sleep Disorders in 1990 (Schenck et al., 1986; Thorpy, 1990).

Somatic muscle atonia is one of the defining characteristics of REM sleep. The supraspinal mechanisms responsible for REM-atonia originate in the perilocus ceruleus (LC)-alpha nucleus in the pons that excite neurons of the nucleus reticularis magnocellularis in the medulla, which then transmit descending inhibitory projections – more powerful than the competing descending excitatory projections – to the spinal alpha motoneurons, resulting in hyperpolarization and thence muscle atonia. This atonia is felt to be mediated by glycine (Chase and Morales, 1994) and may be influenced by medullary enkephalinergic neurons (Fort et al., 1998). Therefore, ‘REM-atonia’ represents an active paralysis involving specific neuronal circuitry, and not passive relaxation of somatic muscles (sparing the diaphragm, permitting respiration during REM sleep). During normal REM sleep, the motor system is paralyzed at the level of the spinal motoneurons, but highly activated at higher levels of the neuraxis (Chase and Morales, 1994). Loss of muscle tone during REM sleep is very complex, and has been shown to be due to a combination of inactivation of brainstem motor inhibitory systems and inactivation of brainstem facilitatory systems (Mileykovskiy et al., 2000, 2002).

Loss of REM-atonia is alone insufficient to permit complex behaviors during REM sleep. Presumably, there must also be disinhibition of motor pattern generators in the mesencephalic locomotor region to result in over-excitation of phasic motor activity with behavioral release during REM (Morrison, 1988). Studies in dogs by Lai and Siegel have revealed a colocalization of the atonia and locomotor systems of REM sleep in the pons, providing an anatomic basis for the simultaneous dysregulation of these two systems in RBD (Lai and Siegel, 1988). The valuable animal model of REM without atonia will serve to reveal important state-dependent changes in brain

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function. One recent study using this model combined with unilateral amygdalar lesions demonstrated the release of violent behaviors during RWA, confirming that behavioral state is a powerful modifier of the expression of aggressive behaviors (Zagrodzka et al., 1998). Animal models suggest that abnormalities at multiple levels of the central nervous system may produce RWA and RBD (i.e., mice lacking the histamine H3 receptor (Dugovic et al., 2002) and cats with neurotoxic lesions of the ventral mesopontine junction (Lai et al., 2002)).

Inasmuch as REM sleep is a state of high activation of the CNS, it is likely that REM-atonía may serve as a protective mechanism, preventing motor manifestations and accompaniments of the highly activated brain during REM sleep.

The typical complaint of a patient with RBD is violent dream-enacting behaviors, which are potentially injurious to the individual or bed partner (Olson et al., 2000; Schenck and Mahowald, 2002). There are acute and chronic forms of RBD.

Acute RBD is almost always induced by medications (most commonly tricyclic antidepressants, monoamine oxidase inhibitors, SSRIs) or associated with their withdrawal (alcohol, barbiturate or meprobamate) (Schenck and Mahowald, 1992; Loudon et al., 1995; Carlander et al., 1996; Schutte and Doghramji, 1996; Silber, 1996; Iranzo and Santamaria, 1999; Onofri et al., 2003). Caffeine abuse and chocolate ingestion has been implicated in causing or unmasking RBD (Stolz and Aldrich, 1991; Vorona and Ware, 2002). Few studies are available in cases associated with drug or alcohol withdrawal, because of its transient nature, and the presence of impressive withdrawal symptoms, making formal sleep studies technically difficult to perform and interpret (Mahowald and Schenck, 1993).

The chronic form of RBD has two striking demographic characteristics: it is overwhelmingly a disorder affecting older individuals (above age 50) and men (80–90%), although females and virtually all age groups may be affected (Schenck et al., 1993; Sheldon et al., 1994). One fourth of the patients have a prodrome, often lengthy, involving subclinical behavioral release during sleep. Few patients with RBD have histories of childhood sleepwalking or sleep terrors. The fact that many patients with RBD display prominent periodic and aperiodic extremity movements during NREM sleep suggests a strong tendency for generalized sleep motor dysregulation during both REM and NREM sleep (Fantini et al., 2002). Also, the fact that

there is an elevated percentage of slow-wave sleep in three-quarters of the patients suggests an additional component of NREM sleep dysregulation in RBD (Schenck et al., 1993).

RBD behaviors occur within REM sleep, often without associated tachycardia, and not during arousals from REM sleep. Complex RBD behaviors are generally aggressive or exploratory, and never appetitive (feeding, sexual). There is a strong link between altered dreams and dream-enacting behaviors, suggesting a mutual pathophysiology: patients do not enact their customary dreams, but rather they enact distinctly altered dreams, usually involving confrontation, aggression and violence.

Despite the impressive behavioral and EMG motor activity, few patients with RBD complain of excessive sleep disruption and daytime fatigue. Objective measures of daytime sleepiness such as the multiple sleep latency test rarely document daytime somnolence, apart from cases in which RBD is associated with narcolepsy. The lack of daytime sleepiness may be related to the fact that many patients with RBD have an increased percentage of slow-wave sleep, which may compensate for the REM sleep fragmentation (Schenck and Mahowald, 2002).

The prevalence of RBD is greater than initially suspected. A recent phone survey of over 4900 individuals between the ages of 15–100 years of age indicated an overall prevalence of violent behaviors in general during sleep of 2%, one-quarter of which were likely due to RBD, giving an overall prevalence of RBD at 0.5% (Ohayon et al., 1997). It most frequently presents with the complaint of dramatic, violent, potentially injurious motor activity during sleep. These behaviors include talking, yelling, swearing, grabbing, punching, kicking, jumping or running out of the bed. Injuries are not uncommon and include ecchymoses, lacerations or fractures involving the individual or bed partner. The violence of the sleep-related behavior is often discordant with the waking personality. The reported motor activity usually correlates with remembered dream mentation, leading to the complaint of ‘acting out my dreams’. Less frequently, the primary complaint is one of sleep interruption. It may be that the presentation of RBD is different in males (violent dream-enacting behaviors) than in females (less violent dream-enacting behaviors), skewing the reported male predominance (Tatman and Sind, 1996). Bruxism, somniloquy or periodic limb movements of sleep may be the heralding or primary manifestation of this disorder (Baker,

1993; Tachibana et al., 1994, 1997; Taniguchi et al., 1995). The duration of behaviors is brief, and upon awakening from an episode there is usually rapid return of alertness and orientation. Some patients adopt extraordinary measures to prevent injury during sleep: they may tether themselves to the bed with a rope or belt, sleep in sleeping bags or sleep on a mattress on the floor in a room without furniture.

Due to its association with REM sleep, the timing of the behaviors during the sleep period ranges from 90 minutes after sleep onset to the final awakening in the morning. RBD rarely occurs during daytime naps in that REM sleep during naps is exceptional. There may be a prodromal period lasting years or decades of progressively more prominent sleep talking, yelling or limb jerking during sleep. Many patients with RBD report that dreams have become more vivid and 'action-packed', coincident with the onset of the dream-enacting behavior. The frequency of the episodes ranges from once every few weeks to multiple nightly episodes (Mahowald and Schenck, 1994). Complications include fractures, lacerations and ecchymoses (Schenck et al., 1993). RBD-related sleep injury has resulted in subdural hematomas (Dyken et al., 1995). Sleep-related violence may have forensic science implications (Mahowald and Schenck, 1995).

Many cases are still considered to be idiopathic (at the time of presentation) without demonstrable neuroanatomic brainstem structural abnormalities, consistent with experimental animal data that indicate that the determination of REM-atonía is complex and may result from dysfunction of a number of neural networks. This is in contrast to the classic animal model of RBD involving the perilocus ceruleus regions (Schenck et al., 1993). Extensive neurologic evaluation (evoked potentials, CT, MRI, etc.) is warranted only if the history or neurologic examination is suggestive of structural CNS pathology.

Systematic study of patients with neurologic syndromes indicates that RBD and REM sleep without atonia may be far more prevalent than previously suspected. Initially, the chronic form of RBD was felt to be predominantly idiopathic; however, systematic longitudinal monitoring of patients with RBD suggests that up to two-thirds will eventually manifest symptoms of neurodegenerative disorders, most notably the synucleinopathies (Parkinson's disease, multiple system atrophy – including olivopontocerebellar degeneration and the Shy-Drager syndrome, and dementia with Lewy bodies disease). RBD often precedes the appearance of other symptoms of these

disorders by more than a decade (Tachibana et al., 1995a,b; Tison et al., 1995; Pareja et al., 1996; Schenck et al., 1996; Kimura et al., 1997; Montplaisir et al., 1997; Turner et al., 1997; Boeve et al., 2001, 2003a). Combined animal and human studies have identified physiological and anatomical links between RBD and neurodegenerative disorders, leading to the proposal that neurodegeneration can begin in either the rostroventral midbrain or the ventral mesopontine junction and progressively extend to the rostral or caudal part of the brainstem. When the lesion starts in the ventral mesopontine region, RBD will develop first, but when the lesion initially involves the rostroventral midbrain, Parkinson's disease will be the initial manifestation (Lai and Siegel, 2003).

Although the prevalence of RBD in Parkinson's disease is unknown, subjective reports indicate that 25% of patients with Parkinson's disease have behaviors suggestive of RBD or sleep-related injurious behaviors, and polysomnographic studies found RBD in up to 47% of patients with Parkinson's disease with sleep complaints (Comella et al., 1998; Eisensehr et al., 2001; Gagnon et al., 2002). In one large series of patients with multiple system atrophy (MSA), 90% were found to have REM sleep without atonia and 69% had clinical RBD (Plazzi et al., 1997). In another, nearly half had RBD (Ghorayeb et al., 2002). The presence of RBD may differentiate pure autonomic failure from MSA with autonomic failure (Plazzi et al., 1998). The finding of incidental Lewy body disease in one patient asymptomatic for Parkinson's disease suggests that this condition may explain idiopathic RBD in some older patients (Uchiyama et al., 1995). The presentation of RBD and dementia is suggestive enough of dementia with Lewy body disease that RBD has been proposed as one of the core diagnostic features of dementia with Lewy body disease (Ferman et al., 2002). Selegiline or mirtazapine prescribed for patients with Parkinson's disease and cholinergic agents for Alzheimer's disease may trigger RBD in these populations (Louden et al., 1995; Carlander et al., 1996; Ross and Shua-Haim, 1998; Onofri et al., 2003). Other reported associations include: mitochondrial encephalomyopathy, normal pressure hydrocephalus, Tourette's syndrome, Machado-Joseph disease (spinocerebellar ataxia type 3), cerebellopontine angle tumors, group A xeroderma, multiple sclerosis, ischemic or hemorrhagic cerebrovascular disease, brainstem neoplasms, autism, and Guillain-Barré syndrome (Uchiyama et al., 1991; Kohyama et al., 1995; Nozawa et al., 1995; Bianchin

et al., 1997; Trajanovic et al., 1997; Kimura et al., 2000; Thirumalai et al., 2002; Friedman, 2002; Fukutake et al., 2002; Plazzi and Montagna, 2002; Zambelis et al., 2002; Syed et al., 2003).

Narcolepsy is also a risk factor for the development of RBD. Furthermore, tricyclic antidepressants, MAOIs and SSRIs, prescribed to treat cataplexy, can trigger or exacerbate RBD in this population. The demographics (age and sex) of RBD in narcolepsy conform to those of narcolepsy, indicating that RBD in these patients is yet another manifestation of state boundary dyscontrol seen in narcolepsy (Schenck and Mahowald, 1992). The recent description of low levels of ventricular CSF orexin/hypocretin levels in advanced Parkinson's disease may provide an interesting link between the increased prevalence of RBD in both narcolepsy and Parkinson's disease (Drouot et al., 2003).

Neuroimaging studies indicate dopaminergic abnormalities in RBD. SPECT studies have found reduced striatal dopamine transporters (Eisehsehr et al., 2000, 2003), and decreased striatal dopaminergic innervation has been reported (Albin et al., 2000). Decreased blood flow in the upper portion of the frontal lobe and pons has been reported (Shirakawa et al., 2002), as has functional impairment of brainstem neurons (Miyamoto et al., 2000). PET and SPECT studies have revealed decreased nigrostriatal dopaminergic projections in patients with multiple system atrophy and RBD (Gilman et al., 2003). Decreased blood flow in the upper portion of the frontal lobe and pons has been found in one MRI and SPECT study (Shirakawa et al., 2002). Impaired cortical activation as determined by electroencephalographic spectral analysis in patients with idiopathic RBD supports the relationship between RBD and neurodegenerative disorders (Fantini et al., 2003).

Minimum diagnostic criteria of RBD have been proposed (Mahowald and Schenck, 1994):

- (1) PSG abnormality during REM sleep: elevated submental electromyographic (EMG) tone and/or excessive phasic submental and/or limb EMG twitching.
- (2) Documentation of abnormal REM sleep behaviors during PSG studies (prominent limb or truncal jerking; complex, vigorous, or violent behaviors) or a history of injurious or disruptive sleep behaviors (Figure 19.1).
- (3) Absence of EEG epileptiform activity during REM sleep.

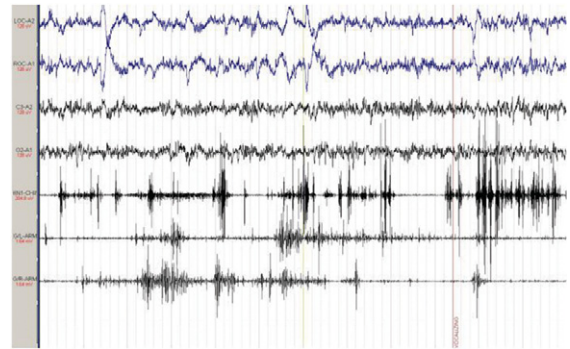


Fig. 19.1. One-minute polysomnographic epoch of REM without atonia in a patient with REM sleep behavior disorder. Note the prominent phasic muscle activity involving the chin, anterior tibialis and extensor digitorum muscles. The patient vocalizes during this epoch.

Regardless of gender, age or presence/absence of an underlying neurological disorder, the polysomnographic and behavioral features of RBD are indistinguishable. This suggests the presence of a final common pathway in RBD that can be accessed by a wide variety of pathologic states. It is important to remember that RBD is a clinical syndrome associated with a characteristic PSG finding – RWA. Finding RWA on a PSG does not necessarily mean that the patient has clinical RBD. RWA without the clinical symptoms of dream-enacting behaviors may be seen in many other conditions, including narcolepsy and neurodegenerative disorders such as PD and MSA or may be a medication effect (particularly SSRIs and tricyclic antidepressants) (Schenck and Mahowald, 1992; Schenck et al., 1992; Schutte and Doghramji, 1996).

The acute form is self-limited following discontinuation of the offending medication or completion of withdrawal.

About 90% of patients with chronic RBD respond well to clonazepam administered one-half hour prior to sleep time. The dose ranges from 0.5–2.0 mg, and there has been little, if any, tendency to develop tolerance, dependence, abuse or adverse sleep effects despite years of continuous administration and efficacy (Schenck and Mahowald, 1990, 1996). Interestingly, despite a dramatic clinical response to clonazepam, polygraphically there is little change in the muscle tone during REM sleep following effective treatment (Watanabe and Sugita, 1998). Clearly, clonazepam does not restore REM atonia. Melatonin, often at doses of 3–12 mg at night, may also be

effective (Kunz and Bes, 1999; Takeuchi et al., 2001; Boeve et al., 2003b). Although tricyclic antidepressants may sometimes induce or potentiate RBD, imipramine has been reported effective in three clonazepam-resistant cases (Matsumoto et al., 1991). Carbamazepine has been effective in one case (Bamford, 1993). Levodopa may be effective, particularly in cases where RBD is the harbinger of Parkinson's disease (Tan et al., 1996). There have been anecdotal reports of response to gabapentin, MAOIs, donepezil and clonidine (Mike and Kranz, 1996; Ringman and Simmons, 2000). In RBD associated with narcolepsy, the tricyclic antidepressants or MAOIs administered for cataplexy may be continued, and clonazepam added (Schenck and Mahowald, 1992). The treatment of medication-induced or Parkinson's disease-associated RBD is the same as for idiopathic RBD (Schenck et al., 1996). Pallidotomy has been effective in one case of RBD associated with Parkinson's disease, whereas chronic bilateral subthalamic stimulation was not (Rye et al., 1997; Arnulf et al., 2000; Iranzo et al., 2002).

There are a number of conditions which likely represent variations on RBD. These include the 'parasomnia overlap syndrome' characterized by patients with sleep-related complex behaviors with both clinical and PSG features of both RBD and disorders of arousal (confusional arousals, sleepwalking, and sleep terrors). These cases demonstrate motor-behavioral dyscontrol extending across NREM and REM sleep, and suggest the possibility of a unifying hypothesis for disorders of arousal and RBD: the primary underlying feature is motor disinhibition during sleep – when predominately during NREM sleep manifesting as disorders of arousal, when predominately during REM sleep manifesting as RBD – with the parasomnia overlap syndrome occupying an intermediate position, with features of both (Schenck et al., 1997).

Another likely related condition is 'agrypnia excitata', a recently described syndrome characterized by generalized overactivity associated with loss of slow-wave sleep, mental oneiricism (inability to initiate and maintain sleep with wakeful dreaming), and marked motor and autonomic sympathetic activation seen in such diverse conditions as delirium tremens, Morvan's fibrillary chorea and fatal familial insomnia (Lugaresi and Provini, 2001; Montagna and Lugaresi, 2002; Plazzi et al., 2002). Oneiric dementia is likely a related condition (Cibula et al., 2002). Agrypnia excitata is similar to 'status dissociatus', which may be the most extreme form of RBD, appearing to rep-

resent the complete breakdown of state-determining boundaries. Clinically, patients with status dissociatus, by behavioral observation, appear to be either awake or asleep; however, clinically, their behavioral sleep is very atypical, characterized by frequent muscle twitching, vocalization, and reports of dream-like mentation upon spontaneous or forced awakening. Polygraphically, there are no features of either conventional REM or NREM sleep; rather, there is the simultaneous admixture of elements of wakefulness, REM sleep and NREM sleep. 'Sleep' may be perceived as 'normal' and restorative by the patient, despite the nearly continuous motor and verbal behaviors and absence of polysomnographically defined REM or NREM sleep. Conditions associated with status dissociatus include protracted withdrawal from alcohol abuse, narcolepsy, olivopontocerebellar degeneration and prior open heart surgery. One AIDS-related case with prominent brainstem involvement has been identified. The abnormal motor and verbal nocturnal behaviors of status dissociatus may respond to treatment with clonazepam (Mahowald and Schenck, 1991, 1992).

A common thread linking RBD and the disorders of arousal is the appearance of motor activity dissociated from waking consciousness. In RBD, the motor behavior closely correlates with dream imagery, and in disorders of arousal, it often occurs in the absence of (remembered) mentation. This dissociation of behavior from consciousness may be explained by the presence of locomotor centers (LMCs), from the mesencephalon to the medulla, capable of generating complex behaviors without cortical input (Berntson and Micco, 1976; Mogenson, 1986; Mori, 1987; Grillner and Dubic, 1988). These areas project to the central pattern generator of the spinal cord, which itself is able to produce complex stepping movements in the absence of supraspinal influence (Mori et al., 1980). This accounts for the fact that decorticate experimental and barnyard animals are capable of performing very complex, integrated motor acts. Dissociation of the LMCs from the parent state of REM or NREM sleep would explain the presence of complex motor behavior seen in both RBD and disorders of arousal.

In summary, RBD is a REM-sleep-related parasomnia, presenting with potentially violent or injurious behaviors. 'Idiopathic' RBD is becoming progressively scarce (and may cease to exist) as more patients with RBD are being thoroughly evaluated and meticulously followed longitudinally. Drug-induced

RBD is becoming increasingly common, and non-drug-induced RBD is clearly very often a harbinger of degenerative neurologic conditions – particularly the synucleinopathies. Rigorous study of these relationships affords an exciting opportunity for basic scientists and sleep medicine clinicians working together to expand understanding of both sleep and neurological function.

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CHAPTER 20

Sleep in dementia

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20.1. Introduction

Over the past several decades, the elderly population (65 and older) has grown dramatically, partially the result of better healthcare and the considerable increase in human life expectancy. As a result of this growing number of older adults who are living longer, there has been an increase in the prevalence of late-life dementia in this population. Current estimates suggest between 2 and 4 million older adults currently suffer from the most common type of dementia, Alzheimer's disease (AD) (Brookmeyer et al., 1998).

Multiple different neurodegenerative diseases, including Parkinson's disease, Lewy body disease, vascular disease or strokes, and AD, can cause late-life dementia. Brain areas, which are known to be involved in the regulation of sleep and wake, are also vulnerable to these neurodegenerative changes common to all forms of dementia. Therefore, it is not surprising that sleep disturbances are extremely common among persons with dementia, with between 13% and 46% of patients with dementia and/or their caregivers complaining of the patients' sleep problems (Devanand et al., 1992; Carpenter et al., 1995; McCurry et al., 1999). The sleep disturbances, such as primary sleep disorders and circadian rhythm sleep disorders, can be very complex and may lead to severe insomnia or hypersomnia. Disturbances in sleep/wake circadian rhythms have also been associated with the highly disruptive behavioral symptoms commonly seen in dementia, such as agitation, morning confusion and wandering at night.

Given that research into sleep disorders in demented elderly is relatively new, little is currently

known about the etiology and the risk factors for the development sleep problems in this population. However, there is increasing evidence that sleep disturbances are strongly associated with co-morbid medical and psychiatric conditions (e.g., conditions causing pain such as arthritis and malignancies, neurological disorders such as Parkinson's disease, restless legs, stroke, or organ system failure disorders such as pulmonary disease, congestive heart failure, asthma, and gastrointestinal disorders and medication intake, in particular, CNS stimulants, beta blockers, bronchodilators, calcium channel blockers, corticosteroids, decongestants, stimulating anti-depressants, stimulating anti-histamines and thyroid hormones are all known to contribute to insomnia (Bliwise et al., 1992; Hoch et al., 1994). The older adult is often required to take many of these medications. Furthermore, several studies have reported an association between chronic insomnia and excessive daytime sleepiness with institutionalization, morbidity and mortality in the elderly (Pollak et al., 1990; Newman et al., 2000). Foley et al. (2001) found that cognitively intact older adults reporting excessive daytime sleepiness at baseline were twice as likely to be diagnosed with incident dementia than were those not reporting daytime sleepiness, suggesting that daytime sleepiness in older adults may be an early indicator of decline in cognitive functioning and onset of dementia. The implications of these reports suggest that in persons with dementia, targeting the underlying causes for the sleep problem is central to treating the sleep disturbance. Assessment and treatment of the primary medical and/or psychiatric condition, which may be affecting or underlying the secondary sleep disorder, should therefore be a treatment priority for all adults with dementia.

The consequences of sleep disturbances can be very debilitating to the patient with dementia; sleep disturbances have been associated with increased

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memory and functional impairment in community-dwelling patients with dementia (Moe et al., 1995; McCurry et al., 1999), as well as with more rapid cognitive decline (Mortimer et al., 1992). In addition, difficulties with the management of the patient's sleep disturbances (e.g., night-time confusion and wandering, agitation) is one of the caregivers' most often cited reason for the patient's institutionalization (Pollak and Perlick, 1991). Success in treating the sleep disorder will likely not only ameliorate the patient's sleep quality, physical and/or psychological health and quality of life, but that of their caregivers' as well.

20.2. Clinical neurophysiology techniques used in sleep research in dementia

20.2.1. Polysomnographic sleep (PSG) recordings

Polysomnography (PSG) is the gold standard for the evaluation of sleep. Polysomnographic recordings are usually necessary for the assessment and diagnosis of primary sleep disorders such as sleep-disordered breathing (SDB) and periodic limb movements in sleep (PLMS). However, as overnight recordings are usually conducted in a sleep laboratory, which can be disruptive to normal sleep routines, and as the device is bulky and to a certain degree invasive, it may also disrupt sleep architecture, especially during the first night of recording. These difficulties may be even more apparent in persons with dementia, who have difficulty adjusting to new environments and may wake up confused and/or agitated during the night. Therefore, when possible, conducting in-home, or in-institution, ambulatory PSG recordings may be a better option. A second option would be having the patient's caregiver sleep with the patient at the sleep laboratory.

20.2.2. Actigraphy

Newer devices, called actigraphs, have provided the clinical and research fields of sleep an alternative to traditional PSG recordings. Most actigraphs are wrist-worn devices (sometimes worn on the leg, depending on the type of patient studied), usually the size and weight of a wristwatch (Ancoli-Israel et al., 2003a). The actigraph collects physical movement data and scores it for sleep and wake, using the general premise that during sleep there is typically less movement than during wake. One advantage of

actigraphy over PSG is that data can be recorded for several 24-hour periods so that napping behavior can also be examined. Several validation studies have compared actigraphy to PSG sleep variables, including one study in patients with dementia (Ancoli-Israel et al., 1997a). Actigraphs can be particularly useful with patients with dementia who often suffer from severely disturbed sleep and circadian rhythms. As mentioned, older patients, especially demented patients, are often unable or unwilling to sleep in the laboratory and may have difficulties sleeping away from home or with their spouse absent. However, patients with dementia may also become agitated by the actigraph device and may attempt to remove it. When testing a patient with dementia, it is important for the clinician and the patient's caregiver to continuously remind the patient about the purpose and temporary nature of the device, and if possible, adapt the actigraph wristband to reduce the likelihood of removal.

20.3. Common sleep disorders in persons with dementia

The most common sleep disturbances of patients with late-life dementia include sleep architecture changes, nocturnal wandering and confusion, SDB, PLMS, and impairment of the endogenous circadian (24-hour) sleep/wake rhythm (Prinz et al., 2002), often leading to insomnia or hypersomnia and excessive daytime sleepiness. Although these disturbances seem to be more prevalent in severely demented patients (Bliwise et al., 1995), they are common among all types and severities of dementing illnesses (McCurry and Ancoli-Israel, 2003).

These sleep disorders have been associated with affective disorders, decreased cognitive function and concentration difficulties. However, one of the main consequences of decreased sleep quality, primary sleep disorders, and circadian sleep/wake rhythm changes is an increase in excessive daytime sleepiness (EDS). EDS results in an increased tendency to take inadvertent nap(s) during the day, again leading to a disruption of night-time sleep and therefore perpetuating the sleep disturbance ever further. In addition, EDS greatly interferes with the patient's ability to function to an optimal level on a day-to-day basis and therefore often leads to a significant reduction in quality of life. The most common sleep disturbances will be discussed in more detail in the following sections.

20.3.1. Sleep pattern and architecture changes

Sleep architecture changes can only be evaluated using PSG studies; however, as it is practically difficult to record sleep in severely demented patients, therefore most studies have been conducted with mildly demented patients. In addition, patients with dementia often show diffuse slowing of the EEG, which makes it difficult to both differentiate between sleep and wake and between sleep stages in this population (Ancoli-Israel et al., 1997a). Nonetheless, PSG studies have shown lower sleep efficiency (SE; hours asleep/hours in bed), increased number of night-time awakenings and stage 1 sleep, and decreased slow-wave (SWS; stages 3–4) sleep and rapid eye movement (REM) sleep in patients with dementia when compared to health controls (Allen et al., 1987; Vitiello and Prinz, 1989).

The sleep quality and architecture changes in demented patients are highly similar to those found in the sleep of healthy (non-demented) older adults; however, they occur more often in persons with dementia and tend to be more serious with increasing dementia severity. The prevailing theory is that with aging, loss of or damage to neuronal pathways that initiate and maintain sleep result in these sleep changes; with dementia, this neuronal deterioration is more advanced and consequently the sleep and EEG pattern changes are more severe as well (Vitiello and Prinz, 1994).

Patients with dementia also suffer from severe insomnia or hypersomnia (Boeve et al., 2002). Observation studies of patients with dementia have shown that they spend a significant portion of the night in bed awake and a significant proportion of their daytime hours asleep (Ancoli-Israel et al., 1989); however, each sleep or wake period may be as short as several minutes. Actigraphic studies conducted in nursing homes have confirmed these results indicating that institutionalized patients with dementia suffer from severe sleep fragmentation, i.e. frequent transition between sleep and wake over the course of the 24-hour day (Vitiello et al., 1991; Ancoli-Israel et al., 1997b); one study even found that not even one hour of the day or night consisted of total sleep or wake (see Figures 20.1 and 20.2) (Ancoli-Israel et al., 1989). When examining hour-by-hour actigraphic sleep/wake profiles, patients with mild–moderate dementia exhibited excessive wakefulness during the night while patients with severe dementia exhibited more EDS during the day (Pat-Horenczyk et al.,

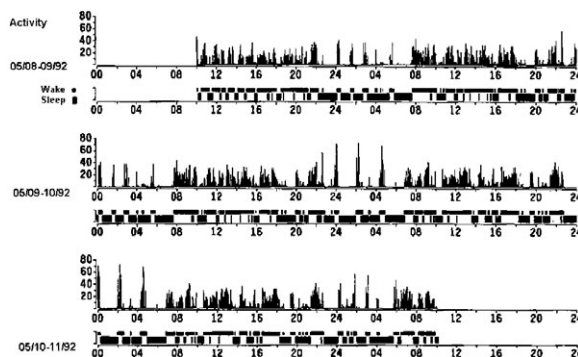


Fig. 20.1. Actigraph double-plot of a nursing home patient with dementia. Sleep is relatively well preserved with distinct night and day differences, although sleep is still fragmented.

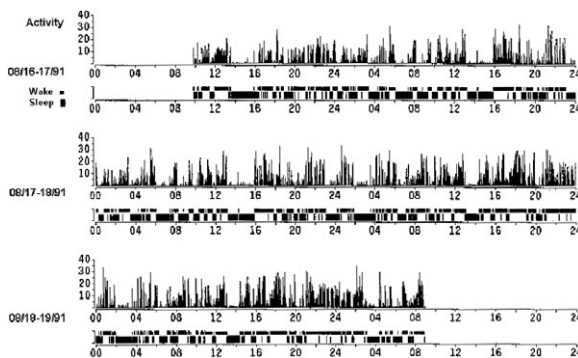


Fig. 20.2. Actigraph double-plot of a nursing home patient with dementia and severe sleep fragmentation. There were no distinct periods of consolidated sleep or consolidated wake.

1998). It is important to note that this increase in sleep during the day does not compensate for night-time sleep loss, as sleep stages during the day in this population are restricted to stage 1 and 2 and thus does not compensate for the SWS and REM sleep decrease during the night (Vitiello et al., 1991).

20.3.2. Sleep/wake circadian rhythms changes

As mentioned previously, one of the major sleep difficulties in late-life dementia is lack of sleep consolidation or sleep fragmentation. This may be partially due to the decrease in the robustness of the endogenous sleep/wake rhythm (i.e. lower amplitude rhythms and/or less rhythmic). Actigraphic studies have shown that the disruption of the sleep/wake rhythm in patients with dementia can lead to severe shifts in the

circadian rhythmicity, such as extreme circadian phase advances and delays (i.e. shifts earlier or later in time, respectively), or day–night reversals, and in severe cases even a complete lack of sleep/wake circadian rhythmicity (Allen et al., 1987).

The disruption in the circadian system in late-life dementia has been associated with biological and environmental factors. The endogenous circadian rhythm is controlled by the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus. The SCN and other brain structures, which control the circadian timing system and determine propensity for sleep and wake across the 24-hour day, have been associated with neurodegenerative changes in normal aging and in dementia (Van Someren, 2000). β -amyloid plaques commonly found in brains of patients with AD, have also been found in the SCN, but not in other areas of the hypothalamus (Swaab et al., 1992). Furthermore, the sleep/wake cycle disturbance has been shown to correlate with the severity of the dementia in AD patients (Witting et al., 1990).

Exogenous or life-style factors may also be associated with the disruption of the sleep/wake circadian rhythm in this population. The endogenous circadian rhythm is entrained or synchronized using environmental cues, called ‘zeitgebers’. The circadian light/dark cycle is the strongest photic zeitgeber for the sleep/wake rhythm, with light stimulating wakefulness and dark stimulating sleepiness. Older adults and specifically institutionalized elderly (often with dementing illnesses) have been known to have significantly reduced exposure to environmental bright light than healthy younger subjects (Campbell et al., 1988). Results of studies using specialized actigraphs with built-in light sensors have indicated healthy younger and older adults are exposed to approximately 60 minutes of bright light a day (≥ 2000 lux) (Espiritu et al., 1994), non-institutionalized AD patients 30 minutes a day (Campbell et al., 1988), whereas institutionalized AD patients receive 1 minute of bright light and only 10–19 minutes greater than 1000 lux light a day (Ancoli-Israel et al., 1991a; Shochat et al., 2000). Shochat et al. (2000) found an association between the amount of time spent in bright light and subsequent sleep fragmentation and phase advance shift of the sleep/wake circadian rhythm. These results were primarily due to the reduced amount of time patients with dementia spent outdoors in natural sunlight and the amount of time spent in low ambient light of nursing home facilities. In addition, the increased prevalence of eye disease and blindness in

this population is likely to result in a decreased sensitivity to the photic zeitgebers, and thus a reduction in the entrainment of the endogenous circadian rhythm. Several recent treatment studies have indicated increased exposure to bright light both in the morning and in the evening is associated with more consolidated night-time sleep and an increase in the robustness of the sleep/wake circadian rhythm in nursing home patients with dementia (Ancoli-Israel et al., 2002, 2003b). Other non-photic zeitgebers which result in increased risk of circadian rhythmicity deterioration in this population, specifically in institutionalized patients with dementia, include little social interaction, low levels of physical activity, and chronic bedrest. Alessi and colleagues (1999) have shown that improving the environment and increasing physical activity also improve sleep.

20.3.3. *Sundowning*

Many patients with late-life dementia also suffer from a phenomenon called ‘sundowning’, a cyclic worsening of agitation and confusion during the late afternoon to early evening with improvement or disappearance of these symptoms during the day (Bliwise, 1994). Because sundowning has been linked to the light/dark cycle, it has been hypothesized to be associated with an underlying circadian rhythm disturbance (Sanford, 1975), specifically a phase delay of body temperature (Little et al., 1995; Harper et al., 2001); however, the results are not conclusive at this time. Recent research suggests that sundowning occurs throughout the day (Cohen-Mansfield et al., 1989), with the peak occurring at 1:00 p.m. (Martin et al., 2000). Other studies have indicated sundowning worsens in the winter season, with the decrease in natural light during this time (Bliwise et al., 1993). The degree of patient agitation has also been associated with more disrupted 24-hour sleep rhythms, night-time light exposure (higher indoor illumination levels during the night common in nursing homes), and medication use (Martin et al., 2000). However, a recent large study of agitated patients with severe AD found that increased light exposure had no effect on the agitation (Ancoli-Israel et al., 2003c).

20.3.4. *Primary sleep disorders*

Primary sleep disorders such as SDB and PLMS are highly prevalent in older non-demented and demented adults (Bliwise et al., 1989; Ancoli-Israel et al.,

1991b). SDB is characterized by frequent complete (apnea) and/or partial (hypopnea) cessations in breathing during sleep, typically lasting longer than 10 seconds. PLMS is characterized by intermittent repetitive leg (and rarely arm) jerks during sleep. These limb movements typically occur every 20–40 seconds in multiple sequences over the course of the night. Both these sleep conditions are coupled with numerous night-time arousals that greatly affect sleep architecture and sleep quality.

Interaction between these primary sleep disturbances and the dementing condition may further exacerbate the patient's sleep. Recent research has focused on the possible relationship between SDB and dementia, as they are both known to affect cognitive function. In patients with severe SDB, sleep fragmentation and night-time hypoxemia have been associated with reductions in cognitive abilities, such as attention and memory, when compared to patients with mild or no SDB (Bliwise, 1993). One study found SDB to be correlated with dementia severity, i.e. increases in dementia severity were associated with increases in SDB severity (Ancoli-Israel et al., 1991b). In the clinical setting, patients with dementia and SDB have presented with increased morning confusion (Bliwise et al., 1989). A recent study showed a relationship between SDB and agitation and suggested that treating the SDB might improve agitated behavior (Gehrman et al., 2003).

20.4. Sleep research in healthy and non-demented elderly

The gradual sleep architecture changes and the development of sleep disturbances (see above) in patients with late-life dementia are similar to those found in non-demented older adults; however, they tend to be more common and more severe in patients with dementia. As mentioned previously, age-related changes and damage to neuronal pathways of several brain structures involved in the initiation and maintenance of sleep is the most probable underlying cause of these sleep changes in the elderly.

Compared to young and middle-aged adults, older adults report significantly more sleep problems, with recent estimates suggesting approximately 50% of older adults are suffering from some type of chronic sleep difficulty (Foley et al., 1995). Sleep complaints of elderly patients increase with age, with the most common complaints being difficulties falling asleep, frequent night-time awakenings, early-morning awak-

enings and EDS. Elderly women tend to complain of more sleep-related problems than their male counterparts (Newman et al., 1997). Although the actual amount of sleep may not change with advancing age, the quality and distribution of sleep over the 24-hour day changes considerably (Bliwise, 1993). Older adults often spend a substantial amount of their sleep period awake in bed, resulting in a dramatic reduction in their sleep efficiency and frequent sleep complaints. There is no clear consensus as to whether older adults require less sleep (or consolidated sleep), but it is fairly clear that older adults have reduced ability to acquire more or better quality of sleep.

According to a large epidemiological study, at least 28% of elderly persons suffer from some type of insomnia (Foley et al., 1999), including sleep-onset insomnia (difficulties with sleep initiation), sleep maintenance insomnia (difficulties maintaining sleep during the early, middle, or late part of the sleep period). However, Foley et al. (1999) have shown that these sleep disturbances are not a result of age per se, but rather are a result of medical conditions (such as heart disease, stroke, and diabetes), or use of prescribed sedatives and widowhood.

As discussed above, primary sleep disorders, such as SDB and PLMS are highly prevalent in the elderly, with between 24–62% of community-dwelling older adults suffering from SDB (Ancoli-Israel et al., 1991d) and approximately 44% of community elderly suffer from PLMS (Ancoli-Israel et al., 1991c). Additionally, elderly adults often suffer from SDB and PLMS simultaneously.

As a result of the weakening and desynchronization of the sleep/wake circadian rhythm with age, older adults suffer from more sleep/wake circadian rhythm disturbances than young or middle-age adults. In addition to the risk factors mentioned above, the sleep/wake circadian cycle is greatly affected by the secretion of endogenous melatonin, which is known to gradually decrease with older age (van Coevorden et al., 1991). The most common circadian sleep disorder affecting older adults is advanced sleep phase syndrome (ASPS), characterized by advancing of the sleep/wake rhythm resulting in sleepiness earlier in the evening resulting in earlier bedtimes and thus earlier morning rise times. ASPS is not a harmful condition per se; however, it may be somewhat difficult for some older adults to change their schedule, and may therefore require treatment for this condition.

There is increased evidence that medical and/or psychiatric co-morbidity are more strongly correlated

with the development of sleep disturbances than age or gender (Bliwise et al., 1992; Hoch et al., 1994). Increased medical and psychiatric conditions in this population are also associated with an increase in type and amount of medication intake. Many classes of medication, including prescription and over-the-counter drugs, have some effect on sleep and wakefulness. As older adults are prescribed proportionally more medications and usually have slower metabolisms, sleep complaints in this population may often be related to medication intake.

20.5. Future advances and applications in sleep research of dementia

A large proportion of patients with late-life dementia develop sleep problems. The sleep disturbances have been associated with harmful effects on physical and mental health as well as quality of life for the patient and their caregiver. The majority of basic sleep research in the area of dementia has focused on examining the biological brain mechanisms underlying this disorder. Clinical sleep research has utilized polysomnographic studies to examine sleep architecture changes, and actigraphic studies to examine sleep pattern and sleep/wake circadian rhythms changes in dementia. There are still many unanswered questions both in the basic and clinical sleep research arenas, including further understanding the exact degeneration of the SCN in dementia and the pathways with which this directly affects different aspects of sleep.

There has been less emphasis in sleep research on the risk or protective factors associated with the development of or resilience from sleep problems in this population. Future research will need to examine additional risk factors which may affect the onset, progression and severity of the sleep disturbances as well as examine protective factors which may be associated with resilience/resistance to development of sleep problems in dementia. Finally, as older non-demented adults with co-morbid physical and psychiatric disorders are known to be more vulnerable to the development of sleep disorders, this relationship also needs to be examined in older adults with dementia and other co-morbid conditions.

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CHAPTER 21

The nocturnal manifestations of waking movement disorders: focus on Parkinson's disease

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21.1. Introduction

The nature and prevalence of disturbed sleep across the spectrum of waking movement disorders is complex, and their pathophysiologies are poorly defined. In this chapter we briefly review the nocturnal manifestations of waking movement disorders using Parkinson's disease (PD) as the prototypical disorder.

Sleep disorders in patients with PD are common and have long been recognized; however, their pathophysiological basis remains ill-defined, and universal treatment strategies have not been established. Reasons for these deficiencies are many, including the pathological heterogeneity of parkinsonian syndromes and coincident factors such as medication use, aging, dementia, and mood disturbances, each of which independently affect sleep parameters. The most common sleep complaints in PD and the other neurodegenerative diseases are reduced and fragmented sleep, and abnormal dream-enactment that manifests as both motor and vocal behaviors. Polysomnographic studies in PD patients frequently demonstrate marked sleep fragmentation, reduced sleep efficiency, REM sleep behavior disorder (RBD) and periodic leg movements in sleep (PLMS) (Traczynska-Kubin et al., 1969; Wilson et al., 1969; Kales et al., 1971; Bergonzi et al., 1974, 1975; Mouret, 1975; Rye et al., 2000; Gagnon et al., 2002; Arnulf et al., 2002). Reported changes in REM sleep appear highly dependent on dose and length of dopaminomimetic treatment and individual patient differences (Kales et al., 1971; Bergonzi et al.,

1974, 1975; Schneider et al., 1976; Rabey et al., 1978; Lavie et al., 1980a, 1980b). Given the REM-sleep-suppressant effects of L-dopa (Gillin et al., 1973), many have hypothesized that REM sleep rebound underlies hallucinations experienced by many PD patients (Sharf et al., 1978; Moskovitz et al., 1978; Lesser et al., 1979; Nausieda et al., 1982, 1983, 1990; Comella et al., 1993). The recent demonstration of REM sleep intrusions into daytime naps in hallucinating and non-hallucinating patients provides electrophysiologic evidence supporting these conclusions (Arnulf et al., 2000a, 2002; Rye et al., 1999, 2000). The intrinsic pathology in PD itself is likely to be the major contributor of sleep impairment, because early and untreated PD patients exhibit disturbed sleep that includes excessive nocturnal movement (Kales et al., 1971; Bergonzi et al., 1974; Rye et al., 1999). Moreover, rats (Decker et al., 2000) and non-human primates (Daley et al., 1999) depleted of striatal dopamine bilaterally exhibit excessive nocturnal movement, and sleep in the parkinsonian patient deteriorates with disease progression (Schneider et al., 1976; Friedman, 1980; Emser et al., 1987). The fact that nocturnal movements are generally best controlled when waking motor symptomatology is best treated medically, argues further that their pathophysiological bases are firmly rooted in nigrostriatal dopaminergic neuron loss – the pathological hallmark of idiopathic PD. Clinical improvements of parkinsonism in PD seen with surgical interventions that restore balance in basal ganglia neurotransmission also improve sleep architecture and subjective sleep quality, although RBD and PLMS are not modified (Rye, 1997; Arnulf et al., 2000b; Iranzo et al., 2002). Some of the sleep disorders in PD appear to be related to a deficit of dopaminergic stimulation during the night, mainly in patients with motor fluctuations, as nocturnal akinesia and early-morning dystonia are

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alleviated by long-acting dopaminergic treatments and continuous subthalamic stimulation. It is likely that long-acting dopamine agonists or a sustained dopaminergic stimulation obtained by dopamine agonists administered via subcutaneous or transdermal routes may prove to be equally effective (Grandas and Iranzo, 2004). The majority of experimental findings argue against a significant role for serotonergic, noradrenergic or cholinergic pathologies in the nocturnal motor disturbances of PD. Nevertheless, the proposition that extra-nigral, non-dopaminergic pathology pre-dates the extensive loss of midbrain dopaminergic neurons traditionally thought to underlie PD (Braak et al., 2003), may account for the fact that RBD can presage the development of parkinsonism.

21.2. Sleep onset and maintenance insomnia

In most instances, sleep-onset problems in PD can be related to anxiety or to agitated depression. Pain, nocturia, restless legs syndrome (RLS), and severe motor parkinsonism and evening levodopa-induced dyskinesias may also cause sleep-onset insomnia. When treatment with L-dopa is instituted, some patients may experience sleep-onset insomnia that typically resolves with time. Amantadine, particularly if taken in the late afternoon or evening, may also cause insomnia. Sleep fragmentation is the most common nocturnal complaint in PD and is primarily caused by rigidity and bradykinesia with subsequent inability to turn over, or to rise to use the bathroom. Nocturnal akathisia precipitated by L-dopa, may be another cause of sleep onset and maintenance insomnia which may resolve with clozapine (Lang and Johnson, 1987; Linazasoro et al., 1993). Early awakenings may be a sign of depression or the consequence of early morning painful dystonia, that shares the same pathophysiology of the off-period dystonia that patients with motor fluctuations experience during the day. In subjects with multiple system atrophy (MSA), sleep fragmentation is more common than in PD, reflecting the more severe clinical condition and the more widespread involvement of brainstem circuits by the pathology of MSA (Ghorayeb et al., 2002). In subjects with progressive supranuclear palsy, reduced sleep efficiency and REM sleep are very frequent, particularly in advanced cases, reflecting the characteristic severe brainstem cell loss that occurs in this condition (Aldrich et al., 1989).

Treatment strategies in PD patients with difficulties in initiating and maintaining sleep need to be highly

individualized. In some subjects, sleep hygiene can be very effective. Dosing L-dopa, particularly in sustained-release form, and dopaminergic agonists closer to bedtime improves parkinsonism and 'off' phenomena during the night, therefore improving sleep-onset insomnia and frequent awakenings. High evening doses, however, can increase sleep latency and disrupt sleep in the first half of the night. In subjects with insomnia and sleep fragmentation short-acting benzodiazepines such as triazolam in non-demented cases and clonazepam may be effective. Antidepressants, particularly serotonin reuptake inhibitors, should be avoided if the subject is not depressed, because they may unmask or worsen RBD and PLMs.

21.3. Restless legs syndrome (RLS)

Although the pathophysiology of RLS is unknown, a dopaminergic dysfunction is thought to be involved since this syndrome is exquisitely sensitive to dopaminomimetics and some neuroimaging studies have detected impairments – albeit minor – in markers of striatal dopamine signaling (Garcia-Borreguero et al., 2003). In MSA, a condition that involves neurodegeneration in the basal ganglia and substantia nigra, RLS occurs in 10–12.5% of the subjects (Iranzo et al., 2000; Ghorayeb et al., 2002). Several investigators have failed to note the coincidence of RLS in patients with PD (Nausieda et al., 1990; Aldrich et al., 1994; Tan et al., 2002a). However, in our experience and that of others (Ondo et al., 2002; Krishnan et al., 2003), the two frequently coexist ranging from 7.9–20.8%. Ferritin levels are lower in PD with RLS when compared with PD without RLS and idiopathic RLS, suggesting a dysfunction of iron metabolism in the brain. When PD and RLS coexist, PD most commonly precedes RLS. Therefore, it is tempting to speculate that dopaminergic treatment that is used to treat parkinsonism reflects an unmasking of RLS in treated PD subjects (viz., a form of augmentation encountered in idiopathic RLS). An anecdotal report of alleviation of RLS in PD with pallidotomy is consistent with suggestions that the basal ganglia and their connections are intimately involved in the expression of RLS (Rye and DeLong, 1999). Large controlled studies, however, are needed to assess whether there is an association between RLS and PD. Suspected RLS in a PD patient should be very carefully differentiated from akathisia, which is also encountered in PD patients.

21.4. Periodic leg movements of sleep (PLMs)

Although PLMs exhibit high prevalence rates in the general population over the age of 60 (Ancoli-Israel et al., 1991), they are more prevalent in PD and MSA patients (Bliwise et al., 1998; Wetter et al., 2000). The clinical significance of PLMs in PD and MSA is unknown, since in most patients with PD and MSA, PLMs are asymptomatic and are not associated with arousals in PSG (personal observations). Because the neurophysiological abnormalities delineated in patients with PLMs but not suffering from PD and MSA (Wechsler et al., 1986) approximate those seen in PD and MSA patients (Delwaide et al., 1993), a common pathophysiology is suspected. However, it remains unclear why PD and MSA patients treated with dopaminomimetics frequently exhibit PLMS in light of the fact that lower doses of these medications are so effective in eliminating PLMs in subjects with idiopathic and secondary RLS. It is tempting to speculate that a marked PLM laterality may be seen in hemi-PD patients given the facts that: (1) EEG asymmetry is found in hemi-PD subjects (Myslobodsky et al., 1982); and (2) unilateral PLMs have been reported in asymmetric corticobasal degeneration with contralateral basal ganglia hypometabolism (Iriarte et al., 2001). In spinocerebellar ataxia type 3 (SCA 3), an autosomal dominant neurodegenerative disorder, dopamine transporter binding is decreased (Tzu-Chen et al., 2000) and PLMs are almost universal while RLS affects 45–55% of the subjects (Schöls et al., 1998; Iranzo et al., 2003). In contrast, most of the PD patients with PLMS do not complain of restless legs symptomatology. PLMs in subjects with PD lacking RLS have also been associated with reduced striatal dopamine transporter binding (Happe et al., 2003).

RLS and PLMs can be treated with long-acting dopaminergic agents in the evening, but to avoid potential dopaminomimetic-related complications, we advocate treatment with gabapentin (900–2100 mg in divided doses before bedtime). Antidepressants should be avoided since they have been noted to exacerbate RLS and PLMs in an unknown number of patients.

21.5. REM sleep behavior disorder (RBD)

Chronic RBD is commonly encountered in neurodegenerative diseases that involve the brainstem such as idiopathic PD (Gagnon et al., 2002), dementia with Lewy bodies (Boeve et al., 1998), and is almost universal in MSA (Plazzi et al., 1997; Iranzo et al., 2000).

Box 21.1

REM sleep behavior disorder characteristics in PD

- (1) It occurs in approximately half of the patients.
- (2) In some patients RBD can precede the waking motor and dysautonomic symptoms of PD.
- (3) It is more common in males than in females.
- (4) It can result in injuries to the patient or the bed partner.
- (5) Some patients are unaware of their abnormal sleep behaviors and clinical history suggestive of RBD can only be obtained by the bed partners' reports.
- (6) Polysomnography with synchronized audiovisual monitoring is needed to diagnose RBD.
- (7) In some patients without a history of RBD, PSGs demonstrate REM sleep without atonia.
- (8) It is possible that brainstem abnormalities of the dopaminergic, cholinergic and glutamatergic systems are involved in the pathophysiology of RBD.
- (9) Treatment of choice is clonazepam (0.25–4 mg) at bedtime.
- (10) It is unclear if dopaminergic agents improve or worsen the symptomatology of RBD.

RBD, or REM sleep without atonia, are also common in non-synucleinopathologies associated with cell loss in the mesopontine tegmentum such as SCA3 (Iranzo et al., 2003; Syed et al., 2003), progressive supranuclear palsy (Rompre et al., 2004) and parkinsonism with *parkin* mutations (Kumru and Santamaria, personal communication) (Box 21.1). Nearly 65% of RBD cases initially diagnosed as having idiopathic RBD presage the development of the waking motor manifestations of parkinsonian states by several to many years (Schenck et al., 2003). RBD is more frequently encountered in the male PD patient, as is the case with idiopathic RBD (Olson et al., 2000; Schenck and Mahowald, 2002). In MSA, however, the male:female ratio is closer to 1:1 (Olson et al., 2000; Iranzo et al., 2004). Histories consistent with RBD can be obtained from nearly one in six patients with idiopathic PD (Comella et al., 1998; Gagnon et al., 2002). PSG analysis reveals 'subclinical' evidence of RBD in 50% of PD patients (Gagnon et al., 2002), and this electrophysiologic correlate of RBD appears significantly specific in distinguishing parkinsonian subjects from age-matched controls and Alzheimer's disease patients (Gagnon et al., 2002; Bliwise et al., 2003).

When compared to subjects with MSA, patients with PD have significantly longer disease duration, lower REM sleep without atonia percentage and periodic leg movements index in sleep, and more total sleep time. Subjects with either MSA or PD, as compared to those with idiopathic RBD, are less frequently male, have lesser self-reported clinical RBD severity and are less aware of their abnormal sleep behaviors. The nature of unpleasant dream content and motor and vocal expression of RBD are similar between subjects with PD, MSA and the idiopathic form (personal observations; Iranzo et al., 2004) (Table 21.1). The waking EEG in PD with RBD and without dementia demonstrates subtle abnormal slowing that distinguishes

them from control and PD patients lacking RBD (Gagnon et al., 2004). It has not been established whether there are demographic, clinical and PSG differences between patients with PD who have, and have not, developed RBD, although it seems that RBD frequently occurs in subjects with hallucinations and sleep-onset REM periods during episodes of daytime sleepiness (Nomura et al., 2003).

To establish the diagnosis of RBD, PSG with audio-visual recording is essential to detect increased EMG activity and abnormal behaviors during REM sleep, and to exclude other sleep disorders that can resemble RBD in PD, such as severe obstructive sleep apnea, nocturnal hallucinations and confusional awakenings. Although the pathophysiology of RBD in PD is unclear, it is thought to result from direct or indirect effects of PD-related pathology upon brainstem structures that modulate REM sleep, such as the pedunculo-pontine and subcoeruleal regions. The most relevant indirect pathways to these regions are those from the internal pallidal segment and substantia nigra pars reticulata, other basal ganglia nuclei (e.g., the subthalamic nucleus), hypothalamus and amygdala. The degree of dysfunction of these structures is probably reflected in the degree of REM without atonia and excessive phasic activity, and the occurrence and severity of RBD symptoms. It is tempting to speculate, for example, that RBD characterized by frightening dreams reflects dysfunction of the amygdala or other limbic structures and their connections with the substantia nigra or the brainstem. Recently, autopsy studies in PD have suggested that the degenerative process begins in the lower brainstem, and advances upwards through the pons, before reaching the mid-brain and cerebral hemispheres (Braak et al., 2003). This is an attractive postulate, because it may account for the observation that RBD precedes the onset of waking PD. An alternate sequence of neuropathologic events, however, must be posited to account for the more common finding of parkinsonism preceding, rather than succeeding, the occurrence of RBD. Disturbances in the dopaminergic system have been implicated in the pathogenesis of RBD, since this parasomnia is common in PD and neuroimaging studies have revealed decreased striatal dopamine transporters in patients with idiopathic RBD (Albin et al., 2000). However, RBD symptoms are not consistently responsive to dopamine agonists or L-dopa/carbidopa medications (personal observations) or deep brain subthalamic nucleus stimulation (Iranzo et al., 2002).

Table 21.1

Type of dreams and abnormal behaviors reported in a group of 65 nondemented PD patients with RBD confirmed by video-PSG.

	Parkinson's disease (<i>n</i> = 65)
Male (%)	70.8
Age (years)	65.8 ± 7.5
Unpleasant dream recall (%)	86.2
Most frequent unpleasant dreams	
Attacked by someone (%)	67.7
Arguing with someone (%)	53.1
Chased by someone (%)	53.8
Falling from a cliff (%)	44.6
Attacked by animals (%)	32.3
Self-awareness of abnormal sleep behaviors (%)	35.4
Most frequent abnormal behaviors	
Talking (%)	95.4
Shouting (%)	89.2
Swearing (%)	29.2
Crying (%)	49.2
Laughing (%)	47.7
Singing (%)	13.8
Punching (%)	69.2
Kicking (%)	66.2
Falling out of bed (%)	38.5
Patients self-injured (%)	15.4
Bed partners injured (%)	10.8

No placebo-controlled trials have been conducted for treatment of RBD. For unknown reasons, RBD symptoms in PD, and all the other chronic conditions, respond to modest–large doses of clonazepam (0.25–4 mg) preceding bedtime (Olson et al., 2000; Schenck and Mahowald, 2002). If clonazepam is ineffective, associated with significant side-effects, or worsening of pre-existing obstructive sleep apnea, melatonin (Kunz and Bes, 1999), donepezil (Ringman and Simmons, 2000), carbamazepine (Bamford, 1993), levodopa (Tan et al., 1996) and pramipexole (Fantini et al., 2003) have been reported to be effective in anecdotal cases. In refractory cases, methods of self-protection from injury such as placing a mattress on the floor or removal of furniture from the room may be needed. It is recommended to minimize the use of antidepressants such as venlafaxine (personal observations), mirtazapine (Onofrj et al., 2003) and lipophilic beta-adrenergic blockers such as bisoprolol (Iranzo and Santamaria, 1999), because these medications have been reported to induce or aggravate RBD.

21.6. Sleep-disordered breathing and stridor

Nocturnal respiratory disturbances probably are no more likely to occur in PD, given their high prevalence in the normal adult population (Aldrich, 1994; Bliwise et al., 1994; Rye et al., 2000). Central or obstructive sleep apnea, hypoventilation and irregular patterns of respiration likely contribute to sleep fragmentation in a small subpopulation of PD patients, however, few detailed studies have been reported (Apps et al., 1985; Hardie et al., 1986). Increased tone or dyskinesias in the upper airway muscles, caused by either the disease itself or medications (Vincken et al., 1984), can predispose the PD patient to obstructive apneas. Dyscoordination of respiratory muscle activity and abnormalities in respiratory drive have also been observed that might contribute to nocturnal respiratory disturbances (Rosen et al., 1985; Feinsilver et al., 1986). The severity of respiratory abnormalities is greater in patients with coincident autonomic dysfunction (Apps et al., 1985). Although in PD it is generally felt that respiratory disturbances correlate with the severity of rigidity and tremor, they do not typically improve with administration of L-dopa (Aldrich, 1994). Treatment of sleep apnea in PD and other neurodegenerative conditions is, therefore, similar to that when these problems are encountered in the normal adult population. For obstructive and central sleep

apnea, treatment with continuous positive airway pressure (CPAP) offers the best chance of success and can be used effectively by most patients.

Stridor is a sign that indicates obstruction in the upper airway at the level of the larynx. In subjects with sporadic PD, stridor is a rare condition caused by rigidity of the vocal cord adductors and tensors. Stridor in PD occurs during wakefulness and rarely during sleep, particularly in subjects with severe dysphagia during the late stages of the disease (Isozaki et al., 1995). Recurrent, acute life-threatening episodes of dystonic laryngospasm with stridor during wakefulness may occur in subjects with juvenile parkinsonism–dystonia syndrome requiring elective tracheostomy (personal observations). In MSA, stridor occurs during sleep in up to 35% of the subjects and is associated with short survival (Silber and Levine, 2000; Yamaguchi et al., 2003) and sudden death during sleep (Munschauser et al., 1990). In MSA subjects with severe laryngeal obstruction, stridor also appears during wakefulness. In MSA, the pathophysiology of laryngeal narrowing is thought to be related to either denervation of the vocal cord abductors (Hayashi et al., 1997) or hyperactivation of the vocal cord adductors (Isono et al., 2001), although it probably results from an unbalanced co-activation of both muscles in response to increased upper airway resistance. Age, MSA duration and clinical severity are not different between patients with stridor and without stridor. Compared to MSA subjects without stridor, patients with stridor have higher apnea–hypopnea indexes, oxyhemoglobin desaturations and vocal cord abductor abnormalities on laryngoscopy. Tracheostomy is usually considered an optimal treatment for stridor in MSA because it bypasses the vocal cord obstruction, but it is a surgical procedure associated with local complications and frequently is refused by patients. Non-invasive nasal CPAP eliminates video-polysomnographic documented stridor in MSA subjects with vocal cord abnormalities (Iranzo et al., 2000). Long-term follow-up of an expanded series demonstrated high CPAP tolerance and compliance with no major side-effects, no recurrence of stridor, subjective improvement in sleep quality, and a median survival time that approximated that seen in a parallel group of MSA patients lacking stridor. Thus, in MSA, CPAP appears to be an effective long-term therapy for nocturnal stridor. However, subjects with stridor during wakefulness may develop subacute respiratory failure requiring tracheostomy (Iranzo et al., *in press*).

21.7. Excessive daytime sleepiness

Sleepiness in PD is common, very real, and potentially as severe as manifested by narcoleptics. In PD, hypersomnolence is probably related to either the disease itself or the effect of dopaminergic medications. Dopamine cell death in PD not only profoundly alters nocturnal movement, but also, thalamocortical arousal state. This manifests as daytime sleepiness, unintended sleep episodes, and intrusion of REM-sleep into daytime naps (sleep-onset REM-sleep (SOREMs)) (Rye et al., 2000; Rye and Jankovic, 2002). PD represents an underlying diathesis to sleepiness and SOREMs expression that can be exaggerated by numerous coexistent factors including use of dopamine agonists and L-dopa, sedative-hypnotic and potentially other medications, primary sleep disorders, and potentially comorbid conditions such as dementia and depression. The objective findings in a small number of newly diagnosed, unmedicated or young PD patients (Rye et al., 1999) emphasize that the parkinsonian state itself is a major factor in the expression of sleepiness and SOREMs. The initial report of dose-related sudden-onset sleep episodes ('sleep attacks') in eight PD subjects while driving with pramipexole and ropinirole was interpreted as a novel, idiosyncratic response specific to the new non-ergot D2/D3 receptor agonists (Frucht et al., 1999). Clinical experience and more comprehensive assessments agree that sleepiness has long been under-recognized in PD, but that it is a phenomenon not restricted to a specific class of dopaminomimetics. Sleepiness or 'sleep attacks' associated with dopaminomimetics in a subset of PD patients appear to be dose-related, but are not clearly related to specific class of agent (e.g., L-dopa vs. ergot and non-ergot derived D2/D3 receptor-like agonists). Sudden-onset sleep events have been described in PD subjects taking L-dopa/carbidopa, bromocriptine, pergolide, ropinirole, pramipexole and carbegoline (Schapira, 2000; Ferreira et al., 2000a, 2000b, 2002; Hauser et al., 2000; Ryan et al., 2000; Montastruc et al., 2001; Ondo et al., 2001; Hobson et al., 2002; O'Suilleabhain and Dewey, 2002). These reports are largely anecdotal and only a few have documented or investigated the nature of related sleep-architecture changes (Tracik and Ebersbach, 2001; Ulivelli et al., 2002). It is still unclear whether unintended sleep events are a unique physiopathologic entity or an extreme manifestation of daytime hypersomnolence.

In community-based samples of PD patients, the rate of sleepiness ranges from 7–14% as compared to

1–2% in healthy, elderly controls (Tandberg et al., 1999; Tan et al., 2002b), and longitudinal studies have demonstrated that the rate increases by 6% per year (Gjerstad et al., 2002). In clinic-based samples, the rate is much higher (20–50%) (Montastruc et al., 2001; Ondo et al., 2001; Hobson et al., 2002). Employing a standardized measure of physiological sleep tendency across five daytime nap opportunities, the authors and others have objectively documented 'pathological' sleepiness in 30–50% of patients, and a narcolepsy-like phenotype in a similar number (Rye et al., 2000; Arnulf et al., 2002). Sleepiness bears little relationship to the primary motor manifestations of disease (e.g., disability scale, medication burden), or sleep architecture measures (e.g., total sleep time, stage amount, etc.). Remarkably, contrary to what one would expect based upon the demands of sleep homeostatic mechanisms, poor nocturnal sleep is generally associated with greater, rather than lesser, degrees of daytime alertness. Advanced disease or disease duration have been contributing factors noted in several studies (Rye et al., 2000; Ondo et al., 2001; O'Suilleabhain and Dewey, 2002). Other potential risk factors include benzodiazepine use (Rye et al., 2000), male sex (Ondo et al., 2001), comorbid dementia or psychosis (Gjerstad et al., 2002), and autonomic failure (Montastruc et al., 2001). Coexisting obstructive sleep apnea and PLMS may also contribute to sleepiness but rarely are they the main cause. Although the motor manifestations of RBD disrupt sleep EEG continuity, this parasomnia is not a direct cause of hypersomnia (personal observations). Treatment of daytime sleepiness with waking-promoting agents such as modafinil is only moderately effective (Högl et al., 2002). Management of hypersomnolence in PD is summarized in Box 21.2.

The pathophysiological bases underlying the spectrum of PD-related changes in sleep–wake tendencies are complex and unique to the individual patient. The dissociation of arousal state from the motor manifestations of disease and homeostatic sleep drives (viz., sleep propensity should be inversely rather directly related to the quality and quantity of prior nights' sleep) in PD has several implications. First, it emphasizes that dopamine pathway integrity is critical for maintaining homeostatic sleep mechanisms. Second, it points to the pathophysiological basis of impaired thalamocortical arousal state residing outside of the sensorimotor sub-circuit of nigrostriatal pathways traditionally thought to underlie parkinsonian motor disabilities. The cellular and subcellular substrates underlying these disease-

Box 21.2**Treatment of sleepiness in PD****Medication adjustments**

Reduce sleeping aids with anti-histaminergic activity
 Minimize benzodiazepine use
 Minimize 'sedating' antidepressant use
 Dopaminomimetic dose adjustment (reduce the daily dose or switch to another dopaminergic agent) if dosing temporally associated with sleepiness

Treat documented sleep or other disturbance

Continuous positive airway pressure (CPAP) for sleep apnea
 Night-time dosing of dopaminomimetics or gabapentin for PLMS
 Consider treatment of orthostatic hypotension

Treat 'residual' daytime sleepiness*Hygiene measures*

Scheduled naps
 More frequent, smaller meals

Pharmacologic measures

Bupropion (75–150 mg two or three times per day)
 Modafinil (100–200 mg each morning and noon)
 Dextroamphetamine sulfate (5–30 mg each morning and noon), combination of sustained release and regular tablets

related effects remain ill-defined. These phenomena may reflect loss of dopamine's effects upon neural excitability in any one of a number of brain regions necessary for maintaining normal states of thalamocortical excitability. One plausible substrate given the narcolepsy-like phenotype seen in nearly half of 'sleepy' PD patients, is hypocretin-containing neurons in the lateral hypothalamus known to degenerate in primary narcolepsy/cataplexy (Silber and Rye, 2001). Recently, it has been shown that patients with late-stage PD may have low levels of ventricular CSF hypocretin (Drouot et al., 2003). Other plausible neural substrates that deserve future investigation include targets of ventral tegmental area dopamine neurons including the prefrontal cortex, the cholinergic magnocellular basal forebrain and midline thalamic nuclei. Alternatively, sleepiness and SOREMs may reflect extranigral pathology, e.g., in nuclei comprising the traditional ascending reticular activating system such as the dorsal raphe, locus coeruleus and pedunculopontine tegmental nucleus (Jellinger, 1991).

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CHAPTER 22

Restless legs syndrome and periodic limb movements in sleep

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22.1. Clinical features of restless legs syndrome (RLS)

22.1.1. Essential clinical features of RLS

According to a recent NIH consensus conference, RLS is characterized by the following four characteristics which are the minimal and essential features for the diagnosis of RLS (Allen et al., 2003):

- (1) An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs.)
- (2) The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting.
- (3) The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
- (4) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present.)

22.1.2. Supportive clinical features of RLS

The following features are supportive of the diagnosis of RLS as outlined by the NIH consensus confer-

ence on RLS (Allen et al., 2003), but are not invariably present in RLS. Although the previously listed essential features are necessary for the diagnosis of RLS, the supportive clinical features can help resolve any diagnostic uncertainty.

22.1.2.1. Positive family history of RLS

A positive family history compatible with an autosomal dominant mode of inheritance is present in about two-thirds of cases.

22.1.2.2. Response to dopaminergic therapy

Patients so regularly respond to dopaminergic therapy that such responsiveness can be viewed as supportive of the diagnosis.

22.1.2.3. Periodic limb movements

Involuntary jerking movements of the legs that recur every few seconds can be seen in either sleep or wakefulness in patients with RLS. These movements are recorded by placing bilateral surface electromyographic (EMG) leads on both anterior tibialis muscles. According to standards set by the American Academy of Sleep Medicine, to be classified as periodic limb movements in sleep (PLMS), involuntary movements during sleep must be at least 25% as tall on electromyography (EMG) as the patient's voluntary foot dorsiflexions prior to polysomnography. During polysomnography at least four such movements must occur in a row that are 0.5–5 seconds in duration and 5–90 seconds apart (Atlas Task Force of the American Sleep Disorders Association 1993, American Sleep Disorders Association, 1990) (Figure 22.1). Pseudo-PLMS may occur as part of the arousal response after cyclically occurring sleep apnea events and should not be scored as true PLMS. PLMS may occur without RLS either as an isolated phenomenon or in conjunction with a variety of other medical problems. However, 80% of patients with RLS have

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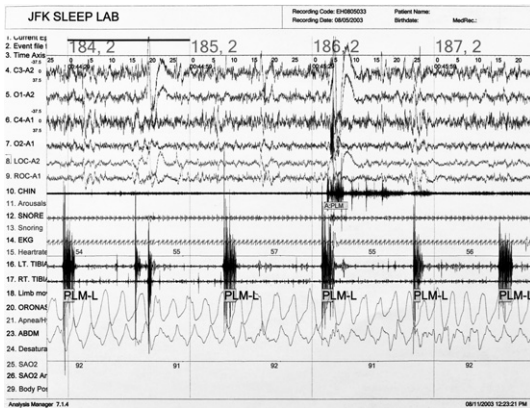


Fig. 22.1. Periodic limb movements in sleep (PLMS) shown on anterior tibialis EMG. To be scored as PLMS, there must be at least four recurrent leg movements in a row, 0.5–5 seconds in duration and 5–90 seconds apart.

PLMS. If PLMS occur together with RLS, the primary diagnosis is considered to be RLS. If PLMS in the absence of RLS are accompanied by symptomatic sleep disruption and daytime fatigue, the term periodic limb movement disorder (PLMD) is used. PLMS, however, only rarely cause extreme daytime drowsiness (Bixler et al., 1982; Mendelson 1996; Nicolas et al., 1998; Karadeniz et al., 2000). Patients are often unaware of the PLMS, but the sleep of the spouse is often interrupted by the kicking movements.

Periodic limb movements in sleep may vary depending on the time of night. In the type I pattern periodic limb movements have a peak frequency early in the night with reduced frequency later in the night, whereas the type II pattern shows a relatively even distribution across the night. Patients with periodic limb movements alone and those who have it associated with restless legs syndrome have a type I pattern, whereas those who have the syndrome associated with sleep disorders such as narcolepsy or sleep apnea have a type II pattern (Coleman et al., 1980; Culpepper et al., 1992; Montplaisir et al., 1994a; Hening et al., 1999; Trenkwalder et al., 1999).

Periodic leg movements also occur during wakefulness in RLS while patients are at rest, e.g. sitting or lying, but they are disruptive to function in only a minority of patients. These movements disappear when the patients move or get up to ambulate. Montplaisir and colleagues have devised a technique for monitoring and quantitating these movements called the 'suggested immobilization test' (SIT). During a 60-minute period patients are asked to lie perfectly still with relaxed muscles to allow the periodic leg

movements during wakefulness to emerge. The movements are then recorded by bilateral anterior tibialis surface EMG and quantitated (Montplaisir et al., 1998).

22.1.3. Associated clinical features of RLS

In addition to the essential and supportive clinical features of RLS, there are certain additional significant clinical features associated with the disorder.

22.1.3.1. Natural clinical course of the disorder

Most patients seen in clinical practice are middle to older age, but onset may occur in childhood and such cases may be misdiagnosed as 'growing pains'. Patients tend to progress in severity over the years both in terms of the number of days per week and the number of hours per day that the patients experience symptoms as well as the intensity of the leg discomfort at the time it is actually experienced. However, static courses have been seen and unexplained remissions of a month or more occur in about 15% of the cases.

22.1.3.2. Sleep disturbance

Sleep disturbance is the main complaint that brings RLS patients in for treatment, but sleep disturbance is not necessary for the diagnosis of RLS. The leg discomfort and periodic leg movements in wakefulness in RLS may cause difficulty in initiating and maintaining sleep. Patients may experience daytime drowsiness due to the insomnia. The periodic limb movements in sleep usually do not cause conscious awareness of sleep disturbance in the patient, but spousal sleep disruption due to such leg kicks is common.

22.1.3.3. Medical evaluation/physical examination

The neurological examination is normal in the idiopathic and familial forms of the disorder. Cases associated with peripheral neuropathy and radiculopathy are also seen. There is an increased frequency of RLS in cases of renal failure and RLS may be temporarily exacerbated during pregnancy. Iron deficiency makes the symptoms of RLS worse and every patient should be screened for deficiency of the iron-binding protein, ferritin. Even if ferritin levels are in the bottom third of normal, patients may respond to iron therapy, ferrous sulfate 325 mg tid. However, iron therapy does not work immediately and more standard traditional therapy (not covered in this chapter) should be used simultaneously with iron therapy.

22.2. Neurophysiology of restless legs syndrome and periodic limb movements in sleep

The cause of periodic limb movements is unknown. Although there are contradictions in the literature, the bulk of the scientific evidence suggests that there is a sleep-related failure of motor inhibition presumably occurring at the level of the brainstem. The disinhibition produced by the brainstem generator activates a secondary motor center in the lumbosacral spinal cord resulting in periodic limb movements. The brainstem generator by the reticular activating system may also cause periodic cortical arousals that occur at approximately the same time as the periodic limb movements. Altered peripheral input (e.g., from peripheral neuropathy associated with restless legs syndrome) may trigger the brainstem generator to produce periodic limb movements. The sympathetic nervous system and altered dopamine or opioid activity of the central nervous system are also presumed to play a role.

22.2.1. Possible role of the pyramidal tracts and cerebral cortex

The site of the generator of periodic limb movements in sleep remains unknown, and the results of neurophysiological studies are conflicting (Mosko and Nudleman, 1986; Wechsler et al., 1986; Martinelli et al., 1987; Smith et al., 1992). As dorsiflexion of the large toe accompanied by fanning of the small toes resembling the Babinski sign may be a component of periodic limb movements in sleep, it has been suggested that periodic limb movements in sleep occur as a result of sleep-related failure of the pyramidal tracts to inhibit spinal cord reflexes or of higher cortical centers to properly convey their inhibitory message through the pyramidal tracts to the spinal cord (Smith, 1987). Although not all studies are positive, hyperactive brain stem and spinal cord reflexes in patients with periodic limb movements in sleep or restless legs syndrome found on neurophysiological studies suggest suprasegmental disinhibition of these reflexes, although alternative explanations have been offered (Mosko and Nudleman, 1986; Wechsler et al., 1986; Martinelli et al., 1987; Smith et al., 1992; Bucher et al., 1996; Briellmann et al., 1996; Entezari-Taher et al., 1999; Tergau et al., 1999; Bara-Jimenez et al., 2000). Techniques employed in the studies include examination of the blink reflex, H reflex, elicitation of the flexor response by stimulation of the foot and comparison to PLMS, brainstem auditory evoked responses, somatosensory evoked responses, central magnetic

stimulation, paired transcranial magnetic stimulation, and examination of the cortical silent period. Additional evidence supporting suprasegmental disinhibition as a cause of periodic limb movements include: (1) the observation that periodic limb movements in sleep can be seen in patients with myelopathy due to spinal cord injury, multiple sclerosis, resectable schwannoma or syringomyelia and that the periodic limb movements remit along with remission of motor weakness (Yokota et al., 1991; Dickel et al., 1994; de Mello et al., 1996, 1997, 1999; Lee et al., 1996; Nogues et al., 2000); (2) the observation that periodic limb movements in sleep can occur with epidural and spinal anesthesia and that the periodic limb movements disappear as the anesthesia wears off (Watanabe et al., 1990); and (3) the observation that periodic limb movements in sleep can occur despite complete transection of the spinal cord (Yokota et al., 1991; de Mello et al., 1996).

If suprasegmental disinhibition does occur, it is likely that it originates subcortically and not in the cerebral cortex. A reticular or other subcortical origin has also been proposed based on observations that periodic limb movements in sleep almost never involve the face, suggesting that the generator of periodic limb movements in sleep is below the level of the facial nucleus in the brainstem. In addition, no electrically generated cortical potential has been found to precede the periodic limb movements in sleep when the EEG signal prior to the periodic limb movements in sleep is back-averaged (Trenkwalder et al., 1993).

In one study but not another, electrophysiological studies have shown simultaneous sequential activation of muscle groups both distal and proximal to the lumbosacral spinal cord in patients with periodic limb movements and restless legs syndrome (Trenkwalder et al., 1996; Provini et al., 2001). If this evidence is true it suggests that the final generator for periodic leg movements is in the lumbosacral cord (Trenkwalder et al., 1996). The authors proposed a brainstem disinhibition phenomenon as the pathological mechanism for activation of the spinal cord generator (Trenkwalder et al., 1996). This hypothesis is also consistent with the spinal cord lesion data, as damage to the spinal cord would be expected to lead to such disinhibition (Yokota et al., 1991; de Mello et al., 1996; Lee et al., 1996).

It should be emphasized that the neuronal pathways responsible for the clinical manifestations of an upper motor lesion such as that seen in a stroke or spinal cord lesion are not fully understood. Although the pyramidal tracts are involved in such lesions, accompanying non-pyramidal pathways may be responsible

for some of the clinical manifestations of an upper motor neuron lesion. In an analogous fashion, the arguments that apply to involvement of the pyramidal tracts in RLS may be more broadly understood to apply to the pyramidal tracts or accompanying tracts such as the dorsoreticulospinal tract or descending diencephalospinal dopaminergic pathways (Yokota et al., 1991; Bara-Jimenez et al., 2000; Ondo et al., 2000). Lesioning of diencephalospinal dopaminergic pathways leads to restlessness in rats, for example (Ondo et al., 2000). The fact that patients with idiopathic RLS and accompanying PLMS have a normal neurological examination without clinical signs of an upper motor neuron lesion such as weakness or exaggerated deep tendon reflexes (Allen et al., 2003) indicates that, at best, there is only a partial overlap of pathway involvement between an upper motor neuron lesion and PLS/PLMS.

22.2.2. Possible role of the reticular system and subcortical structures

The periodic limb movements in sleep also resemble the flexor withdrawal reflex, and because the dorsal reticulospinal tract modulates this response, this tract has also been implicated in the pathogenesis of restless legs syndrome (Yokota et al., 1991; Bara-Jimenez et al., 2000).

The subcortical reticular system has also been implicated by the observation that certain biological rhythms thought to be modulated by the reticular formation have fluctuations in response similar in their periodicity to periodic limb movements in sleep, e.g., fluctuations in blood pressure, respiration, pupil diameter, intraventricular fluid pressure and electroencephalographic arousal in normal human sleep and coma (Lundberg, 1960; Coccagna et al., 1971; Lugaresi et al., 1972; Evans, 1976; Droste et al., 1996). These fluctuations are also apparent in neuronal activity, e.g., a 30-second periodicity evident in the lumbar monosynaptic reflex in decerebrate cats (Barnes and Burnham, 1969). Because the periodicity of these other biological phenomena is similar in their periodicity to periodic limb movements, it has been proposed that there is a brainstem generator for periodic limb movements (Coccagna et al., 1971; Lugaresi et al., 1972).

Although the origin of intrinsic rhythmicity of the nervous system is not known for certain, there are times when the sleeping brain displays recurrent periods of brief cortical arousal or arousal equivalents that are independent of any sleep-disrupting event. It seems logical that the brainstem reticular formation

may be the originator of these periodic arousals. This is because the reticular activating system is a well-known mediator of cortical arousal and these brief episodes of cortical activation are similar in their periodicity to those of the aforementioned biological activities that are presumably mediated by the subcortical reticular system (Coccagna et al., 1971; Lugaresi et al., 1972; Montplaisir et al., 1994b, 1996; Droste et al., 1996; Parrino et al., 1996). When brief cortical arousal or arousal equivalents recur on a regular predictable basis in NREM sleep, a cyclic alternating pattern is said to be present. In the cyclic alternating pattern, arousals (bursts of alpha of 3 seconds or slightly more), arousal accompaniments (e.g., enhancement of muscle tone, postural changes, and acceleration of heart rate), or arousal equivalents (e.g., vertex sharp waves, K-complexes, delta bursts) alternate every several seconds with periods of sleep quiescence. When there are no recurrent arousals or arousal equivalents but there is primarily peaceful sleep, a non-cyclic alternating pattern is said to be present (Terzano and Parrino 1993; Zucconi et al., 1995; Droste et al., 1996; Parrino et al., 1996; Terzano et al., 1996). Periodic limb movements in sleep are associated with the arousal phase (phase A) of the cyclic alternating pattern as opposed to the tonic phase (phase B) (Montplaisir et al., 1994b, 1996; Droste et al., 1996; Parrino et al., 1996). It is emphasized that the cyclic alternating pattern is a normal phenomenon thought to originate in thalamo-cortical circuits. Thus, individuals are more predisposed to have periodic limb movements in the A phase as opposed to the B phase. The fact that A phase phenomena like K-alpha complexes recur periodically even after periodic limb movements have been suppressed by L-dopa therapy suggests that the arousals are more likely to cause the periodic limb movements rather than vice versa or, alternatively, that the arousals and periodic limb movements are independent manifestations of a single causative factor (Montplaisir et al., 1996; Parrino et al., 1996).

Involvement of the brainstem in the pathogenesis of periodic limb movements in sleep is also suggested by the observation that multiple sclerosis patients with periodic limb movements in sleep had larger lesion loads in this area (Ferini-Strambi et al., 1994). Functional MRI studies have provided strong evidence that the red nucleus and brainstem areas close to the reticular formation are involved in the generation of periodic limb movements in patients with restless legs syndrome (Bucher et al., 1997) and that the sensory phenomena in RLS are associated with activation of the thalamus and cerebellum (Bucher et al., 1997). In

patients with multiple sclerosis and periodic limb movements in sleep, a larger lesion load was found in the cerebellum and brainstem (Ferini-Strambi et al., 1994).

22.2.3. Possible role of the peripheral nervous system

Although periodic limb movements in sleep are generated centrally, the stimulus to the central nervous system generator could be peripheral. Patients who have both restless legs syndrome and periodic limb movements in sleep sometimes have evidence of peripheral neuropathy, and the abnormal sensory input from the damaged peripheral nerves could cause the brain or spinal cord to generate periodic limb movements in sleep (LaBan et al., 1990; Salvi et al., 1990; Shafor 1991; Iannaccone et al., 1995; Polydefkis et al., 2000). Against this hypothesis is the observation that the abnormal leg sensations in restless legs syndrome (perhaps generated by peripheral neuropathy) are not always most intense just prior to the periodic limb movements while awake (Pelletier et al., 1992). A study of 154 patients with peripheral neuropathy found an incidence of restless legs syndrome of 5.2%, which, despite the authors' contentions, is close to the prevalence of restless legs syndrome in the general population (Rutkove et al., 1996). This suggests that peripheral neuropathy may act as a triggering factor or be coincidentally associated with restless legs syndrome in predisposed individuals rather than being the primary cause.

22.2.4. Possible role of the sympathetic/adrenergic systems

The bulk of the following evidence suggests that an overactive sympathetic nervous system is involved in the propagation of periodic leg movements. Sympathetic overactivity leading to vasoconstriction has been postulated to play a role in the genesis of periodic limb movements in sleep (Ancoli-Israel et al., 1986; Watanabe et al., 1990; Ware et al., 1988). A reduction in blood flow caused by epidural or spinal anesthesia is offered as an alternate explanation for the periodic limb movements in sleep seen with the anesthesia (Watanabe et al., 1990). Patients with periodic limb movements in sleep may have cold feet and reduced peripheral pulses, suggesting reduced blood flow to the extremities (Ancoli-Israel et al., 1986; Ware et al., 1988). Thermal biofeedback reduced the number of periodic limb movements in sleep in a

patient (Ancoli-Israel et al., 1986). In addition, sympathetic overactivity leading to vasoconstriction was presumably reversed when periodic limb movements in sleep were reduced by two 10mg tablets of the alpha-1 postsynaptic adrenergic receptor blocker phenoxylbenzamine in a 'chemical sympathectomy' (Ware et al., 1988). The adrenergic hypothesis for the generation of periodic limb movements in sleep is further supported by the observation that tricyclic antidepressants, which are presynaptic nerve terminal reuptake blockers of noradrenaline (norepinephrine), can increase periodic limb movements in sleep. However, the inhibitory presynaptic alpha-2 adrenergic receptor may be less critical to the generation of periodic limb movements in sleep: clonidine, which activates this receptor and inhibits noradrenaline (norepinephrine) release, improved restless legs syndrome but not periodic limb movements in sleep (Wagner et al., 1996). Sympathetic nerve blockade relieved movements that were by their description periodic limb movements while awake in two patients who probably had restless legs syndrome (Uchiyama et al., 1990).

There is some evidence of 20–40-second periodicity of sympathetic nervous system activity that corresponds to the most commonly seen intermovement interval between periodic limb movements in sleep (Ware et al., 1988). Ware and colleagues (1988) have suggested that the sympathetic nervous system acts centrally as well as peripherally and that the central component may propagate periodic arousals that are of survival advantage. An overactive central component could, therefore, also generate periodic limb movements in sleep. The intrinsic rhythmicity of the sympathetic nervous system is not only similar to that seen with periodic leg movements but is also similar to that seen in biological activity presumably mediated by the brainstem (Coccagna et al., 1971). The sympathetic hypothesis is thus not incompatible with the hypothesis that the brainstem is the mediator of periodic limb movements.

22.2.5. Restless legs syndrome, periodic limb movements in sleep and the autonomic and cardiovascular symptoms

In a survey of 18980 members of the general population in five European countries, the prevalence of RLS was 5.5%. Heart disease was associated with both RLS and PLMS and hypertension was associated with RLS alone (Ohayon and Roth, 2002). In a Swedish survey of 4000 men, 5.8% had RLS and RLS sufferers more frequently reported hypertension (OR 1.5,

95% CI 0.9–2.4) and heart problems (OR 2.5, 95% CI 1.4–4.3) (Ulfberg et al., 2001). A single patient with congestive heart failure, insomnia and severe periodic limb movements in sleep had resolution of his symptoms after heart transplantation (Hanly and Zuberi, 1992). In a follow-up study, 52% of 23 men with severe congestive heart failure and only 11% of nine healthy control subjects had periodic limb movements in sleep in the moderately severe range of more than 25 per hour of sleep (Hanly and Zuberi-Khokhar, 1996). Eighteen percent of 91 subjects with hypertension had periodic limb movements in sleep, and the prevalence of periodic limb movements in sleep was directly proportional to the severity of the hypertension. Patients with grade III hypertension had a 36.4% prevalence of periodic limb movements in sleep as opposed to a 13% prevalence in patients with grade I and II hypertension (Espinar-Sierra et al., 1997). Tachycardia accompanies periodic limb movements in sleep, and spectral analysis of the accompanying EEG shows that there appears to be a hierarchy of arousals accompanying the periodic limb movements in sleep going from autonomic activation to bursts of delta activity to alpha activity to a full awakening. When periodic limb movements were accompanied by theta or alpha activity, the heart rate was even faster (Sforza et al., 1999, 2002; Winkelman 1999). The order of these events suggests that the arousal response begins at the level of the brainstem and progresses cortically (Sforza et al., 2002). In a single patient rises in blood pressure on the order of 23% have also been found to accompany periodic limb movements in sleep (Ali et al., 1991). This needs to be verified by further studies. Whether these temporary rises in heart rate and blood pressure have any ultimate consequences is unknown (Sforza et al., 1999; Winkelman 1999), but the fact that daytime hypertension is associated with an increased prevalence of periodic limb movements in sleep suggests an association (Espinar-Sierra et al., 1997). Finally, vasoconstriction, cold feet and decreased peripheral pulses may be associated with periodic limb movements in sleep (Ancoli-Israel et al., 1986; Ware et al., 1988; Watanabe et al., 1990).

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CHAPTER 23

Sleep and epilepsy

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23.1. Introduction

The complex interaction between sleep and epilepsy is important from both a neurophysiologic and a clinical perspective. Neurophysiologically, the techniques most important in both epilepsy and sleep disorders rely (at least in part) on recordings of normal and abnormal brain activity. Electroencephalography and polysomnography are complementary techniques, and some understanding of both is essential for optimal interpretation of either. A few centers now have the capacity to perform video-EEG polysomnography, where simultaneous recording of parameters is performed.

Clinically, quality sleep is important for optimal functioning in all people, but is particularly essential for patients with epilepsy. In these individuals, sleep disturbance can result not only in daytime drowsiness and poor performance, but also in deteriorating seizure control. In a few patients, recognition and treatment of a coexisting sleep disorder can make the difference between complete seizure control and refractory epilepsy. Sleep disorders, certain anticonvulsant drugs, and seizures themselves can all contribute to this problem. Patients with epilepsy can therefore find themselves in a cycle of worsening seizures, further sleep disruption and intractable epilepsy.

There are a number of ways sleep has an impact on the treatment of patients with epilepsy. Sleep has effects on interictal epileptiform discharges, with implications particularly for diagnostic studies. Various sleep disorders can coexist with epilepsy leading to errors in diagnosis and worsening of seizures. Some specific syndromes demonstrate

unique properties related to sleep. Seizures are now known to disrupt sleep, even when occurring during the day, with the potential for persistent drowsiness and, perhaps, further memory dysfunction. Finally, most patients with epilepsy are treated with anticonvulsant drugs, some of which can have adverse (or beneficial) effects on sleep.

Although sleep is clearly important in epilepsy patients, it is frequently overlooked as a potential cause of drowsiness, memory impairment and worsening seizures.

23.2. Clinical neurophysiological techniques used in the study of sleep and epilepsy

Three techniques are useful in the study of the interactions between sleep and epilepsy: electroencephalography (EEG), polysomnography (PSG) and (in a few specialized centers) a combination known as video-EEG/polysomnography. Each is discussed extensively elsewhere in this book. Here we will review only the aspects most relevant to the sleep/epilepsy interaction.

EEG is best suited to determining abnormal brain patterns occurring in epilepsy, both interictally and ictally. The chief distinction between this and polysomnography is the number of EEG channels. Although polysomnography does of course include EEG, the few channels in a typical setup are not generally sufficient to reliably detect highly focal discharges.

Conversely, EEG alone is limited in its ability to diagnose certain sleep disorders. It can be difficult to distinguish certain sleep/wake states based on EEG alone (most notably quiet wakefulness, light sleep and REM sleep). Lack of respiratory and leg monitors makes diagnosis of two common sleep disorders, obstructive sleep apnea and restless legs syndrome, difficult or impossible. Lack of chin EMG limits the ability to diagnose cataplexy.

With modern equipment and many available channels, as well as the ability to analyze data afterwards

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with altered time bases and filters, it is possible to acquire all the data necessary for both EEG and PSG simultaneously. In cases where both epilepsy and sleep disorders are present or likely, or when there is a diagnostic dilemma involving epilepsy versus sleep disorder, video-EEG polysomnography can be the most efficient means of evaluating the patient. The interpreting physician must, of course, have expertise with both techniques to give a meaningful interpretation.

23.3. Issues in sleep and epilepsy

23.3.1. Diagnostic issues

A number of normal and abnormal sleep phenomena can frequently or infrequently be confused with seizures. Similar to epileptic seizures, sleep disorders are rarely observed by the evaluating physician and diagnosis is often based on history. Also as with epileptic seizures, this history can be unreliable or even misleading. These phenomena almost always occur at night, so that the beginning of even dramatic episodes is unwitnessed, and patients frequently have little or no recall of the events.

The general classes of events to be discussed are normal sleep phenomena, insomnias and parasomnias.

The latter are divided into those most commonly associated with non-REM and REM sleep (Tables 23.1 and 23.2).

23.3.2. Normal sleep phenomena

Most aspects of normal sleep are easily distinguished from epilepsy. 'Sleep starts' occur in nearly all people at one time or another, and consist of a sudden extension of one or more limbs that occurs while falling asleep. This can be associated with a brief dream image, such as that of falling. Sleep starts can be exacerbated by sleep deprivation or by excessive use of stimulants, including caffeine. Only rarely would these be confused with seizures, perhaps when they are unusually violent or frequent.

23.3.3. Insomnia and excessive daytime sleepiness

Insomnia and daytime sleepiness are extremely common phenomena. Symptoms of sleepiness are not often confused with epilepsy; however, they are so pervasive that unusual presentations could occasionally be confused with seizures. Excessive sleepiness can occur with sleepiness due to a number of disorders, including psychophysiological insomnia, obstructive sleep

Table 23.1

Characteristics of specific NREM sleep disorders and seizures.

	Seizure	Sleep drunkenness	Sleep Terrors	Somnambulism	Somniloquy	Sleep Enuresis	PLMS
Incontinence	+	—	—	—	—	+	—
Tongue biting	+	—	—	—	—	—	—
Confusion	+	+	+	+	+	—	—
Tonic-clonic movements	+	—	—	—	—	—	—
Drooling	+	—	—	—	—	—	—
amnesia	+	+	—	+	+	—	—
Occur awake	+	—	—	—	—	—	—
EEG: background	Spikes	Normal	Normal	Normal	Normal	Normal	Normal
PSG: background	Spikes*	Normal	Normal	Normal	Normal	Normal	Normal
EEG/PSG during episode	Synchronous discharge	Excess delta	Excess delta	Excess delta	Normal	Normal	Normal

* Interictal spikes and spike-wave discharges are often difficult or impossible to see on routine PSG with limited EEG channels.

Table 23.2

Characteristics of specific REM sleep disorders and seizures.

	Seizure	Nightmares	Cataplexy	Sleep paralysis	Hypnic hallucinations	REM behavior disorder
Incontinence	+	—	—	—	—	—
Tongue biting	+	—	—	—	—	—
Confusion	+	—	—	—	—	—
Tonic-clonic movements	+	—	—	—	—	—
Drooling	+	—	—	—	—	—
Amnesia	+	—	—	—	—	—
Occur awake	+	—	+	+	+	—
EEG: background	Spikes	Normal	Normal	Normal	Normal	Normal
PSG: background	Spikes ¹	Normal	Normal or excess REM, decreased sleep latency ²	Normal or excess REM, decreased sleep latency ²	Normal or excess REM, decreased sleep latency ²	Lack of EMG suppression during REM
EEG/PSG during episode	Synchronous discharge	REM sleep	Decreased EMG, rapid eye movements, low voltage mixed frequencies	Decreased EMG	Decreased EMG, rapid eye movements, low voltage mixed frequencies	Rapid eye movements, low voltage mixed frequencies

¹ Interictal spikes and spike-wave discharges are often difficult or impossible to see on routine PSG with limited EEG channels.² In patients with narcolepsy.

apnea, restless legs syndrome or periodic limb movements of sleep. Rare patients report that they have lost a period of time, or suddenly find themselves in bed or on a sofa not knowing how they have gotten there. If the events are unwitnessed it may be impossible to distinguish an epileptic seizure from such a 'sleep attack', except through video-EEG monitoring (see below).

23.3.4. Disorders predominantly associated with non-REM sleep

Sleep terrors are much more common in children, and are also referred to as pavor nocturnus (or, in adults, as incubus attacks). They usually resolve by adolescence; in adults they can be a manifestation of severe emotional stress (Kales et al., 1980) or be triggered by medication (sedative-hypnotics, stimulants, neuroleptics), alcohol or sleep deprivation. Typically, the

sleeping patient will suddenly sit up and scream. He or she may be very confused, and a parent or onlooker who hears the cry and finds the patient disoriented may then give a history compatible with a nocturnal seizure. The patient is usually amnesic for the episode, adding to potential confusion with seizures.

Sleep terrors usually occur during the deeper, non-REM stages of sleep and therefore are more common in the early part of the night. EEG may therefore show polymorphic or rhythmic delta activity consistent with delta sleep or arousal. Episodes can be precipitated by agents that increase deeper sleep, and by sleep deprivation. Treatment is usually not required, but tricyclic antidepressants and benzodiazepines have been used (Fisher et al., 1973). Sleep terrors can usually be distinguished from seizures by their exclusive occurrence in sleep combined with the characteristic dream imagery, predominant fear, and rapid recovery. Abnor-

mal movements, prolonged confusion, drooling, and tongue biting are suspicious for seizures. If in doubt, 24 hour ambulatory EEG or video-EEG monitoring should confirm the diagnosis.

Sleep walking (somnambulism), somniloquy (sleep talking) and sleep enuresis (bedwetting) are all very common in childhood, and rare in adults. Somnambulism consists of leaving the bed and performing complex activities, such as walking, without memory for the event. It begins during slow-wave sleep, and is of various duration and complexity. The prevalence in children is between 1–17%, with the peak incidence at age 12. In adults the prevalence is lower but somnambulism remains relatively common (up to 2.5%; Bixler et al., 1979; Klackenberg, 1982). Somniloquy can occur in NREM or REM sleep. Unlike seizures, speech during somniloquy is random (although may be slurred and nonsensical); ictal speech tends to be stereotyped in a given individual. With somniloquy there should be no abnormal movements, drooling, tongue biting or incontinence. Sleep enuresis is more common in NREM sleep. The cause remains unknown, although genetic, behavioral, and psychological factors have been suggested (Mahowald and Schenck, 1996). As these episodes are typically unwitnessed, atypical characteristics suggestive of seizure, including nocturnal injury, tongue or lip biting, or morning muscle soreness, warrant neurological evaluation and probably video-EEG monitoring to rule out unrecognized seizures.

‘Sleep drunkenness’ consists of prolonged confusion when awakening, usually from the deeper non-REM stages of sleep. There can be complex behaviors without conscious awareness (Guilleminault et al., 1975). Patients (typically children) may arise from bed, stumble while walking, have slurred or incomprehensible speech, and have no memory of the event. The occurrence of sleep drunkenness is increased by factors that deepen sleep (such as sleep deprivation) and impair arousal (such as hypnotic medication) or disturb sleep (as in sleep apnea) (Broughton and Mullington, 1994). Potential confusion with seizures occurs because the awakening may be unwitnessed, and the subsequent, transient confusion consistent with a complex partial seizure or postictal state.

23.3.5. Disorders predominantly associated with REM sleep

Nightmares consist of frightening dreams, which often awaken the patient from sleep, and can be

accompanied by agitation. Unlike NREM phenomena like sleep terrors, there is usually no limb thrashing or ambulation. History usually identifies these as benign events; however, if specific dream imagery is not recalled, a history of sudden fear followed by confusion might be mistaken for nocturnal seizures.

Narcolepsy is a complex disorder in which various sleep phenomena associated with REM sleep invade normal wakefulness. It is defined as a clinical tetrad that includes excessive daytime sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis. Only 10–15% of patients, however, experience all symptoms (Overeem et al., 2001). All have excessive daytime somnolence, and associated cataplexy occurs in about 70%, hypnagogic hallucinations in 30%, and sleep paralysis in 25%. The individual symptoms can all be confused with epilepsy, including somnolence that can result in sleep attacks (Mihaescu and Malow, 2003).

Narcolepsy is a relatively unusual disorder. Incidence is about 0.05% in Caucasians but may be higher in other populations (Bassetti and Aldrich, 1996). There is a positive family history of hypersomnolence in up to 50% of cases, with cataplexy also common in families (Yoss and Daly, 1960). Onset typically occurs in adolescence or young adulthood; onset after 55 years of age is very uncommon (Broughton and Mullington, 1994; Overeem et al., 2001).

Cataplexy is generally more disturbing to the patient and can be mistaken for epilepsy. Episodes consist of sudden loss of muscle tone (most commonly in the face or knees) with preserved consciousness. This can result in falling and paralysis, but more often is limited to buckling of the knees or slurring of speech. Because of the slow onset, injury is very uncommon. Brief twitching of facial or limb muscles can occur and, when rhythmic, add to potential confusion with epilepsy. Cataplectic attacks classically occur in the setting of strong emotion, most commonly laughter (Guilleminault et al., 1974; Parkes et al., 1975) but also anger, fear, surprise, or excitement (Bassetti and Aldrich, 1996). The association with external emotion can aid in the distinction from epileptic seizures.

Sleep paralysis consists of the inability to move or speak with onset during the process of falling asleep (or, less commonly, upon awakening). It typically lasts less than 10 minutes although it can persist for up to half an hour. The episode may be quite frightening for the patient. It can sometimes resolve when someone touches the patient. Hypnagogic (or hypnopompic) hallucinations also occur while falling asleep (or

waking up). The content can be simple (a brief image of a face) or complex (an entire scene occurring in the room), and is usually visual although auditory, somatosensory, vestibular and olfactory hallucinations also can occur. The sensation is incorporated into the waking background, and the patient is fully aware during the episode.

Polysomnography in patients with narcolepsy shows decreased sleep latency (less than 10 minutes) and decreased REM latency (less than 20 minutes). MSLT can show a mean sleep latency of less than 5–8 minutes, with two or more sleep-onset REM periods considered highly suggestive of narcolepsy. Sleep-onset REM can also occur with severe REM sleep deprivation due to any cause (including sleep apnea). HLA subtypes are highly sensitive for narcolepsy in whites, but are a poor marker in African Americans and up to 35% of the general population carry the same subtypes (Overeem et al., 2001).

Cataplexy, hypnagogic hallucinations, and sleep paralysis can occur in the absence of narcolepsy, and in these cases are more likely to be mistaken for epilepsy. Episodes of cataplexy are reported in up to 29% of young adults (Hublin et al., 1994; Billiard et al., 1987). Sleep paralysis is quite common, occurring in up to 60% of normal subjects (Dahlitz and Parkes, 1993; Bassetti and Aldrich, 1996) although the prevalence of repetitive episodes is probably about 5% (Roth et al., 1968). Hypnagogic and hypnopompic hallucinations occur in up to 19% of normal subjects (Aldrich 1996); these are also unlikely to be repetitive when benign. Sleep deprivation increases the likelihood of all these phenomena.

REM behavior disorder was described relatively recently, in the 1980s (Schenck et al., 1985; Schenck et al., 1987). It is characterized by agitated, sometimes violent movements occurring during REM sleep. Kicking, punching, jumping, and running from the bed are commonly seen. Injury is common, and can occur to either the patient or the bed partner. Patients will typically report that a dream sequence occurs during the episode. Most patients are male, and the majority are over age 60 years (Olson et al., 2000; Husain et al., 2001). About half of patients have known neurological disorders, most commonly Parkinson's disease, dementia or multisystem atrophy (Schenck and Mahowald, 1996; Olson et al., 2000). There may also be an association with post-traumatic stress disorder (Husain et al., 2001). Physiologically, the disorder consists of absence of normal atonia and increased phasic and tonic EMG activity during REM

sleep; these can be documented on routine polysomnography with chin and axial EMG.

The pathophysiology of REM behavior disorder almost certainly involves dysfunction in the pontine tegmentum, an area known to be responsible for atonia during REM sleep (Jouvet and Delorme, 1965). Most patients do not have structural lesions of the pons, but the disorder is thought to arise from an imbalance of neuronal regulation in this area which is responsible for regulating REM and NREM sleep.

The history of bizarre, semipurposive behavior with confusion may be impossible to distinguish from seizures or postictal behavior. Unlike most partial seizures, REM behavior disorder will be restricted to sleep, and usually occur in the early morning when REM is most prevalent. The memory of a dream sequence, if present, is helpful in distinguishing the two. If in question, diagnosis is readily made with video-EEG monitoring, ideally with simultaneous examination of polysomnographic parameters. Treatment with benzodiazepines (typically clonazepam) is usually successful (Husain et al., 2001).

23.3.6. Effects of sleep on interictal epileptiform activity

It has long been realized that sleep deprivation and recording of sleep increases the yield of interictal epileptiform activity on EEG. This has further been refined through all-night recordings performed routinely during video-EEG monitoring, and with the introduction of automated spike detection programs. Increased yield of interictal epileptiform discharges (IEDs) during sleep was first reported by Gibbs and Gibbs (1947). More recently, Malow et al. (1999) compared interictal discharges in routine awake EEGs with overnight EEG recordings in 24 patients with refractory temporal lobe epilepsy. All showed IEDs in the overnight study (as opposed to 46% during daytime recordings) and there was high concordance with seizure onset site, confirming the value of sleep recordings when routine EEG is normal. Sleep-deprived EEGs have become standard practice in EEG laboratories; however, there is continued debate as to whether sleep deprivation increases interictal discharges independent of increased likelihood of recording sleep. In a retrospective report comparing routine sleep EEG to subsequent sleep-deprived EEG with sleep, a 52% activation rate for epileptiform activity was seen in the latter group (Fountain et al., 1998)

independent of sleep duration or depth. Therefore, sleep deprivation is useful independent of sleep.

Specific increases in interictal spikes and sharp waves during slow-wave sleep, with decreases during REM sleep, was convincingly demonstrated by Sammaritano et al. (1991). An increase in spike frequency is also seen with increasing delta power, a measure of increasing sleep depth (Malow et al., 1998). Furthermore, it has been shown that focal epileptiform spikes that occur during REM sleep are more accurate for seizure localization compared with other sleep states (Sammaritano and Saint-Hilaire, 1998; Malow and Aldrich, 2000).

23.3.7. *Sleep disorders in patients with epilepsy*

Sleepiness is common in the general population, and nearly universal among certain populations with epilepsy, but sleep disorders are frequently missed. Many practitioners attribute consistent tiredness in epilepsy to an unavoidable adverse effect of anti-seizure medication. A careful history and, when indicated, overnight polysomnography can reveal specific, treatable disorders which can greatly improve patient quality of life and, in some cases, seizure control.

Several studies have confirmed that sleepiness and sleep disorders are common in epilepsy. Malow et al. (1997b) used the Epworth Sleepiness Scale to demonstrate that patients with epilepsy are more drowsy than were control patients. Epilepsy was not a predictor of high score when a sleep apnea scale was included, suggesting that this treatable condition may be responsible for much of the problem. A similar investigation was performed prospectively in children by Stores et al. (1998) using a non-standardized sleep questionnaire and the Conners Revised Parent Rating Scale. Children with epilepsy showed higher scores for poor-quality sleep, anxiety about sleep and disordered breathing. Cortesi et al. (1999) showed that children with idiopathic epilepsy showed more sleep problems than did controls, and these were associated with seizure frequency, age, paroxysmal activity on EEG, duration of illness and behavioral problems.

Studies of epilepsy patients with sleep disorders show a variety of mostly treatable conditions. In a retrospective study of 63 epilepsy patients who underwent polysomnography (Malow et al., 1997a), the vast majority (78%) were referred for obstructive sleep apnea, with many (46%) for excessive sleepiness, and 19% for characterization of nocturnal spells. Studies diagnosed obstructive sleep apnea in 71% of referrals,

96% of whom were referred for that reason. Other diagnoses found were narcolepsy, insufficient sleep syndrome, and nocturnal seizures. Five out of nine patients with active seizures treated with CPAP showed improved seizure control, although antiepileptic medication was optimized in several of these patients. Six patients had frequent periodic limb movements, but these were not clinically significant. In a similar investigation, Beran et al. (1999) reported on 50 patients with epilepsy referred to a sleep laboratory for all night polysomnography. Fifty-four percent had sleep apnea, and 32% had periodic limb movements of sleep (six requiring medication). Of the 36 patients who were prescribed therapy based on the evaluation, six had significant improvement in seizures.

All of these studies stress the prevalence of sleep disorders (particularly obstructive sleep apnea) in the epilepsy population, and the underutilization of polysomnography in these patients.

23.3.8. *Specific syndromes of sleep and epilepsy*

Sleep has an influence on a number of epilepsy syndromes, but in a few instances there is a particularly close relationship. The most important of these are nocturnal frontal lobe epilepsy, juvenile myoclonic epilepsy, benign epilepsy with centrotemporal spikes, childhood epilepsy with occipital paroxysms and electrical status epilepticus during slow-wave sleep.

Frontal lobe epilepsies may represent a diagnostic dilemma for a number of reasons. Because seizures occur mostly or exclusively during sleep, they may be unwitnessed. When a description is available semiology is often bizarre and can consist of posturing, ambulation, complex behaviors, or violent outbursts (Provini et al., 1999; Oldani et al., 1998). Prominent choking and abnormal motor activity can lead to a misdiagnosis of sleep apnea (Oldani et al., 1998) or other sleep disturbance (Tachibana et al., 1996). Twenty-eight percent occur in stage 3–4 sleep and only 3% during REM. Only about a third of patients showed clear epileptiform abnormalities on routine EEG (Nakken et al., 1999; Provini et al., 1999), which can cause further diagnostic difficulty. Even with ictal recordings, many or most patients will not show clear epileptic activity and the record is often obscured by muscle artifact due to prominent motor activity (Figure 23.1; Provini et al., 1999). In some patients, pedigree analysis was consistent with autosomal dominant inheritance (Oldani et al., 1998). All of these

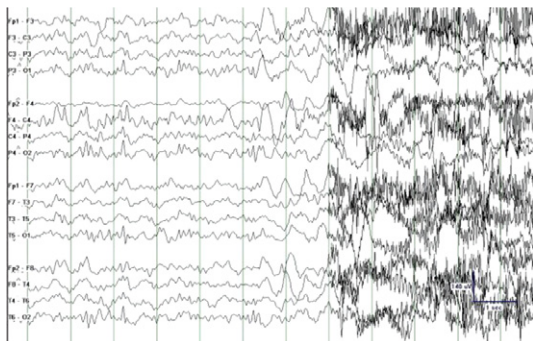


Fig. 23.1. Left frontal onset seizure in a 20-year-old man with intractable epilepsy. Seizures began exclusively during sleep, in this case slow wave.



Fig. 23.2. Frequent centrotemporal spike-wave discharges in a 9-year-old boy with benign rolandic epilepsy.

studies suggested that nocturnal frontal lobe epilepsies are frequently misdiagnosed but easily controlled with medication.

Juvenile myoclonic epilepsy (JME) commonly presents with myoclonic jerks during adolescence. Generalized tonic-clonic seizures can occur independently or precede myoclonus, and both show a strong relationship to sleep deprivation and commonly occur after awakening (Wolf and Schmitt, 2002). JME is probably related to the syndrome of awakening grand mal, which is clinically similar except that myoclonus is absent. This is one of the few epilepsy syndromes where patients may try to control seizures through careful sleep hygiene, although this is rarely completely successful (Wolf and Okujava, 1999). Fortunately, control with drug treatment is typically complete (Wolf and Schmitt, 2002).

Benign epilepsy with centrotemporal spikes (BECS) has a characteristic clinical picture. Seizures occur predominantly or exclusively during sleep, and consist of hemifacial twitching lasting less than 2 minutes. Characteristic centrotemporal spikes always increase with sleep, typically dramatically (Lerman and Kivity 1975; Dalla Bernardina and Beghini, 1976; Figure 23.2). The diagnosis is often possible with clinical description in classic cases, although an EEG is usually performed for confirmation. The universally benign prognosis makes this a particularly important diagnosis.

Llandau–Kleffner syndrome is a condition of acquired aphasia, frequently (but not always) with epileptic seizures and a markedly epileptiform EEG, particularly during sleep. O'Regan et al. (1998) studied 25 children with an acquired disorder of communication and seizures, but not strictly meeting cri-

teria for the Landau–Kleffner syndrome (LKS). EEGs were uniformly epileptiform, usually (16/25) worsening with sleep. MRI was typically normal, but SPECT was abnormal (22/25). Most were considered to have a receptive aphasia. They hypothesize that the language deficits result from the persistent epileptic discharges, as evidenced by hypometabolism on SPECT. A study of 32 patients with continuous spike-wave activity during slow-wave sleep (CSWS; Veggiotti et al., 1999) showed a variety of clinical syndromes, including LKS, acquired opercular syndromes, typical CSWS syndrome and other symptomatic epilepsies (Figure 23.3).

23.3.9. Effect of sleep and sleep deprivation on the occurrence of seizures

The amount of baseline rhythmicity occurring in the brain differs considerably between the states of sleep and wakefulness. It is therefore not surprising that various seizure types begin preferentially in specific sleep states. Crespel et al. (1998) specifically examined the occurrence of frontal and temporal lobe seizures in 15 patients with each, using 5 days of continuous video-EEG monitoring. Sixty-one percent of frontal seizures began during sleep, compared with only 11% of temporal lobe seizures. In a larger study, Bazil and Walczak (1997) retrospectively studied over a thousand seizures in 188 consecutive patients to look at patterns of onset in relationship to sleep. A similar, prospective study was performed later restricted to patients with partial seizures (Herman et al., 2001). Overall, 20% of seizures occurred during sleep. Both studies showed that most sleep seizures began during

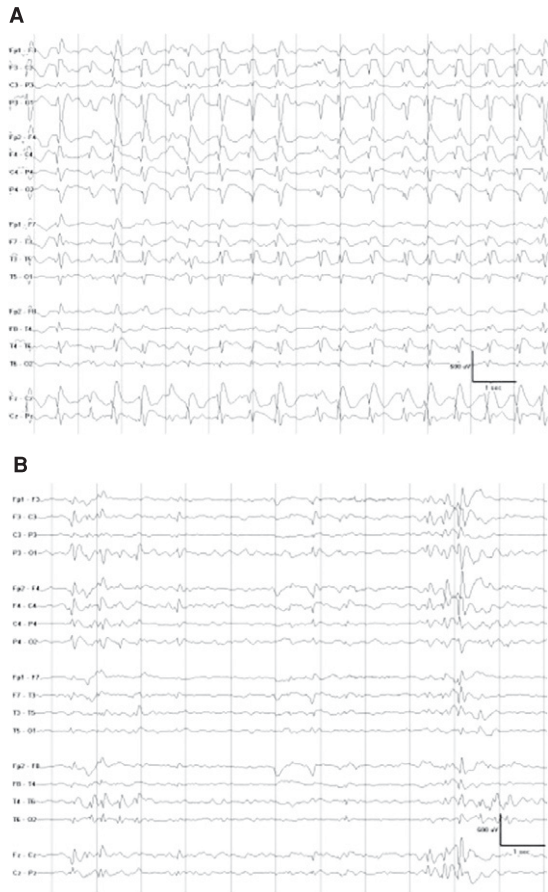


Fig. 23.3. Four-year-old girl with epileptic status epilepticus of sleep (ESES). Top: Asleep. Bottom: awake.

stage 2, with few during slow-wave sleep and few or none during REM. Frontal lobe seizures began during sleep more often than temporal lobe seizures, a finding which has been appreciated clinically. Both studies also showed that temporal lobe seizures were more likely to secondarily generalize when beginning during sleep, but frontal lobe seizures were not. This intriguing finding suggests differences in the pathways of spread in partial epilepsy, which could have implications for treatment if better understood. Seizures that occur only during sleep may represent a distinct class with a particularly good prognosis, except in patients with a history of head trauma or central nervous system lesions (Yaqub et al., 1997; Park et al., 1998).

Sleep deprivation has long been thought to increase the risk of seizures, which is clinically readily apparent in a few syndromes such as juvenile myoclonic epilepsy. However, a controlled study of patients with

refractory partial epilepsy failed to show an effect (Malow et al., 2002). Seventeen patients were sleep deprived on alternate nights, and 13 received 8 hours of sleep per night. There was no difference in the number of seizures or time to first seizure. This brings into question the common practice of sleep deprivation in epilepsy monitoring units.

Circadian rhythms may influence seizures independently of sleep. Both rats with a model of limbic epilepsy and humans with medial temporal seizures have increased seizures during daylight, an effect not seen with human extratemporal seizures (Quigg et al., 1998). This is likely independent of sleep, of course, because rats are primarily nocturnal and humans diurnal. Humans with intractable temporal lobe epilepsy show abnormal secretion of melatonin, a sleep-related hormone with a characteristic circadian pattern (Bazil et al., 2000a). Exogenous melatonin has been shown to help control seizures in a few small studies (Fautek et al., 1999; Peled et al., 2001), raising the possibility that it may be useful in the treatment of some patients.

23.3.10. Effects of seizures on sleep structure

Intuitively, nocturnal seizures disrupt sleep structure. Most will cause at least a brief awakening, and normal sleep is unlikely during a postictal state. Many studies have shown improvement in sleep with treatment of nocturnal seizures (Besset, 1982; Touchon et al., 1987; Tachibana et al., 1996). Importantly, patients with partial seizures have been shown to have relatively normal sleep on seizure-free nights except for slightly decreased sleep efficiency with temporal lobe epilepsy (Crespel et al., 1998).

The effects of individual temporal lobe seizures on sleep structure were examined by Bazil et al. (2000b). Patients in an epilepsy monitoring unit were recorded with polysomnography under baseline conditions (seizure free), and each patient was also studied following complex partial or secondarily generalized seizures. With daytime seizures, there was a significant decrease in REM the following night (18% vs 12% for baseline) without significant changes in other sleep stages or in sleep efficiency. When seizures occurred at night, this decrease in REM was more pronounced (16% vs 7%) and there were increases in stage 1 and decreases in sleep efficiency. These effects were even more pronounced when seizures occurred early in the night. Therefore, seizures can have a profound effect on sleep lasting much longer than the

apparent postictal period. This could account for decreased functioning on the day following seizures.

23.3.11. Effects of anticonvulsant medications

Early studies of anticonvulsant medications showed an increase in sleep stability with all agents. In retrospect, much of this effect was likely due to a reduction in seizure activity, rather than an independent effect of the drug. More recently, the effects of anticonvulsant drugs has been studied independently of seizures, showing different effects (both detrimental and beneficial) of various anticonvulsants.

Benzodiazepines and barbiturates are used less commonly for chronic treatment of seizure disorders, but have the most convincing evidence for detrimental effects on sleep. While both classes of medication reduce sleep latency, they also decrease the amount of REM sleep (Wolf et al., 1984; Wooten and Buysse, 1999). The effects of other anticonvulsant drugs are somewhat variable between studies, but a few conclusions can be made. Phenytoin may increase light sleep and decrease sleep efficiency; however, effects on REM sleep are variable (Choroverty and Quinto, 1999; Sammaritano and Sherwin, 2002). Findings for carbamazepine are more variable, but there also seems to be a reduction in REM sleep (Drake et al., 1990) particularly with acute treatment (Placidi et al., 2000).

Studies of newer agents suggest fewer detrimental effects on sleep. Lamotrigine has been shown to have no effect on sleep (Placidi et al., 2000) or slightly decrease slow-wave sleep (Foldvary et al., 2001). Gabapentin increases slow-wave sleep (Rao et al., 1988; Placidi et al., 2000; Legros and Bazil, 2003) as does tiagabine (Mathias et al., 2001). Levetiracetam has no effect on number of awakenings, sleep efficiency, or amount of slow-wave or REM sleep (Bell et al., 2002). The effects of several of the newest drugs (zonisamide, oxcarbazepine and topiramate) on sleep and sleep disorders are not known. Valproate, benzodiazepines and levetiracetam decrease the frequency of interictal epileptiform discharges (Van Colt and Brenner, 2003; Cavitt and Privitera, 2004).

23.4. Conclusions

The interactions between sleep and epilepsy are complex, and affect clinical treatment strategy as well as interpretation of neurophysiologic studies. Familiarity with both techniques is critical for the interpretation of either polysomnography or electroencephalography.

Polysomnography and electroencephalography are distinct but overlapping techniques, each of which has usefulness in the evaluation of patients with suspected epilepsy or sleep disorders. Both may be needed for the complete evaluation of many patients. Increasingly, it is practical and efficient to consider evaluation with both techniques simultaneously.

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CHAPTER 24

Sleep-related erections: historical background, technical considerations and clinical indications

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24.1. Introduction

Penile erections are a naturally occurring phenomenon during rapid eye movement (REM) sleep in all males from infancy to the elderly (Karacan et al., 1976). Similar clitoral erections and vaginal engorgement also occurs in females during REM sleep (Fisher et al., 1983). This strong temporal association between REM sleep and erectile activity allows for clinical evaluation of erectile function in males experiencing erectile dysfunction.

Difficulty initiating or maintaining erections may be secondary to numerous known organic etiologies, including vascular pathology, pelvic injury, or from complications related to diabetes mellitus to name a few. However, erectile dysfunction may also be caused either entirely or in part by psychological influences, including depression, lack of desire or performance anxiety. Most cases of organic pathology include an additional psychological component. The etiology of erectile dysfunction thus often remains elusive to the clinician, particularly when known organic causes appear absent. Moreover, even when potential organic etiology is present, such as pelvic or spinal cord injury, it may be difficult to determine the true potential of erectile function when psychological factors may complicate the clinical picture.

A major advantage of sleep-related erection (SRE) testing is that the erection occurs during a stimulus, i.e., REM sleep, which is minimally influenced by psychological factors. There are 4–5 cyclically occur-

ring REM periods during a typical night's sleep, lasting 15–25 minutes each in duration. REM sleep thus provides approximately 2 hours of total erection time during any given night's sleep. If properly performed, an objective monitoring of these REM-related erections can provide tremendous clinical information regarding an individual's underlying erectile capability.

The advent of a new class of medications, known as the phosphodiesterase inhibitors, have revolutionized the treatment of erectile dysfunction and have decreased the reliance on invasive surgical implants. Some have even questioned the necessity of SRE testing given the expense of formal polysomnography (Levine and Lenting, 1995), particularly when an individual may regain erectile function simply by using medication. Sildenafil (Viagra) and related medications have become the new screening tools to determine subjective erectile capability. However, these medications rely on sexual desire or excitement for the pro-erectile effects to become apparent. As a result, an absence of erection in patients using such medications does not help elucidate the etiology of the erectile dysfunction since both organic or psychological factors may result in treatment failure. There still remains a clear need for SRE testing. The historical background and techniques of SRE testing, as well as the clinical indications for formal SRE evaluation, will be discussed.

24.2. Historical perspective

Sleep-related erection cycles were first described by Ohlmeyer and colleagues in 1944 (Ohlmeyer et al., 1944), 10 years prior to the discovery of REM sleep. These authors found that all tested men typically demonstrated 4–5 erection cycles in sleep occurring approximately every 85 minutes and lasting an

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average of 15–25 minutes each in duration, identical to the cyclicity and duration of REM sleep discovered a decade later. With the discovery of REM sleep by Aserinsky and Kletman (1953), several authors hypothesized that these two events were likely temporally related. Fisher and Karacan independently demonstrated this strong temporal association in the mid 1960s (Fisher et al., 1965; Karacan et al., 1966). The universal nature of such erections during REM sleep was later demonstrated in all age groups of males from infancy to the elderly (Karacan et al., 1976). The presence of REM-related clitoral erections and vaginal engorgement was also subsequently discovered (Karacan et al., 1970; Fisher et al., 1983).

SRE testing is used to differentiate psychogenic from organic erectile dysfunction (Fisher et al., 1975, 1979; Karacan et al., 1977). These erections in sleep have also been referred to as nocturnal penile tumescence (NPT). Normal occurring erection cycles during REM sleep in an individual complaining of difficulty initiating or maintaining waking erections provides strong evidence of a psychogenic etiology since the physiology presumably remains intact. However, an individual failing to demonstrate normal erection cycles in the presence of normal REM sleep suggests that an organic pathology is the cause of the erectile dysfunction.

Although SRE evaluation without polysomnography continues to be commonly used in urology to evaluate erectile dysfunction (Morales et al., 1990; Levine and Lenting, 1995; Moore et al., 1997), there are four primary reasons why SRE testing currently is not commonly undertaken in the sleep laboratory for the evaluation of erectile dysfunction. First, formal SRE testing, which includes polysomnography, was criticized as not being cost effective when used as a mass screening tool to differentiate psychogenic vs organic erectile dysfunction (Levine and Lenting, 1995). Generally, two nights of polysomnography are required for formal SRE evaluation at a considerable cost.

Second, the introduction of non-surgical, or medical, therapies for the treatment of erectile failure has provided new treatment approaches and measures to avoid costly surgical implants and formal SRE testing. Following the discovery of REM-related erections in the mid 1960s, treatment options for erectile dysfunction were initially limited to surgical prosthetic implants or psychotherapy. Since a prosthetic implant destroys the erectile tissue and would irreversibly cause organic erectile failure if placed in a

patient with psychogenic impotence, the ability to differentiate organic from psychogenic erectile dysfunction using SRE testing prior to surgery became an essential component of the pre-surgical work-up. The introduction of intracavernous injections using vasoactive substances to treat impotence decreased reliance on surgical implants during the 1980s. More recently, phosphodiesterase inhibitors, such as sildenafil (Viagra), have simplified even further the treatment of erectile dysfunction by eliminating the need for needle injections directly into the penis. Sildenafil and related substances may be administered orally shortly before the anticipated sexual encounter. Simply stated, phosphodiesterase inhibitors have now become a first-line therapy for erectile dysfunction regardless of its etiology, and they have even become a screening tool to evaluate subjective erectile capability.

A third reason why formal SRE evaluation has become less utilized is because of the belief that there are patients who may have normal erectile functioning during wakefulness yet demonstrate abnormal SRE activity, thus providing a false positive result (Wasserman et al., 1980; Morales et al., 1990). Although decreases in total tumescence time in sleep have been described in patients with depression or anxiety, these patients still exhibit robust erections in sleep with total erection time typically still exceeding total REM time (Thase et al., 1987). Hypogonadal states also have been shown to adversely affect SREs (Cunningham and Hirshkowitz, 1995; Hirshkowitz et al., 1997) yet such men continue to demonstrate normal erections when watching erotic films (Carani et al., 1992). These data have led some to suggest that SREs are 'androgen dependent', whereas visually induced erections to be 'androgen independent' (Carani et al., 1992). Although REM-related erections may be adversely affected in hypogonadal men as described, SREs should more appropriately be termed 'androgen sensitive' since such erections generally persist and often still remain in the normal range (Cunningham et al., 1990). It is considered extremely unusual to have normal waking erectile function yet not exhibit SREs in the presence of adequate and uninterrupted REM sleep. REM-related erections are a robust physiological phenomenon in humans and false positive SRE results are considered rare, particularly after eliminating technical recording deficiencies or conditions that affect the stability of REM sleep. Indeed, prior reports describing abnormal or fluctuating SREs in depressed patients with normal waking

erections have not adequately evaluated the contributing instability or fragmentation of REM sleep (a common phenomenon in depression) as a potential cause for the abnormal SRE results in such patients.

Finally, the psychogenic/organic dichotomy in the classification of erectile dysfunction has been criticized as an oversimplification since even psychogenic impotence may ultimately be reduced to an abnormal functioning of the neuronal network responsible for generating penile erections. A more recent conceptual framework complements recent discoveries in neuroscience demonstrating that higher central mechanisms of penile erections are likely context specific (Sachs, 1995).

24.3. Anatomy and physiology of penile erections

The penis is composed of two separate erectile tissue systems, the paired corpora cavernosa of the penis (CCP) and the single corpus spongiosum of the penis (CSP) that surrounds the urethra. The paired CCP separate proximally at the level of the pubic symphysis and lie along the lateral aspect of the ischiopubic rami. The CSP lies in the midline and is composed of three distinct anatomical regions, the bulb proximally, the body and the glans which are all contiguous with each other. The proximal portions of the CCP and CSP are surrounded by skeletal muscles important for the rigidification process of the erection. The ischiocavernosus (IC) muscles surround and insert on the crura of the CCP, whereas the bulbospongiosus (BS) muscles surround and insert onto the bulb of the CSP.

The erectile tissues are composed of a trabecular framework of smooth muscle cell bundles that form tiny islets known as the cavernous sinuses. The smooth muscle cells are tonically contracted in the flaccid state and minimize blood flow into the erectile tissues. Maintenance of the flaccid state is believed to be primarily a sympathetic phenomenon. With a reduction in sympathetic output and an increase in parasympathetic tone, the smooth muscle cells relax and allow blood flow into the erectile tissues that produces engorgement of the penis (Giuliano et al., 1995). During the engorgement process, the IC and BS muscle at the base of the penis contract at regular intervals, forcing blood from the proximal to the distal portions of the erectile tissues. With simultaneous recording of IC/BS EMG activity and penile circumference using penile strain gauges, the muscle contractions are associated with transient increases in penile circumference known as penile pulsations and

are most prominent during the tumescent phase of the erection.

Once the erectile tissues are fully engorged, the IC and BS muscles demonstrate brief contractions when pressure is applied to the glans penis (Lavoisier et al., 1989). This reflex is known as the bulbocavernosus reflex and plays a role in the rigidification process of the erection during vaginal penetration (Lavoisier et al., 1988a, 1988b). Phasic contractions of the IC and BS muscles in response to glans stimulation create suprasystolic pressure peaks within the cavernous sinuses several times in excess of the systolic arterial blood pressure. When the pressure within the erectile tissues exceeds that of the systemic arterial system, blood flow into the erectile tissues momentarily ceases, transiently creating a closed vascular system within the penis (Purohit and Beckett, 1976; Lavoisier et al., 1986).

24.4. Sleep-related erection testing

24.4.1. Recording devices

Numerous recording devices have been utilized over the years to monitor sleep-related erections. Ohlmeyer and colleagues (1944) utilized a non-expandable outer metal ring that contained an expandable inner ring with a metal contact. The expandable inner ring surrounded the penile shaft. During an erection, the increase in penile circumference caused the expandable inner ring to make contact with the non-expandable outer ring. When the metallic surfaces of the inner and outer rings came in contact, an electrical circuit was completed and the occurrence of the erection was simply recorded as an on or off phenomenon. This type of recording technique did not allow for the assessment of the quality of the erection such as circumference increase or degree of rigidity.

Fisher and colleagues (1965) used a water-filled, doughnut-shaped pressure cuff placed around the shaft of the penis and connected to a manometer. Water within the cuff was displaced during the circumference increase of the erection and an increase in the water level of the monometer could be observed during the erection while the patient was sleeping.

Both Fisher and Karacan independently developed the now commonly used strain gauge technique (Fisher et al., 1965; Karacan et al., 1966). The strain gauge is a Silastic tubing filled with mercury. A wire is placed into each end of the tubing and the ends are tied together, forming a loop that is placed around the

shaft of the penis. A small electrical current is continuously passed through the mercury loop. The circumference increase during an erection causes the Silastic tubing to stretch, thus thinning the diameter of the mercury column in the loop and thereby causing the electrical resistance through the loop to increase. The advantage of this technique is that the strain gauge allows for a linear calibration so that the exact increase in penile circumference can be recorded. This technique is combined with full polysomnography to monitor sleep-wake states, most importantly REM sleep. Moreover, the patient is typically awakened several times to visualize and measure the axial rigidity of the penis. Axial rigidity is measured with a buckling force device (see below).

The RigiScan device is widely used by urologists as a diagnostic tool to evaluate sleep-related erections (Levine and Lenting, 1995). This recording system is done at the patient's home and without any recording of sleep-wake states (Kaneko and Bradley, 1986). The loop device placed around the penile shaft contains a moveable wire. At regular intervals a 10-ounce (284 g) squeezing force is applied around the penile shaft to measure radial rigidity of the penis. The radial (circumferential) rigidity is measured in arbitrary units so that a 100% radial rigidity represents no measurable radial displacement from the 10-ounce force placed around the penile shaft. Radial rigidity decreases by 2.3% for every 0.5 mm loop shortening that is detected. The RigiScan device has two major disadvantages. First, radial rigidity is not a good predictor of axial rigidity as determined with the buckling force device (Allen et al., 1993; Udelson et al., 1999). Second, this recording technique does not evaluate the quantity or quality of the appropriate pro-erectile stimulus, i.e., REM sleep, during the night study.

Many urologists also still use the Snap Gauge device (Ellis et al., 1988; Chen et al., 1999), a slightly more sophisticated version of the postage stamp technique (Marshall et al., 1982; Marshall et al., 1983). This is a simple band placed around the penile shaft that is held together by Velcro. The Snap Gauge typically has three colored bands that break at different levels of circumferential rigidity, ranging from approximately 300–600 grams force. If the bands are broken in the morning upon awakening, the patient is considered to have normal nocturnal erectile functioning. There are several major problems with the Snap Gauge device. First, the appropriate pro-erectile stimulus, i.e. REM sleep, is not monitored. Therefore, the absence of broken bands does not imply the

absence of normal REM-related erections, nor the presence of normal REM sleep. Second, the amount of radial expansion during normal tumescence is highly variable among men, leading to many false positive results, i.e., normal tumescence and rigidity without breaking of the bands. Finally, the breaking of the bands does not ensure that the erection has a rigidity adequate for vaginal penetration since some men may have a marked increase in penile circumference yet still exhibit minimal axial penile rigidity (Wein et al., 1981).

24.4.2. Calibration and recording technique

Calibration of the strain gauges is typically performed before placement on the patient and again the next morning upon awakening after removal of the gauges. Calibration ensures that every millimeter of circumference increase corresponds to one millimeter of pen deflection on a paper polygraph or on a digital acquisition system. Recalibration in the morning ensures that this linear relationship between circumference change and acquired signal deflection has been maintained throughout the entire night.

Strain gauges typically come in 0.5 cm increments in size. A gauge at resting baseline is usually several millimeters smaller than its designated gauge size so that a gauge will fit snugly over a cylinder of the corresponding resting circumference. For example, an 8.0 cm gauge is usually approximately 7.8 cm in circumference. Calibration is performed by placing the strain gauge on a cylinder of identical baseline circumference, i.e., an 8.0 cm gauge on an 8.0 cm circumferential cylinder (see Figure 24.1). The gauge is then placed on a cylinder of 1.0 cm greater circumference and the signal sensitivity is adjusted to correspond to a calibrated signal deflection on the recording system.

Two strain gauges are required for each patient, one placed at the base of the penis and the other at the coronal sulcus just proximal to the glans (also called the tip gauge). Two gauges are typically utilized for two primary reasons. First, the use of two gauges sometimes reveals a discrepancy between base and tip engorgement, suggesting a pathologic vascular engorgement of the penis. A second gauge also provides a backup in the event of a gauge failure, allowing the patient to sleep uninterrupted until a spontaneous awakening occurs and gauge replacement may be performed. However, the placement of two gauges may not be possible in a severely obese male.

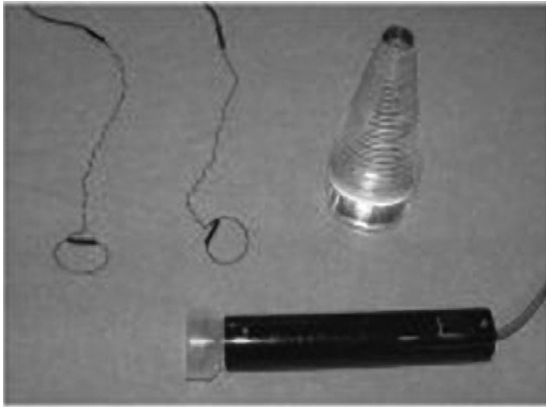


Fig. 24.1. A photograph demonstrating the typical equipment utilized for monitoring SREs in a sleep laboratory. Shown are two silastic strain gauges, the calibration cylinder, and the buckling force device. The calibration cylinder is graduated at 0.5 cm increments.

Although an SRE evaluation historically has required two nights of recording in the sleep laboratory, one study night may suffice if the individual has an entirely normal SRE pattern. The rationale for two nights of recording is that REM sleep may be decreased during the first night, thus affecting overall erection time. This so-called 'first night effect' is only problematic, however, if the individual has markedly decreased REM sleep or poorly defined erections during the first night. Indeed, we have found that an adequate sample of sleep and erection data can actually be obtained from the first night in over 90% of all cases (Schmidt, 1983).

24.4.3. Buckling force and visual inspection

Changes in penile circumference from the flaccid state to penile erection are highly variable among individuals (Wasserman et al., 1980; Wein et al., 1981; Pressman et al., 1989), making reliance on circumference alone inadequate for evaluation of erectile function. Some individuals may have a 3 cm or more increase in circumference yet exhibit minimal rigidity, whereas others may have no more than 1 cm of circumference increase and exhibit maximal penile rigidity. As a result of this inter-individual variability, SRE monitoring requires an evaluation of penile rigidity.

The buckling force device (see Figure 24.1) was developed to measure axial penile rigidity so that the likelihood of successful vaginal penetration can be determined (Hahn and Leder, 1980). A normal male is

generally able to achieve an erection with a rigidity that does not buckle below 1000 grams of force applied axially to the glans (Karacan et al., 1985). A penile shaft that buckles between 500–750 grams of force is considered potentially functional for vaginal penetration. However, if the penile shaft buckles with less than 500 grams force applied to the glans, the rigidity of the penis is rarely adequate to achieve vaginal penetration.

During the first night of recording, the patient is generally left undisturbed so that a determination of maximal circumference increase (MCI) and overall REM-related erection pattern may occur. The second night of recording is generally used to confirm the MCI and to evaluate penile rigidity. However, a buckling force measurement may be performed during the second half of the first night if either the MCI appears well defined during prior REM periods observed in the first half of the night or the individual has a spontaneous awakening during REM sleep and is coincidentally at his estimated MCI.

Accuracy of the buckling force measurement depends on the technician's ability to perform the test, and several factors are important to maximize testing accuracy. First, the patient needs to be well informed regarding the testing procedure on multiple occasions, such as during the initial office visit, during hook-up, and again prior to bedtime. Second, the test should only be performed when the technician is confident that the patient has achieved his personal MCI as determined from prior REM periods or from a review of the first night. Finally, the technique must be standardized so that the measurement can be performed quickly to minimize detumescence prior to buckling force measurement. The technician should enter the room, turn on low-level lighting, pull down the covers (we have patients sleep without pajama bottoms), stabilize the base of the penis between the thumb and index finger, and apply the buckling device against the head of the glans along the longitudinal axis of the penis. The force is gradually, but rapidly, increased until the shaft buckles or until the device reaches 1000 grams of force. Both patient and technician then estimate the quality of the erection between 0–100%. The entire procedure from lights-on to patient estimate of the erection should be less than 30 seconds, generally sufficient time to minimize detumescence.

In addition to the buckling force measurement, visual inspection of the penis by the technician is a very useful component of the procedure. Anatomical abnormalities such as a marked curvature or bend to

the penis may be evident during the erection, as in Peyronie's disease, even though the penis appears anatomically unremarkable in the flaccid state. In addition, it is important to identify any discrepancies between the technician's and the patient's estimate of erection quality. There is clearly a subgroup of patients who have normal SREs, normal buckling force measurements, and a technician estimate of at least a 90% maximum erection, yet the patient subjectively finds the erection to be inadequate with his subjective rating of less than 50%. Such patients with this perceptual discrepancy comprise a particular subgroup of psychogenic impotence. Finally, most patients have mixed organic and psychogenic erectile dysfunction. A patient with mild to moderate organic erectile failure may be surprised by the quality of the nocturnal erection. Knowledge of his underlying erectile capability can be helpful in building confidence during subsequent sexual encounters, thus providing another clinical tool to the physician in managing the psychogenic component of the patient's erectile dysfunction.

24.4.4. Data interpretation

Scoring and interpretation of the recording require an evaluation of both penile erection data and the pro-erectile stimulus, REM sleep. The strain gauges and buckling force measurements provide multiple parameters for SRE evaluation, including frequency, magnitude and duration of the events. The PSG data provide valuable information regarding the sleep architecture, particularly the frequency, duration and continuity of REM sleep. Moreover, the relationship between REM sleep and the timing of the SRE provides information regarding the integrity of erectile mechanisms from brain to the end organ level. For example, patients with spinal cord injury may have spontaneous reflexive erections during sleep or wakefulness. However, the timing of REM sleep and the erectile events are completely independent of each other following spinal cord transection above the midthoracic level (Schmidt et al., 1999). That is, penile erections become random events during sleep, thus confirming a breach in the integrity along the neuraxis that prevents the pro-erectile REM stimulus in the brain from driving the spinal erection generator in a time-locked manner.

Analysis of the strain gauge data begins by first establishing the maximal circumference increase (MCI) for the night and the baseline circumference

prior to each erection episode, which may change somewhat following body movement secondary to minor stretching of the strain gauge silastic tubing. The tumescence up (T_{up}) demarcates the beginning of tumescence and begins when the penile circumference increases more than 2 mm above the preceding flaccid baseline. Penile pulsations, transient increases in penile circumference associated with perineal muscle activity, typically occur during the T_{up} phase of the erection, and their absence is abnormal. The tumescence maximum (T_{max}) refers to the portion of the erectile event where the penile circumference reaches 75% of the MCI for the night. If the MCI of a particular erectile episode does not reach 75% of the entire night's MCI, T_{max} may also be used to describe the point during which a MCI occurred for that episode. Tumescence down (T_{down}) begins when the circumference first falls below 75% of the MCI and ends at tumescence zero (T_{zero}) when the circumference falls to within 2 mm or less from the flaccid baseline. Figure 24.2 demonstrates a schematic representation of an entire night's penile circumference monitoring illustrating these definitions. Finally, the total tumescence time (TTT) is defined as the number of minutes of the recording during which the penile circumference exceeds 2 mm of the baseline flaccid circumference. The TTT is generally 125 ± 50 minutes for a normal male (Karacan et al., 1976; Ware and Hirshkowitz, 2000).

As noted above, the relationship between tumescence episodes and REM sleep is an essential component when interpreting the SRE data. The number of tumescent episodes (TE) during the entire sleep period should equal the total number of REM periods. In healthy males, the erection typically begins prior to the

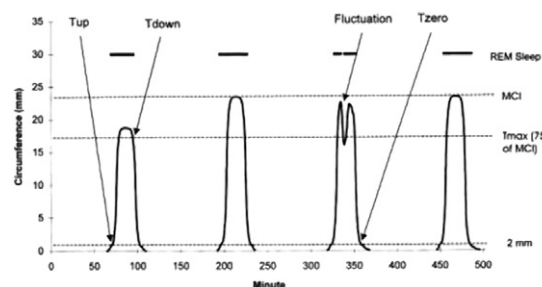


Fig. 24.2. A schematic diagram of the penile circumference changes during an entire night's polysomnogram showing four erection cycles associated with four REM periods (black bars). See text for definitions of the terminology. Reprinted with permission from Ware and Hirshkowitz, 2000.

onset of the REM period and usually ends shortly after the termination of REM sleep. As a result, the TTT-to-REM sleep time ratio (TTT/REM) should be greater than 1 (Karacan et al., 1976). This ratio also allows for a comparison between records with varying amounts of REM sleep. The $T_{\max}$ -to-REM sleep ratio ($T_{\max}$ /REM) provides a similar comparison but includes only the time that the penile circumference was maintained within 75% of the MCI, thus providing a measure of the stability of the erection in the presence of the pro-erectile stimulus, REM sleep. Fluctuations refer to transient decreases in penile circumference during $T_{\max}$ below 75% of MCI but without reaching baseline. Occasional fluctuations in penile circumference are normal, particularly when REM sleep is fragmented. However, frequent fluctuations are abnormal when in the presence of well-maintained and uninterrupted REM sleep, even when a normal buckling force has been obtained during the night.

There are other subtleties with respect to data interpretation that may provide information regarding potential organic erectile dysfunction. The tumescent phase of the erection should progress in a continuous and steady manner from T_{up} to $T_{\max}$, taking approximately 10 minutes to develop. Penile pulsations should be present during the T_{up} phase. The erection should last throughout the entire REM period. An erection with less than 5 minutes of $T_{\max}$ during a normal (15–25-minute non-fragmented) REM period is abnormal and suggests possible venous leakage or other erectile pathology. Prolonged detumescence also is abnormal, typically taking less than 20 minutes to occur. Detumescence usually begins just before the end of REM sleep but usually continues for up to 5–10 minutes in NREM sleep following the end of the REM period and before T_{zero} is again reached.

24.5. Clinical indications for sleep-related erection testing

SRE testing has several distinct advantages in evaluating erectile functioning. First, it evaluates the central nervous system's (CNS) ability to generate erectile events in the presence of an appropriate stimulus, i.e., REM sleep. It is important to note that REM sleep is generated in the brainstem, and REM-related erections require a complex interaction with forebrain structures such as the lateral preoptic area (LPOA) (Schmidt et al., 2000). Therefore, normally occurring erections during REM sleep demonstrate that descending control of erections from the brain, through the spinal

cord and peripheral nerves, to the penis and erectile tissue remains functionally intact. Second, REM-related erections are the only known type of CNS-generated erections that minimize psychological influences yet still utilize virtually all levels of the neuraxis from brain to the end organ level.

Although context-specific erectile failure is an intriguing concept stemming from our recent realization that higher central mechanisms of penile erections may be context-specific (Sachs, 1995), the etiology of erectile dysfunction from a clinical perspective may still be placed into two general categories: those that are primarily organic and those that are primarily psychogenic in nature. Following a failure of known medical therapies for erectile dysfunction, a clinician is still left with only two options for treatment when confronted with a patient experiencing erectile dysfunction. The patient may be directed to a surgeon for prosthetic implant if organic etiology is present, or he may be directed to a psychologist or psychiatrist if psychogenic causes are suggested.

There are currently no standardized indications for performing SRE testing in the 'post-Viagra' era. However, we propose a set of clear guidelines and conditions when SRE evaluation should be undertaken or considered (Schmidt and Schmidt, 2004). Although future consensus regarding these guidelines will need to be reached, SRE testing still remains the best-known technique in differentiating psychogenic from organic erectile dysfunction and can provide useful clinical information regarding subsequent treatment options for any given patient experiencing erectile failure.

24.5.1. Patients who fail medical therapy or psychosexual counselling

Numerous medical options are now available as noted above for the treatment of erectile dysfunction, ranging from intracavernous injections to oral agents. However, approximately 20–30% of patients who try sildenafil are not responsive to this medication (Gresser and Gleiter, 2002). Treatment failure with phosphodiesterase inhibitors does not imply organic etiology since sexual arousal or excitation is required for their pro-erectile benefits. Moreover, patients taking vasoactive substances for underlying cardiac conditions may not be candidates for phosphodiesterase inhibitors. When further treatment options are limited to psychotherapy or surgical prosthetic implantation, SRE testing may be particularly beneficial in guiding the patient and the clinician. Although

formal SRE evaluation utilizing polysomnography may not be cost effective when used as a mass screening mechanism for erectile dysfunction, phosphodiesterase inhibitors have now become the inexpensive screening tool that was previously lacking. SRE testing should be considered in patients who do not respond to these newer medications or those with contraindications to this medical therapy.

Although psychosexual counseling may improve sexual satisfaction in psychogenic impotence, SRE testing with polysomnography should be considered in patients not responsive to such therapy to evaluate a potential organic component of the erectile dysfunction. Patients with organic impotence often suffer from psychopathology, including depression and performance anxiety. Formal SRE evaluation should particularly be considered prior to long-term, in-depth psychotherapy, which can be costly and potentially psychologically harmful if the patient is later found to have a prominent organic component to the erectile failure.

24.5.2. Pre-surgical work-up when considering prosthetic implants

The irreversible destruction of potentially viable erectile tissue following prosthetic implantation necessitates the elimination of potential psychogenic impotence prior to surgery. The placement of a prosthetic implant should be questioned when an individual has normally occurring penile erections during REM sleep. Potential underlying psychological influences secondary to depression or anxiety must be entertained and evaluated prior to any surgical implantation when REM-related erections are normal. Given the common simultaneous association of both organic and psychological contributions to any given patient's erectile failure, many patients may regain adequate erectile functioning once psychological factors have been addressed. On the other hand, the absence of REM-related erections in a patient with known potential organic causes such as spinal cord injury or peripheral neuropathy would increase the clinical confidence that the psychogenic contribution to the erectile dysfunction is minimal.

24.5.3. Patients who have abnormal erections demonstrated with nocturnal erection screening devices that do not include polysomnography

Patients who have apparently abnormal erections during sleep as demonstrated by nocturnal erection

screening techniques such as the RigiScan and Snap Gauge devices should be considered for SRE testing involving formal polysomnography. The direct relationship between the frequency, duration and magnitude of SREs and the frequency, duration and continuity of REM sleep may seem intuitively obvious to those who work in the field of sleep medicine, but this concept is seldom discussed in the urological literature regarding interpretation of RigiScan data. Indeed, all published data combining RigiScan monitoring of erections with formal polysomnography have excluded sleep disorders or patients with reduced REM sleep for the validation process (Licht et al., 1995; Guay et al., 1996). However, a clinician using the RigiScan device does not have this luxury of excluding patients based on abnormal REM sleep. There is an underlying assumption in the RigiScan literature that the frequency, duration and continuity of REM sleep are similar among individuals, even though it is well known that REM sleep architecture can vary greatly from patient to patient. As a result, an absence of erections during sleep using the RigiScan device can not be regarded as proof that REM-related erections are absent, or even impaired, without evidence of REM sleep. Moreover, men with highly fragmented REM sleep tend to have poorly maintained erections, reflecting the instability of the proerectile stimulus. Such patients may be regarded as having an organic erectile dysfunction when relying entirely on the RigiScan data if one incorrectly assumes that REM sleep architecture was normal.

REM sleep time may be markedly diminished or fragmented in numerous medical conditions such as in patients with obstructive sleep apnea (see Figure 24.3) or as a result of REM-suppressing medications, such as many of the antidepressants. Evaluation of REM-related erectile functioning requires knowledge of both the total erection time and total REM time, including the stability of both erections and REM sleep.

24.5.4. Patients with suspected occult sleep disorders

Occult sleep disorders are highly prevalent in the population and increase in prevalence with age and with obesity. For example, approximately one in five American adults has at least a mild obstructive sleep apnea/hypopnea syndrome (OSAH) (Young et al., 2002). OSAH is now recognized as an independent risk factor for the development of hypertension (Nieto et al., 2000; Peppard et al., 2000), largely in part secondary to its major activation of the sympathetic

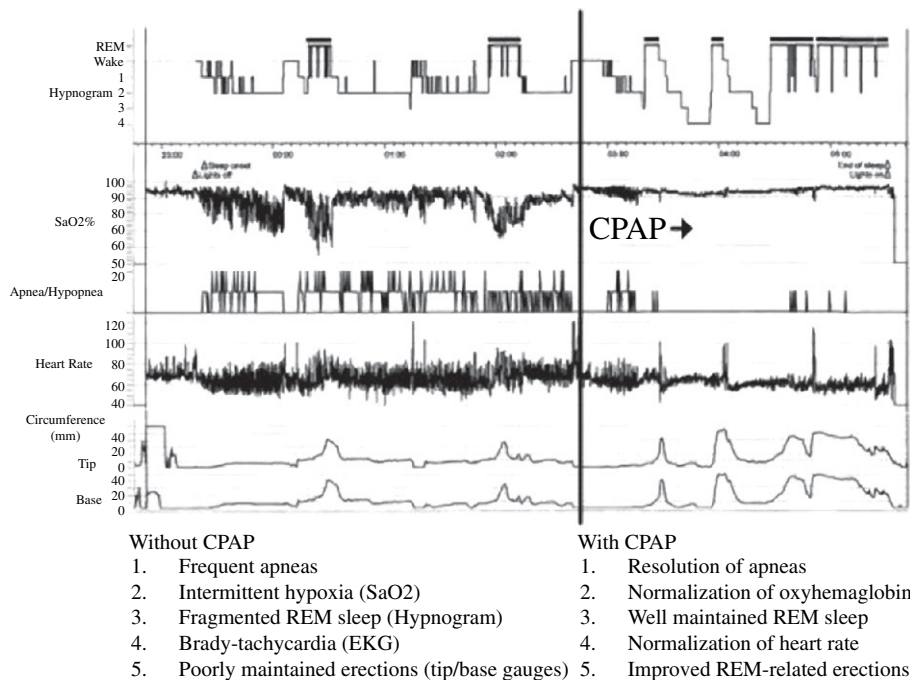


Fig. 24.3. Summary of a split night polysomnogram of a patient complaining of erectile dysfunction. Nasal continuous positive airway pressure (CPAP) titration was initiated after the vertical bar during the second half of the recording. There are frequent apneas and hypopneas during the first half of the recording that are associated with oxyhemoglobin desaturations (SaO₂) and brady-tachycardic events as seen in the heart rate channel derived from the EKG. REM sleep is fragmented secondary to apneic events, and penile erections are poorly maintained without CPAP, as seen by the fluctuating circumference changes at the base and tip gauges. During CPAP titration, on the other hand, REM sleep and penile erections are well maintained. There is also a normalization of the oxyhemoglobin concentration and the heart rate. Reprinted with permission from Schmidt and Schmidt, 2004.

nervous system (Fletcher, 1997; Narkiewicz and Somers, 1997). This sympathetic activation in OSAH patients may explain the high prevalence of erectile dysfunction in this patient population, particularly given the powerful role of the sympathetic nervous system in inhibiting or preventing penile erections (Giuliano et al., 1995). Up to 48% of patients with OSAH have been reported to have difficulty either initiating or maintaining erections (Guilleminault et al., 1977) and between 32–46% of impotent men have been demonstrated to have OSAH (Schmidt and Wise, 1981; Pressman et al., 1986).

Middle-aged, obese men with hypertension are commonly the patient population presenting to an erectile dysfunction clinic, precisely the patient population in which the prevalence of OSAH would be highest (Karacan et al., 1989). Obstructive breathing events in sleep are typically most severe in REM sleep, leading to a marked fragmentation and reduction of REM sleep in many patients, as seen in Figure 24.3. Given the fragmentation of REM sleep in OSAH

patients, REM-related erections are often poorly developed and may lead to a false positive RigiScan result (Pressman et al., 1986). Finally, erectile functioning has been reported to improve in up to one-third of OSAH patients following successful treatment with nasal continuous positive airway pressure (CPAP) devices (Karacan and Karatas, 1995). Although more definitive studies on the effects of OSAH on erectile dysfunction are clearly needed, SRE testing with formal polysomnographic evaluation can evaluate both erectile function and possible sleep-disordered breathing.

Occult sleep disorders, such as OSAH, periodic limb movement disorder (PLMD) and narcolepsy, may also adversely affect erectile function by causing a prominent excessive daytime sleepiness. Pathologic hypersomnolence may exacerbate erectile failure by contributing to decreased sexual drive or desire. Formal SRE evaluation with polysomnography should be considered in patients with erectile dysfunction and a complaint of daytime hypersomnolence.

24.5.5. Medicolegal cases requiring objective evaluation of erectile function

SRE evaluation with formal polysomnography may be used in medicolegal cases as a means of objective assessment of erectile capability. These would include cases in which patients seek financial compensation because of loss of erectile function following spinal cord or pelvic injury. In addition, erectile dysfunction may be used as a defense when a male is accused of sexual assault. The ability to obtain an objective assessment of erectile capability in a court of law becomes obvious when confronted with such cases. One recent review suggested that attended RigiScan assessment is all that is required for such medicolegal evaluations (Levine and Lenting, 1995). However, SRE testing in association with formal polysomnography is the only method that simultaneously assesses the amount of the pro-erectile stimulus (REM sleep) and erectile activity, including the frequency, duration and quality of both REM sleep and erectile events. No other technique has the ability to assess the integrity of the entire neuraxis from brain to end organ level regarding erectile function, yet simultaneously minimizes psychological influences or secondary gain. Finally, the use of attended monitoring by a technician in a sleep laboratory is essential to minimize both unintentional technical errors and intentional deception such as gauge tampering from the subject.

24.6. Summary

SRE evaluation has long played an important role in the evaluation of erectile dysfunction. Following a comprehensive history, physical and initial work-up, SRE testing may be considered as one of several diagnostic tests available to elucidate erectile function. The historical background and technical considerations regarding SRE evaluation were discussed in detail. In addition, the use of home screening devices was also addressed. Indeed, urologists continue to utilize unattended screening methods to evaluate erectile function when differentiating psychogenic from organic impotence. However, such unattended studies may produce false positive results when sleep is fragmented by common sleep disorders such as obstructive sleep apnea, a sleep disorder commonly present in men with erectile dysfunction. SRE evaluation combined with formal polysomnography is the only technique that simultaneously evaluates the quantity and quality of both penile erections and the pro-

erectile stimulus, REM sleep. Clear indications or guidelines when to undergo formal SRE evaluation have been lacking and this has contributed to the decline of SRE testing in the sleep laboratory. Proposed guidelines for SRE testing with attended polysomnography are presented.

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CHAPTER 25

Primary insomnia

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25.1. Introduction

Insomnia is among the most common health complaints in medical practice and the most prevalent of all sleep disorders. It is associated with significant functional impairments, reduced quality of life, and increased health-care costs (Simon and VonKorff, 1997; Ohayon, 2002). Despite its high prevalence and negative impact, the psychological and neurophysiological bases of insomnia are still poorly understood. Not surprisingly, insomnia often goes unrecognized and remains untreated. Although the evaluation and diagnosis of insomnia are based primarily on clinical history (Sateia et al., 2000), several subjective, behavioral and physiological approaches are now available to complement this evaluation and improve diagnostic accuracy. This chapter summarizes these assessment methods available for the evaluation of primary insomnia, with an emphasis on neurophysiological approaches.

25.2. Description of the disorder

25.2.1. Clinical features and presentation of insomnia

Insomnia comprises a spectrum of complaints reflecting dissatisfaction with the quality, duration or efficiency of sleep. These complaints may involve problems with falling asleep initially at bedtime, waking up in the middle of the night and having difficulty going back to sleep, or waking up too early in the morning with an inability to return to sleep. Insomnia may also involve a complaint of non-restorative or

unrefreshing sleep. In addition, daytime impairments such as fatigue, problems with memory and concentration, and mood disturbances are extremely frequent and often the primary concerns prompting patients to seek treatment (Morin and Espie, 2003).

In addition to standard diagnostic criteria (see Box 25.1), several indicators can be used to evaluate the severity and clinical significance of insomnia. Although there is no standard definition, sleep-onset insomnia and sleep-maintenance insomnia are typically defined by a latency to sleep onset and/or time awake after sleep onset greater than 30 minutes, with corresponding sleep efficiency lower than 85%. Likewise, early morning awakening can be operationalized by a complaint of waking up earlier (more than 30 minutes) than desired, with an inability to go back to sleep, and before total sleep time reaches 6.5 h. These criteria, while arbitrary, are useful to operationalize the definition of insomnia. A distinction is also made between acute insomnia, a condition lasting a few days and often associated with life events or jet lag, short-term insomnia (lasting 1–4 weeks), and chronic insomnia, lasting more than 1 month. Finally, it is necessary to consider the impact of insomnia on a person's life to judge its clinical significance. As such, a complaint of insomnia must be associated with marked distress or significant impairments of daytime functioning (American Psychiatric Association, 1994).

The *International Classification of Sleep Disorders* (ICSD; American Sleep Disorders Association, 1997) and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 1994) both make a distinction between primary (syndrome) and secondary (symptom) insomnia. While the essential clinical features of insomnia are similar for the symptom and the syndrome, in secondary insomnia, the sleep disturbance is temporally and causally linked to the underlying condition,

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Box 25.1**Diagnostic criteria for primary insomnia**

- A subjective complaint of difficulties initiating or maintaining sleep, or non-restorative sleep
- Duration of insomnia is longer than 1 month
- The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational or other important areas of functioning
- The sleep disturbance does not occur exclusively in the context of another mental or sleep disorder, and is not the direct physiologic effect of a substance or a general medical condition

including psychiatric (depression and anxiety), medical (pain), circadian (phase-delay syndrome), or other sleep disorders (periodic limb movements, sleep-related breathing disorders). In primary insomnia, the sleep disturbance does not occur exclusively in the context of another medical, psychiatric or substance abuse disorders; it may co-exist with these conditions but it is viewed as an independent disorder. Individuals with primary insomnia often display anxiety and depressive symptomatology, but such clinical findings are not severe enough to reach diagnostic threshold for an anxiety or affective disorder. They are viewed as consequence or co-existing symptoms rather than causes of insomnia. Thus, the diagnosis of primary insomnia is based essentially on the patient's subjective complaint and it is a diagnosis made by exclusion, i.e., after ruling out all other potential causes.

25.2.2. Subtypes of primary insomnia

Whereas DSM-IV (American Psychiatric Association, 1994) recognizes only one form of primary insomnia, the ICSD distinguishes among three different subtypes: psychophysiological insomnia, sleep-state misperception and idiopathic insomnia. Psychophysiological insomnia is the most classic form of primary insomnia. It is a type of conditioned insomnia derived from the repeated pairing of sleeplessness with situational (bed/bedroom), temporal (bedtime) or behavioral (bedtime ritual) stimuli normally associated with sleep. Hyperarousal resulting in part from excessive worrying about sleeplessness and the internalization of psychological conflicts also contributes to this conditioned insomnia (Hauri and Fisher, 1986). The sleep

of individuals with psychophysiological insomnia is sensitive to stress and subject to extensive night-to-night variability. Sometimes, their sleep is unexpectedly improved in a novel environment because the conditioned cues that keep them awake at home are not present in that environment.

Sleep-state misperception, also called subjective insomnia, is a genuine complaint of poor sleep that is not corroborated by objective findings. For example, a patient may perceive very little sleep (e.g., 1–2 hours per night) whereas EEG recordings show normal or near-normal sleep duration and quality. This sleep-state misperception condition is not the result of an underlying psychiatric disorder or of malingering. To some degree, insomniacs tend to overestimate the time it takes them to fall asleep and to underestimate the time they actually sleep. In sleep-state misperception, however, the subjective complaint of poor sleep is clearly out of proportion with any objective finding. This phenomenon is probably due to several factors including the lack of sensitivity of EEG measures, the influence of cognitive (information processing) variables during the early stages of sleep or, it could also represent the far end of a continuum of individual differences in sleep perception. Sleep-state misperception may be a prodromal phase for more objectively verifiable insomnia (Salin-Pascual et al., 1992). However, this condition is still poorly understood and the advent of new assessment technologies may help further our understanding of this puzzling condition.

Idiopathic (childhood) insomnia is, by definition, of unknown origin. One of the most persistent forms of insomnia, it presents an insidious onset in childhood, unrelated to psychological trauma or medical disorders, and is very persistent throughout adult life. It does not present the nightly variability observed with other forms of primary insomnia. A mild defect of the neurological sleep/wake mechanisms may be a predisposing factor; this hypothesis comes from the observations that patients with this condition often have a history of learning disabilities, attention-deficit hyperactivity or similar conditions associated with minimal brain dysfunctions. Despite evidence that their sleep is often more disturbed than in psychophysiological insomnia, individuals with idiopathic insomnia tend to show less emotional distress, perhaps due to resignation or to coping mechanisms they have developed over their lifetime.

Although clinical experience tends to support the existence of different insomnia subtypes, there are still few data to validate these profiles. Additional research

using different assessment methods and technologies will be needed to ascertain the number of etiologically distinct subtypes which warrant clinical attention and also whether they require different treatment.

25.3. Assessment methods and technologies

The evaluation and diagnosis of insomnia is based primarily on a detailed clinical history/assessment of the patient's subjective complaint – nature of sleep difficulties (initial, middle, late insomnia), its duration (acute vs chronic), and course (recurrent, persistent); typical sleep schedule, exacerbating and alleviating factors, perceived consequences, and the presence of medical, psychiatric or environmental contributing factors (Sateia et al., 2000; Morin and Edinger, 2003). Although essential to make the diagnosis, this information needs to be validated or complemented with more systematic data obtained from subjective, behavioral and physiological assessment methods.

25.3.1. Subjective measures

As the diagnosis of insomnia is based primarily on the clinical presentation and patient's subjective complaint, subjective measures play a greater role in the evaluation of this condition than for most other sleep disorders. At the core of insomnia is a subjective feeling of poor sleep quality or duration. Subjective measures are thus essential to evaluate the nature, course and severity of insomnia. Subjective measures include global and retrospective questionnaires and daily self-monitoring of sleep–wake parameters. Brief self-report instruments such as the *Pittsburgh Sleep Quality Index* (Buysse et al., 1989) and the *Insomnia Severity Index* (ISI; Morin, 1993) are useful for an initial screening of patients and for assessing outcome in clinical trials. These measures have been shown to adequately discriminate poor from good sleepers and the ISI has shown adequate convergent validity with standard polysomnographic measures (PSG; Bastien et al., 2001). However, these questionnaires are not diagnostic instruments and can only serve to complement other assessment methods.

Sleep diary monitoring is an invaluable tool to document the perceived severity of insomnia and to monitor treatment progress. A sleep diary usually requires self-recording of bedtime and arising time, along with morning estimates of sleep-onset latency, number and duration of awakenings, total sleep time, and several indices of sleep quality for the previous

night. It is well documented that individuals with insomnia have a tendency to overestimate the time they take to fall asleep and to underestimate their total sleep time in comparison to PSG measures (Coates et al., 1982; Means et al., 2003). These discrepancies appear to be a function of the sleep setting (home vs laboratory) and of psychological/ personality characteristics (e.g., more discrepancies among depressed subjects; Means et al., 2003). In addition, current EEG technology may not be sensitive enough to detect subtle brain wave patterns that may account for a subjective sense of wakefulness, but that are scored as physiological sleep. Studies using spectral analysis have begun to uncover the physiological basis of subjective sleep perception in insomnia. Meanwhile, daily morning estimates of sleep parameters such as sleep-onset latency or wake after sleep onset yield a reliable and valid index of insomnia, even though they do not reflect absolute values obtained from polysomnography (Coates et al., 1982). By tracking sleep over several consecutive nights, a sleep diary is more likely to capture the night-to-night variability that often characterizes the sleep of chronic insomniacs; as such, it may yield a more representative sample of a patient's sleep than one or two nights of polysomnography. Despite some limitations, the sleep diary remains a standard assessment procedure in insomnia outcome research.

25.3.2. Behavioral devices

Several behavioral assessment devices have been designed to obtain more objective and relatively unobtrusive measures of sleep in the patient's home environment. For example, wrist actigraphy is increasingly used in sleep research. The actigraph is a small sensing device that is worn on the wrist and which records motor activity continuously for periods of up to several days. Algorithms have been developed to estimate sleep–wake parameters based on the presence (wake) or absence (sleep) of movement. Studies with healthy adults have shown that actigraphy data are highly correlated with PSG data for global measures of sleep duration and total wake time. However, the validity of actigraphy for estimating more discrete variables such as sleep-onset latency, wake after sleep onset and number of awakenings is more equivocal (Ancoli-Israel et al., 2003). Nonetheless, actigraphy is sensitive to treatment effect among individuals with primary insomnia (Guilleminault et al., 1995; Vallières and Morin, 2003). Although it is not

indicated for the routine evaluation of insomnia, or other sleep disorders, actigraphy represents a useful adjunct to complement other assessment methods (Ancoli-Israel et al., 2003).

Other behavioral assessment modalities include the sleep assessment device (Lichstein et al., 1982) and the sleep monitor (Birrell, 1983), both of which generate tones at regular intervals after which the patient can record a response if he is awake. These time-sampling procedures produce data that correspond reasonably well with PSG evaluations, although they tend to underestimate wakefulness (Lichstein and Johnson, 1991). The switch-activated clock is another device which can provide an objective measure of sleep latency. A clock is activated by pressing a button with the thumb and, upon falling asleep, relaxation of the thumb pressure releases the switch, hence displaying the time required to fall asleep. Of those behavioral devices, only actigraphy is commercially available and used fairly regularly by sleep researchers. Despite its unobtrusive nature, additional research is necessary to improve the accuracy of this device and the validity of the algorithms.

25.3.3. *Neurophysiological methods*

Several neurophysiological methods are available to quantify or qualify sleep complaints associated with insomnia. Along with polysomnography, which remains the gold standard for sleep assessment, new quantitative techniques such as power spectral analysis, period amplitude analysis, evoked potentials, and neuroimaging techniques are just beginning to be used to evaluate the neurophysiological bases of insomnia. Some selected studies on neurophysiological methods are presented in Table 25.1.

25.3.3.1. *Polysomnography*

A standard polysomnographic (PSG) montage for sleep includes electroencephalographic (EEG; central and occipital leads), electrooculographic (EOG) and electromyographic (EMG; chin) monitoring (Rechtschaffen and Kales, 1968). Such montage provides comprehensive data on sleep continuity (sleep latency, time awake after sleep onset, sleep time, sleep efficiency) and sleep architecture (% of time spent in different NREM and REM sleep stages). Most laboratories monitor several additional channels (e.g., airflow, tidal volume, oxygen saturation and anterior tibialis EMG) to detect other sleep disorders such as sleep apnea or periodic limb movements.

PSG is not indicated for the routine clinical evaluation of insomnia (Reite et al., 1995); however, it is a most useful method to validate a subjective sleep complaint and to rule out the presence of other sleep disorders that might contribute to an insomnia complaint. Also, PSG can be particularly helpful in suspected cases of sleep state misperception and can provide valuable qualitative information about atypical EEG features (e.g., alpha-delta sleep) observed in some forms of insomnia. An important limitation of PSG is that it may not provide a valid sample of a patient's typical sleep at home. Indeed, the sleep of otherwise good sleepers is more disrupted during their first night of recording in the sleep laboratory (i.e., first-night effect), whereas the sleep of insomniacs may actually improve in the laboratory (i.e., reverse first-night effect) at least during the first recording night, because the stimuli that keep them awake at home are not present in that environment. For this reason, it is recommended to conduct more than one night of PSG to minimize this effect; ambulatory recording may also attenuate this reactivity effect to the sleep laboratory (Wohlgemuth et al., 1999). A single night of PSG evaluation may not provide a completely valid sample of a patient's sleep problem, but it has a definite advantage of yielding objective data to complement the patient's subjective report.

While the indication of PSG in the clinical evaluation of insomnia remains controversial, it is becoming a fairly standard practice in insomnia research (Morin, 2003). Insomnia protocols typically conduct two or three consecutive nights of PSG recordings, with the first night serving as an adaptation/screening night. In the absence of other sleep disorders on that first night, a sleep montage only is used on the second and third night of recording. Several parameters can be used as indicators of insomnia severity or as endpoints in treatment outcome studies. These include sleep-onset latency, number and duration of awakenings, total sleep time and sleep efficiency. In addition, the percent of time spent in the different sleep stages, the number of arousals and spontaneous events (e.g., K-complexes and spindles) may be used as markers of EEG states.

PSG findings in subjectively defined insomniacs reveal more impairment of sleep continuity parameters (i.e., longer sleep latencies, more time awake after sleep onset, lower sleep efficiency) and reduced total sleep time compared to subjectively defined good sleepers. Also, insomniacs tend to spend more time in stage 1, less time in stages 3–4, and display more

Table 25.1

Neurophysiological methods.

Authors	Groups	Method	Findings
(Coates et al., 1982) <i>PSG</i>	12 INS (6 F, 6 M), 2 of each gender for each of the following age groups 20—35, 30—50, 50—60 12 GS age and sex matched	• 1 week sleep diary • 5 consecutive nights of home PSG monitoring (values reported for nights 2 to 4)	<i>PSG data:</i> • Self-defined INS and GS differed on sleep onset latency, wake-after-sleep onset, total wake time and sleep efficiency. <i>Conclusions:</i> • Reported and recorded measures provide reliable and valid indices of sleep. • There were significant differences in INS between recorded and reported values for sleep onset latency and wake-after-sleep onset. • Frequency of nightly awakenings did not meet validity and reliability criteria in both groups.
(Merica et al., 1998) <i>PSA</i>	20 INS (12 F; 8 M), mean age 30.2 years 19 GS (10 F, 9 M), mean age 25.3 years	• Data from night 2 • PSA of the 4 first NREM—REM cycles	<i>PSG:</i> • INS had shorter total sleep time, longer total wake time, greater % stage 1, lower % REM and lower % sleep efficiency than GS. <i>PSA:</i> • The time course of all frequency bands are similar in INS and GS. • In the INS group, the rise rate for all frequency bands below the beta range is slower and the levels reached are lower during NREM sleep, whereas beta power is significantly increased. • In REM sleep, INS had increased power in faster frequency bands (alpha, sigma and beta) and decreased delta and theta power. • The first sigma peak tends to be lower and wider in INS.
(Bastien et al., 2003) <i>PSA</i>	15 chronic BZ users (INSBZ), (8 F; 7 M) mean age 62.2 years 15 INS (7 F, 8 M) mean age 63.4 years 16 GS (7 F, 9 M) mean age 63.1 years	• Data from night 2 • PSA (absolute power) of the first 4 cycles, stages 2, 3 and 4	<i>PSG data:</i> • Chronic BZ users had greater % stage 2 and lower % stage 3–4 compared to GS. • Chronic BZ users had a higher count of microarousals compared to INS and GS. <i>PSA:</i> • Chronic BZ users had less delta and theta activity over the night compared to GS. • Chronic BZ users had less delta and theta activity in cycle 2 compared to INS. • INS tended to have higher beta 1 density over the night compared to GS. • Chronic BZ users had more beta 1 activity in cycle 3 compared to GS and more than INS and GS in cycle 4.
(Devoto et al., 2003) <i>ERP</i>	11 INS (7 F, 4 M), mean age 22 years 11 GS aged-matched (5 F, 6 M), mean age 21 years	• P300 recorded in the laboratory between 9 and 12 am after a typical good night and a typical bad night • Reaction time	• Total sleep time and sleep efficiency were lower in INS than in GS. • In INS, P300 amplitude is significantly higher after a bad night and lower after a good night compared to GS. • INS have longer reaction time than GS.

Table 25.1

Continued

Authors	Groups	Method	Findings
(Smith et al., 2002) <i>Neuroimaging</i>	5 INS (5F), mean age 37.8 years 4 GS (4F), matched for age, BMI, and education, mean age 34.5 years BMI and education	• Night 1 = adaptation to PSG • Night 2 = PSG evaluation • Night 3 = PSG + PET scan	<i>PSG:</i> • Before the injection : The mean sleep onset latency was significantly longer in INS compared to GS. <i>Cerebral perfusion during NREM sleep:</i> • The INS group showed a pattern of decreased rCBF over all regions. The largest and significant reductions compared to GS are localized in the basal ganglia, the frontal medial cortex, the occipital cortex and the parietal cortex. • There were distinct regions of relative hypoperfusion.

GS, good sleepers; INS, insomnia sufferers; BZ, benzodiazepine; PSA, power spectral analysis; PAA, power amplitude analysis; ERP, event-related potentials; BMI, body mass index; rCBF, regional cerebral blood flow.

frequent stage shifts through the night (Coates et al., 1982; Reynolds et al., 1984; Hauri and Fisher, 1986). There is, however, a significant overlap in the distribution of sleep recordings of subjectively defined insomniacs and good sleepers such that some individuals with insomnia complaints may show better physiological sleep than those without complaints and, conversely, some good sleepers may show more sleep impairments than insomniacs. These overlaps might account for some of the discrepancies between PSG and diary sleep measures discussed in the previous section (i.e., overestimation of time awake and underestimation of sleep time by insomnia sufferers). Investigations of the microstructure of sleep have begun to shed some light on these paradoxical findings. Indeed, recent studies have shown that beta activity is increased in primary insomnia relative to good sleepers, both around the sleep onset period and during NREM sleep (Lamarche and Ogilvie, 1997; Merica et al., 1998; Perlis et al., 2001a). These findings, which are not always correlated with impairments of the macrostructure of sleep, are nevertheless consistent with psychological findings that insomniacs are hypervigilant and ruminative at night and with the presumed contributing role of attentional processes and information-processing factors to insomnia.

Some investigators have conducted more detailed analyses of the PSG-subjective discrepancies by varying the criterion used to define sleep onset and by examining the perception of sleep at different moments

of the night. For instance, Hauri and Olmstead (1983) reported that the best match between subjective and objective measures of sleep-onset latency is obtained when sleep onset is defined as the first epoch of stage 2 sleep that is followed by 15 minutes of uninterrupted sleep. Coates et al. (1983) reported that insomniacs' estimations of elapsed time failed to correlate with EEG data only at sleep onset and spontaneous arousals, while significant correlations between reported and recorded sleep were obtained for most variables among good sleepers. Furthermore, a greater percentage of individuals with insomnia reported being awake at the first spindle while a greater percentage of good sleepers reported being drowsy at that time. Finally, the sleep microstructure of chronic benzodiazepine users is characterized by faster EEG activity and more micro-arousals compared to unmedicated insomniacs and good sleepers (Borbély et al., 1985; Bastien et al., 2003a). Furthermore, the higher count of micro-arousals was correlated with a worse sleep quality among benzodiazepine users than unmedicated individuals.

The complaint of fatigue is almost always associated with insomnia. Some patients may initially report excessive daytime sleepiness, but a more in-depth investigation reveals that patients with primary insomnia typically experience mental and physical fatigue rather than true physiological sleepiness. Findings from the multiple sleep latency test indicate that the degree of daytime sleepiness is comparable among primary insomniacs and good sleepers (Stepanski et

al., 1988). Insomniacs have trouble sleeping at night, in part because of hyperarousal, and this chronic state of hyperarousal may also interfere with their ability to nap during the day. Excessive daytime sleepiness is more common among patients with insomnia secondary to another medical (e.g., pain) or sleep disorders (e.g., periodic limb movements, sleep-related breathing disorders).

The *Nightcap* is a two-channel device designed to provide ambulatory PSG through a headband monitor. Designed initially for monitoring sleep of astronauts during prolonged space flights (Stickgold and Hobson, 1999), this device distinguishes wake, REM sleep and non-REM sleep on the basis of eye movements and body movements. A similar device, *REMview*, has been used recently to evaluate treatment response among patients with insomnia (Kushida et al., 2003). Although initial comparisons with standard PSG are promising, additional studies are needed to evaluate the potential of this device for ambulatory evaluation of insomnia.

25.3.3.2. Power spectral analysis (PSA)

Because the human eye is limited in its reading and interpretation of EEG signals, recent studies have relied on more precise, computerized quantitative techniques such as PSA with fast Fourier transformations. Spectral analysis provides a measure of power in the different EEG frequency bands. An increase of power within a particular frequency band is interpreted as reflecting an increase in the amount of that frequency. Thus, an increase in high-frequency bands would reflect greater cortical arousal. Although the EEG spectrum runs from 0 Hz to 125 Hz, the usual band subdivisions are slow (0–1 Hz), delta (1–4 Hz), sigma (11–14 Hz), beta (14–35 Hz), gamma (35–60 Hz) and omega (60–125 Hz).

PSA may be a sensitive and powerful tool to evaluate and to further circumscribe discrepancies between subjective and objective measures of sleep. For example, several studies have observed that young adults with insomnia show a higher rate of high-frequency activity (beta) and a lower rate of slow-wave activity (delta and theta) relative to good sleepers both before sleep onset and during sleep (Freedman, 1986; Merica et al., 1998; Perlis et al., 2001a, 2001b). Although not specific to this subgroup, this increased rate of fast EEG activity is consistent with hyperarousal, a classic feature of insomnia (Lamarche and Ogilvie, 1997; Merica et al., 1998; Bastien and Bonnet, 2001). A recent study by Krystal et al. (2002)

found greater relative alpha and sigma power densities during NREM sleep in insomniacs compared to controls. After subtyping insomnia patients, this elevated alpha activity remained present only among those whose sleep complaints were not confirmed by PSG. A recent study by our group (Bastien et al., 2003a) examined with PSA the sleep microstructure of three groups of older adults including insomniacs using benzodiazepines chronically, drug-free insomniacs, and self-defined good sleepers. There was no significant difference between drug-free insomniacs and good sleepers. However, chronic benzodiazepine users presented significantly less delta and theta activities over the entire night compared to controls and unmedicated insomniacs. Furthermore, benzodiazepine users had more beta than both drug-free insomniacs and good sleepers. In a study examining the microstructure of sleep among insomnia patients treated with behavioral therapy, Jacobs and colleagues (1993) observed a decrease in beta activity with treatment, although beta activity remained higher among treated insomniacs relative to good sleepers.

PSA is increasingly used in research studies and appears to be a promising tool to quantify and circumscribe insomnia complaints. Unlike the extensive variation in PSG data obtained both across individuals with insomnia and recording nights, PSA may provide more stable records showing increased high-frequency activity in insomniacs. As a potential marker of insomnia, PSA would also be useful to study mechanisms and mediators of changes in the treatment of insomnia.

25.3.3.3. Period amplitude analysis (PAA)

PAA is based on a graphical analysis of the number of completed waveforms during an epoch per unit of time. The number of baseline crossings in the EEG is used to determine the periods of each waveform. Only one study has reported on the use of PAA with primary insomnia (Nofzinger et al., 1999). The authors compared subjective reports with standard PSG, PSA and PAA. PAA results showed that insomnia subjects had an increased delta wave count in the second NREM cycle compared to good sleepers. Unlike studies using PSA, there were also increased delta and theta activities for insomniacs compared to controls. Furthermore, there was an increase in beta power (20–32 Hz) observed among patients with insomnia relative to patients with major depression. More research using PAA is needed to further untangle sleep patterns in insomnia.

25.3.3.4. *Event-related potentials (ERPs)*

Information processing of external stimuli remains present during sleep, although reduced relative to wakefulness. ERPs are cognitive responses of the brain to environmental stimuli reflecting on how the brain is able to 'process and classify' these intrusions. ERPs can be used to quantify cortical arousal and to study cognitive processes such as attention, vigilance and memory. Based on PSA findings that insomniacs are cortically hyperaroused and frequent reports of daytime deficits associated with sleep difficulties, ERPs would appear particularly well suited to study primary insomnia. It represents a potentially useful assessment tool to quantify and qualify hyperarousal and the daytime impairments related to poor attention, reduced vigilance and memory lapses.

Despite their clinical usefulness in neurological practice, only few studies have used ERPs in the context of insomnia. In 1993, Hull conducted a classic study by recording ERPs in an oddball paradigm during wakefulness and at sleep onset. The P300 amplitude tended to be higher immediately prior to lights out and response latency was shorter during wakefulness among insomnia subjects relative to good sleepers. During stage 2 sleep, the amplitude of the N350 component was lower for poor sleepers. In a study of ERPs to auditory stimuli during wakefulness, Regestein and his colleagues (1993) found that insomniacs had greater P1N1 amplitude than good sleepers for each sound intensity. Loewy and his colleagues (1998, 1999) also observed a larger N1 and a smaller P2 in poor relative to good sleepers during wakefulness. Wang and colleagues (2001) reported longer latencies and higher amplitude mismatch negativity (MMN) among insomnia subjects compared to controls. Finally, Devoto et al. (2003) presented sounds to both insomnia and control subjects after a subjective good night and a subjective poor night of sleep. These authors reported that P300 amplitude was significantly higher among insomnia subjects compared to good sleepers after the poor night of sleep, whereas it was actually lower among insomnia relative to control subjects after the good night sleep. Also, insomniacs had longer reaction time compared to good sleepers.

Together, these studies suggest elevated cortical arousal in insomnia. It is possible that this 'hyperarousal' reflects an inability or a deficit in information processes of insomniacs. As such, individuals with insomnia would have difficulties in screening out environmental stimulation and to 'shut-down' awake

cognitive processes even during the night. This deficit would then contribute to sleep disturbances.

25.3.4. *Neuroimaging measures*

Sleep researchers are only beginning to use brain-imaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), low-resolution electromagnetic tomography (LORETA) to examine the relationship between EEG activity and changes in activity within cortical and subcortical areas of the brain during sleep. Neuroimaging studies specific to insomnia patients are still rare and remain difficult to interpret. Smith and collaborators (2002) have examined cerebral activity in patients with primary insomnia compared to good sleepers using single SPECT during non-REM sleep. SPECT allows the visualization of cerebral metabolism by analyzing the signal emitted by a short-lived radioactive tracer injected intravenously before scanning. In comparison to good sleepers, insomnia patients were found to show a consistent pattern of deactivation in several cerebral regions, particularly in the basal ganglia, the frontal medial cortex, the occipital cortex and the parietal cortex. The authors interpreted these results as suggesting that cortical deactivation in insomnia may serve as a restorative function for daytime hyperactivity, or as a response to the homeostatic drive to sleep caused by partial sleep deprivation. Using LORETA, a technique allowing the mapping of event-related current density measures according to a standard brain atlas, Szelenberger and Niemcewicz (2001) found that primary insomniacs showed less event-related current density in cerebral regions involved in cognitive and affective functions (i.e., orbitofrontal, medial prefrontal and anterior cingulate cortices) relative to normal controls. These preliminary results only begin to uncover the wealth of hypotheses that future research might address regarding the neuro-functional markers of insomnia.

25.3.5. *Autonomic arousal measures*

In addition to EEG, other physiological measures can provide useful information in the evaluation of insomnia. For instance, several studies comparing individuals with insomnia and normal sleepers on measures of autonomic activity have shown faster heart rate, elevated body temperature, higher frontalis and chin

muscle tension, increased body movements and greater basal skin resistance during sleep as well as during the pre-sleep period among insomniacs (Adam et al., 1986; Bonnet and Arand, 1995, 1998a). Bonnet and Arand (1995) also found that insomnia was associated with higher levels of metabolic rate both during the day and during sleep. Individuals with insomnia also appear to have increased 24-hour cortisol and ACTH secretion, reflecting higher hypothalamic–pituitary–adrenal axis activation (Vgontzas et al., 2001). These results indicate increased autonomic arousal among individuals with insomnia. It remains unclear, however, whether this hyperarousal is a cause or a consequence of poor sleep. Some authors have suggested that increased arousal is a primary condition that does not only disrupt sleep but also produces other daytime symptoms commonly associated with insomnia, such as elevated tension and confusion (Bonnet and Arand, 1997, 1998b). Collectively, however, these cross-sectional studies provide only indirect support that predisposing characteristics (i.e., hyperarousal, worrying, repressive tendencies) may increase the vulnerability of certain individuals to insomnia.

25.3.6. Neuropsychological measures

Reports of performance impairments during the day are almost always associated with insomnia complaints. Several studies have evaluated the nature and extent of those performance deficits by comparing individuals with insomnia and good sleepers on standardized neuropsychological tests. The findings have been inconsistent. Some studies have reported decreased performance on measures of auditory vigilance, digit span, reaction time, verbal memory, logical reasoning and visuo-motor speed (Schneider-Helmert, 1987; Bonnet and Arand, 1995; Hauri, 1997), whereas other studies failed to reveal group differences on measures of reaction time, sustained attention and auditory vigilance (Sugerman et al., 1985; Dorsey and Bootzin, 1997). Other studies have correlated the degree of sleep impairments with neuropsychological performance. For example, Hart and colleagues (1995) found that subjective sleep disturbance was related to performance on tests of vigilance, psychomotor speed, recall memory and executive functions, and PSG sleep disturbance was related to word list retention. Szelenberger and Niemcewicz (2000) found that impaired verbal learning correlates with the severity of insomnia. Bastien and colleagues (2003b) observed that PSG-defined

sleep disturbances were related to objective and subjective daytime impairments among elderly insomniacs and good sleepers. However, subjective poor sleep was related to decreased performance among medicated insomniacs and good sleepers only. Collectively, the evidence suggests that insomnia is associated with selective neuropsychological deficits; performance impairments are more strongly associated with subjective (as measured by daily sleep diaries) than with objective (as measured by PSG) sleep disturbances. It appears that sleep perception and non-specific psychological factors are important determinants of daytime performance. Studies using more sensitive neuropsychological tests and more naturalistic performance measures are warranted to further circumscribe the performance impairments associated with primary insomnia.

25.4. Conclusion

The diagnosis of primary insomnia is based essentially on the patient's subjective complaint and on history. Although a wide range of behavioral and neurophysiological measures is now available to conduct sophisticated sleep assessments and complement the clinical history, these technologies are still infrequently used for clinical or research purposes. A great deal more work is needed to refine the technological aspects of these recording methods and to define standards for guiding the interpretation of the findings derived from these assessments. It is only with additional refinement of these evaluation tools that we will achieve a better understanding of the nature and pathophysiology of insomnia and develop more effective therapies to manage this challenging sleep disorder.

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CHAPTER 26

Psychiatric insomnias

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26.1. Introduction

Sleep and psychiatric disorders are associated in several ways. From a sleep disorders perspective, many cases of insomnia will be associated with a psychiatric disorder that may cause the insomnia complaints. From a psychiatric perspective, a large number of psychiatric disorders are associated with disruptions in sleep. These are recognized at both the subjective level, as well as at the polysomnographic level. Many of the medications used to treat sleep disturbances overlap with those that treat psychiatric disorders. Many of the interventions used to treat psychiatric disorders have distinct effects on sleep, either subjectively or objectively. Finally, recent studies show that many of the neural systems involved in the regulation of sleep overlap considerably with those systems that are implicated in the pathophysiology of mental disorders. Below we review the evidence for each of these general observations.

26.2. Epidemiology of insomnia and psychiatric disorders

Two epidemiological relationships are important to consider. First, the presence of insomnia in an otherwise healthy population is a risk factor for the development of a psychiatric disorder, most often depression and anxiety. Second, of all patients presenting for evaluation of insomnia, a psychiatric disorder is a contributing factor in a large number of cases. As these epidemiological relationships have been covered elsewhere, they will not be reviewed here.

26.3. Psychiatric disorders that are associated with insomnia

26.3.1. Depression

Depression is among the most common of psychiatric disorders that has been associated with insomnia. The majority of patients with mood disorders describe difficulty falling asleep, difficulty staying asleep and early morning awakenings. While insomnia characterizes middle age and elderly unipolar depression, younger patients and bipolar depressed patients will often describe, atypically, difficulty getting up in the morning and hypersomnia during the daytime. Insomnia in depression has been extensively evaluated by polysomnography. The impetus for this research is related to a search for neurobiological mechanisms of the disorder (Benca et al., 1992; Nofzinger et al., 1993). Depressed patients show increases in sleep latency and decreases in sleep continuity. In terms of EEG sleep stages, depressed patients show an increase in the amount of REM sleep, a shortening of the time to onset of the first REM period of the night, a shortened REM latency, and an increase in the frequency of eye movements within a rapid eye movement period. In terms of NREM sleep, depressed patients often show reduced stage 3 and 4 NREM sleep (also known as 'slow-wave sleep' because of the presence of slow EEG delta activity during these stages). In terms of quantitative EEG changes in sleep, many (Borbély et al., 1984; Kupfer et al., 1990) studies have reported reductions in the amplitude or a reduction in the number of low-frequency (0–4 Hz) delta waves during sleep in depressed patients. Increased high-frequency EEG activity has also been reported in depressed patients including alpha (Borbély et al., 1984) and beta. Sleep EEG measures are generally less abnormal in adolescents and pre-pubertal children with depression, and only appear consistently in those adolescents who are hospitalized and/or suicidal (Dahl

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et al., 1991). Other studies have shown that patients with psychotic depression have particularly severe EEG sleep disturbances and very short REM sleep latencies; that patients with recurrent depression have more severe REM sleep disturbances than patients in their first episode; and that sleep continuity and REM sleep disturbances are more prominent early in the depressive episode than later (Dew et al., 1996). Reduced REM latencies, phasic REM measures and sleep continuity disturbances generally move toward control values after remission of depression. Abnormal sleep measures in a depressed patient are associated with increased response rates to pharmacotherapy (Rush et al., 1989), but not to psychotherapy and with increased likelihood or decreased time until recurrence of depression in patients treated with medications or psychotherapy (Giles et al., 1987).

Insomnia associated with life stresses or significant losses is a risk factor for the development of a depressive episode following loss. In a study of elderly volunteers who had lost a spouse, Reynolds et al. (1993) were able to distinguish EEG sleep changes discriminating subjects who did from those who did not develop an episode of major depression. Bereaved subjects with depression had significantly lower sleep efficiency, more early morning awakening, shorter REM latency, greater REM percent, and lower rates of delta wave generation in the first NREM period, as compared to non-depressed bereaved volunteers. In a subsequent longitudinal study of bereaved elders who did not become clinically depressed, only increases in phasic REM activity and density (compared to normal controls) were observed throughout the first 2 years of bereavement.

26.3.2. *Bipolar disorder*

Insomnia is associated with bipolar disorder, or manic-depressive illness, in several respects. Bipolar disorder is a periodic, or cyclic, psychiatric disorder in which patients cycle between periods of depression, euthymia and mania over the course of their lives. Within the extreme states of the disorder, mania and depression, sleep length oscillates in a characteristic manner (Nofzinger et al., 1993a). Sleep length is decreased in mania and increased in periods of depression, or in the least, patients describe a decreased ability to maintain natural levels of alertness when depressed. EEG sleep studies confirm fragmented sleep and shorter sleep durations during hypomanic or manic episodes (Linkowski et al., 1986). There is also

support from EEG sleep studies that the depressed phase of the illness is associated with hypersomnia (Jovanovic, 1977; Duncan et al., 1979; Giles et al., 1986; Jernajczyk, 1986; Mendelson et al., 1987; Thase et al., 1989; Nofzinger et al., 1991; Billiard et al., 1994; Rush et al., 1997). Aside from these general observations it is difficult to make any claims that there are unique EEG sleep patterns, such as alterations in REM sleep timing or duration, that characterize either the manic or depressed phase of the illness, based either on cross-sectional (Jovanovic, 1977; Duncan et al., 1979; Giles et al., 1986; Jernajczyk, 1986; Linkowski et al., 1986; Mendelson et al., 1987; Hudson et al., 1988, 1992; Thase et al., 1989; Nofzinger et al., 1991; Billiard et al., 1994; Rush et al., 1997) or longitudinal study designs (Hartman, 1968; Bunney et al., 1972; Kupfer and Heninger, 1972; Gillin et al., 1977; Gann et al., 1993).

A second manner in which insomnia and bipolar disorder are associated is the observation that a loss of sleep may precipitate a manic episode in a vulnerable individual. In studies using sleep deprivation in bipolar patients, hypomania or mania was precipitated in an average of 24% of cases. Leibenluft et al. (1996) found that a decrease in self-reported sleep duration predicted the occurrence of mania or hypomania on the following day.

26.3.3. *Schizophrenia*

Schizophrenia is a psychiatric disorder that is often associated with insomnia, although it is typically encountered in the context of evaluation and treatment of the thought disorder that disables these patients. Treatment interventions, therefore, are more commonly directed at alleviating the thought disorder as opposed to addressing the sleep complaints of these individuals. Clinically, patients with schizophrenia are reported to have lighter, more fragmented sleep, especially during periods of acute psychosis. In terms of EEG sleep studies, the most consistent finding is a loss of stages 3 or 4 sleep, or a loss of EEG power during NREM sleep in the delta frequency band (Zarcone and Benson, 1994; Keshaven et al., 1998). Slow-wave sleep is of particular interest to schizophrenia because of the implication of the prefrontal cortex in this disorder (Keshaven et al., 1994) and in generation of SWS (Werth et al., 1997). There is evidence (Benson et al., 1993) that following total sleep deprivation, recovery of stage 4 sleep is diminished in schizophrenia. Slow-wave sleep deficits tend to persist over

time in schizophrenia suggesting that they may be trait-related (Keshaven et al., 1996). They have also been found to correlate with negative symptoms (Ganguli et al., 1987) and with impaired outcome at 1 and at 2 years (Keshaven et al., 1995).

In terms of REM sleep changes in schizophrenia, the findings are mixed. Shorter latencies to REM sleep in schizophrenic patients have been found in some, but not all studies (Ganguli et al., 1987; Tandon et al., 1992; Zarcone and Benson, 1994). A short REM latency in schizophrenia may be related to the loss of stages 3 and 4 sleep in the first NREM period as opposed to an alteration in REM sleep itself.

26.3.4. Generalized anxiety disorder (GAD)

Insomnia is often observed in patients with anxiety disorders. GAD is characterized by excessive, generalized anxiety for >6 months; difficult to control worry and associated with three out of six of the following symptoms: feeling keyed up; easily fatigued; difficulty concentrating; irritability; muscle tension; and sleep disturbance (difficulty initiating, maintaining, or non-restorative sleep). EEG sleep studies in GAD patients show long sleep-onset latencies; decreased sleep maintenance; decreased stages 3 and 4 sleep (slow-wave sleep) with no consistent changes in timing, duration or intensity of REM sleep. The lack of REM sleep alterations in GAD patients tends to differentiate GAD patients from those with depression.

26.3.5. Panic disorder

Insomnia in panic disorder takes a somewhat different form than the generalized insomnias seen in other psychiatric disorders. Panic disorder is characterized by a discrete period of intense fear associated with anxiety symptoms: e.g., palpitations, sweating, shaking, shortness of breath, dizziness and a fear of dying. There is also at least 1 month of concern about having attacks. These individuals may develop fears of places where they have experienced panic. This is called agoraphobia. The sleep disturbances associated with panic disorder include panic episodes arising from sleep that occur in 65% of panic disorder patients. Thirty to forty-five percent have recurrent sleep panic episodes. These episodes are similar in quality to those occurring during waking and they increase the frequency of sleep continuity problems in panic disorder patients. In terms of EEG sleep disturbances, they show surprisingly normal EEG sleep;

some increased sleep latency; some poor sleep continuity; and the panic episodes tend to arise from stages 2 and 3 sleep.

26.3.6. Post-traumatic stress disorder (PTSD)

Insomnia associated with PTSD is among the more devastating symptoms of this disorder that is often refractory to treatment. PTSD begins following exposure to threatening situation with intense emotional reaction (e.g. combat or rape). It is associated with recurrent unwanted thoughts; recurrent dreams of the event; flashbacks; and psychological and physiological reactivity to symbolic events. The sleep disturbances in PTSD include repetitive unwanted post-traumatic dreams in 59–68% of patients and severe sleep continuity disturbances. The EEG sleep disturbances include sleep continuity disturbances; increased periodic limb movements; and variable reports of REM sleep disturbances. The recurrent traumatic nightmares may arise out of either REM or NREM sleep, generally early in the night.

26.4. Psychotropic medications and sleep

Medications used to treat sleep disturbances also have applications in the treatment of psychiatric disorders. Medications used to treat psychiatric disorders have very distinct effects on sleep patterns. These observations suggest that a more complete understanding of the psychiatric insomnias can be obtained by a review of the neuropsychopharmacology of both sedative-hypnotics and of psychotropic medications. As sedative-hypnotics have been reviewed elsewhere, they will not be discussed further in this chapter.

26.4.1. Antidepressants

Nearly all effective antidepressant medications show a pronounced inhibition of REM sleep including a prolongation of the first REM cycle and a reduction in the overall percent of REM sleep (exceptions include nefazadone (Sharpley et al., 1992); and bupropion which do not suppress REM sleep (Nofzinger et al., 1995)). This is thought to be related to their increasing brainstem monoaminergic tone which acts to inhibit cholinergic REM generating cells as modeled by the reciprocal interaction model of REM sleep generation (Hobson et al., 1975). An imbalance in monoaminergic/cholinergic tone in the central nervous system has been proposed as a pharmacologic

model for depression. Cholinergic agents such as the muscarinic agonist RS 86, arecoline, physostigmine and scopolamine produce exaggerated REM sleep effects in depressed patients in comparison with patients with eating disorders, personality disorders, anxiety disorders and healthy controls (Gillin et al., 1991). These studies suggest that there may be a supersensitivity of the cholinergic system driving REM sleep in mood disorders patients, although an alternative plausible hypothesis is that there may be reduced monoaminergic (5-HT and/or NE) inhibition of the brainstem cholinergic nuclei in mood disorder patients. Selective serotonin reuptake inhibitors are known to have prominent REM-suppressing activity, most notably early in the night when enhances in REM sleep are most often seen in mood disorder patients (Nofzinger et al., 1993). A tryptophan-free diet, which depletes central serotonin activity, is noted to decrease REM latency in healthy controls and in depressed patients (Bhatti et al., 1998). *s22* and ipsapirone, a 5-HT_{1A} agonist, is noted to prolong REM latency in both normal controls and in depressed patients (Gillin et al., 1996). Anatomically, 5-HT_{1A} receptors have been conceptualized as the limbic receptors given their high densities in the hippocampus, the septum, the amygdala and cortical paralimbic structures. The action in these structures has been shown to be largely inhibitory (hyperpolarizing). Given the importance of limbic and paralimbic structures in REM sleep modulation, the influence of SSRI medications may be mediated by these limbic receptors. Importantly, in the brainstem LDT, a locus of cholinergic cells identified in the generation of REM sleep, bursting cholinergic neurons are inhibited by the action of 5-HT on 5-HT_{1A} receptors. Finally, the effects of the 5-HT_{1A} antagonist pindolol on EEG sleep in healthy subjects was studied and noted to reduce REM sleep. This was interpreted as supportive of a reduction in raphe serotonergic autoregulation resulting in increased serotonergic input to pontine cholinergic centers and inhibiting REM sleep. In part, therefore, the insomnia of depression may be mediated by a monoaminergic/cholinergic imbalance.

26.4.2. Mood-stabilizing medications and sleep

If alterations in sleep and biological rhythms are central to the pathophysiology of bipolar disorder, then medications that improve the clinical symptoms of bipolar patients, such as lithium carbonate, should have demonstrable effects on sleep and biological

rhythms. Mendels and Chernik (1973) studied the effects of lithium carbonate on EEG sleep for 150 nights in five depressed patients. They found that lithium administration led to a significant decrease in mean REM percent and an increase in the latency to REM sleep. They also observed a significant increase (doubling) in mean delta sleep with no significant change in sleep time. Similar findings were noted in a larger confirmatory study (Chernik and Mendels, 1974) where lithium produced a decrease in waking, stage 1 sleep and REM sleep and increases in stages 3 and 4 sleep. Kupfer et al. (1974) studied the effects of 1200–2400 mg per day lithium carbonate on EEG sleep in six bipolar patients in varying clinical states. REM sleep suppression was observed most prominently in the first two-thirds of the night and delta sleep enhancement (doubling) was observed uniformly across subjects. Hudson et al. (1989) studied the effects of lithium carbonate on EEG sleep in nine manic bipolar patients. REM suppression was noted as evidenced by a decreased REM percent, increased REM latency and decreased measures of phasic REM sleep. No significant effects on delta sleep were noted. Reimann et al. (1993) studied the effects of carbamazepine on EEG sleep in a rapid-cycling bipolar patient and in 12 healthy subjects. In the rapid cycling patient, treatment was associated with a prolongation of REM latency. In the healthy subjects, no effects on REM sleep were noted with the exception of a decrease in phasic REM sleep and sleep continuity and slow-wave sleep increased. Post et al. (1987) demonstrated improvements in sleep continuity during carbamazepine treatment in 19 bipolar manic patients. These studies lend support to the idea that the insomnias of bipolar disorder are linked with alterations in REM/NREM sleep and that normalization of these changes via mood stabilizing medications may be important to reversing not only the sleep complaints in these patients, but in stabilizing the manic and depressive symptoms.

26.4.3. Effects of antipsychotic drugs on sleep

Studies of the acute effects of neuroleptics have consistently shown improvements in sleep continuity, as reflected by reduced sleep latencies, improved sleep time and greater sleep efficiency, and prolongation of REM latency (Zarcone and Benson, 1994). However, changes in SWS have been less consistent. Studies that have examined the sedative effect of conventional neuroleptics have reported either no effects, or modest

increases in SWS. One study showed a robust increase in SWS with olanzapine following acute administration (Salin-Pascual et al., 1999). On the other hand clozapine increases stage 2 sleep, but may actually decrease stage 4 sleep (Hinze-Selch et al., 1997).

Attempts to examine polysomnographic characteristics of schizophrenia have to consider potential effects of neuroleptic discontinuation on sleep EEG. Neylan et al. (1992) reported significant worsening of REM and non-REM sleep in a series of schizophrenic patients undergoing controlled neuroleptic discontinuation. Patients experiencing relapse had larger impairments in sleep. The effects of neuroleptic discontinuation continued to worsen from 2–4-week neuroleptic-free condition, and did not correlate with clinical change (Nofzinger et al., 1993b). These findings highlight the importance of controlling for medication state in the investigation of EEG sleep in schizophrenia.

26.5. Neural systems that regulate sleep overlap with those involved in psychiatric disorders

Over the past decade, functional neuroimaging studies have clarified regional variations in brain function across sleep/wake states in humans. Many of the structures involved in these changes have also been implicated in the neurobiology of psychiatric disorders. Below, we briefly review functional neuroimaging results in sleep in healthy subjects prior to describing early results in patients with psychiatric disorders.

26.5.1. Functional neuroimaging findings during sleep in healthy subjects

Studies across laboratories and using various imaging methods have demonstrated that during REM sleep, in contrast to waking, there is activation of the pontine reticular formation, limbic (e.g., amygdala) and paralimbic cortex (e.g., anterior cingulate cortex). Additionally, there is general agreement that as a whole, the brain is functionally as active in REM sleep as it is in waking (Meyer et al., 1981; Buchsbaum et al., 1989; Maquet et al., 1996; Braun et al., 1997; Nofzinger et al., 1997). A number of studies have shown that from waking to NREM sleep there are regional reductions in brain function in heteromodal association cortex in the frontal, parietal and temporal lobes as well as in the thalamus. Globally, NREM sleep is functionally less active than either waking or

REM sleep (Meyer et al., 1981; Heiss et al., 1985; Buchsbaum et al., 1989; Maquet et al., 1992, 1997; Braun et al., 1997; Hofle et al., 1997; Maquet and Philips, 1998; Nofzinger et al., 1998; Maquet, 1999, 2000; Kjaer et al., 2002). Therefore, across the sleep–wake cycle, neocortical function is high in waking and declines in general across sleep periods. This includes the dorsolateral prefrontal cortex. Whole brain function declines from waking to NREM sleep. On entry to REM sleep, there is a re-activation of the cortex, with regional preference for limbic and anterior paralimbic structures such as the amygdala and the anterior cingulate cortex. These functional neuroimaging studies, therefore, have identified a collection of brain structures that have wide variations in function across the behavioral states of waking, NREM and REM sleep. The functional roles of these structures in overall behavior include the regulation of mood, motivation, arousal and many cognitive operations including memory, attention and cognitive control. These behaviors are generally disturbed in some fundamental manner in diverse psychiatric disorders. Therefore, the alterations in REM and NREM sleep in psychiatric populations may reflect fundamental alterations in function in these neural systems that are important for essential human behaviors. Studies are currently underway to test these ideas. Below, we review early evidence to this effect in the area of depression.

26.5.2. Depression: REM sleep

In relation to waking, REM sleep activates limbic and paralimbic structures. The REM sleep alterations observed in depression, therefore, may reflect alterations in function in limbic and paralimbic areas that control emotional behavior. In a preliminary analyses of [18F]FDG PET studies, Nofzinger et al. (1999) studied six unipolar depressed subjects and eight healthy subjects using [18F]2-fluoro-2-deoxy-D-glucose ([18F]FDG) PET scans during waking and during their first REM period of sleep. The primary finding from this study was that, in contrast to healthy control subjects, depressed patients did not show increases in rCMRglu in anterior paralimbic structures in REM sleep compared to waking. Additionally, depressed subjects showed greater increases from waking to REM sleep in rCMRglu in a collection of relatively smaller brain structures including the tectal area and a series of left hemispheric areas including sensorimotor cortex, inferior temporal cortex, uncus

gyrus-amygdala and subicular complex. This pattern of increases provided early evidence that these brain structures may have increased functional activity in depressed patients related to increased electrophysiological arousal in depression. In a follow-up to this finding, Nofzinger et al. (2001) assessed the reversibility of REM-sleep-related anterior paralimbic changes in depression following antidepressant therapy with bupropion SR. Twelve depressed patients underwent EEG sleep studies and [18F]fluoro-2-deoxy-D-glucose ([18F]-FDG) positron emission tomography (PET) scans during waking and during their second REM period of sleep before and after treatment with bupropion SR. Bupropion SR treatment reversed the previously observed deficit in anterior cingulate, medial prefrontal cortex and right anterior insula activation from waking to REM sleep. In secondary analyses this appeared to be related to a significant reduction in waking anterior cingulate metabolism following treatment. This suggests that increased anterior cingulate metabolism characterizes depressed patients and that antidepressant therapy may work in part by imparting an inhibitory influence on abnormally elevated function in the anterior cingulate. This also raised the possibility that the initial finding of a blunted anterior paralimbic response to the waking to REM sleep functional neuroimaging probe may have been due to hypermetabolism in the anterior paralimbic system during waking in the depressed patients.

In an extended analysis (Nofzinger et al., 2004), 24 depressed patients and 14 healthy subjects received EEG sleep and regional cerebral glucose metabolism (rCMRglu) assessments during both waking and REM sleep using [18F]fluoro-2-deoxy-D-glucose ([18F]-FDG) positron emission tomography (PET). Depressed patients showed greater REM sleep percent. While both healthy and depressed patients activated anterior paralimbic structures from waking to REM sleep, the spatial extent of this activation was greater in the depressed patients. Additionally, depressed patients showed greater activation in the midbrain reticular formation and in bilateral dorsolateral prefrontal, left premotor, primary sensorimotor, and left parietal cortices. Increased activation of the midbrain reticular formation is consistent with the monoaminergic/cholinergic imbalance hypothesis of depression and the reciprocal interaction hypothesis of REM sleep generation. Given the high density of cholinergic innervation of limbic and paralimbic cortex, this model could also explain the increased

activation of limbic and paralimbic cortex during REM sleep in depression. Activation of executive cortex may represent an increased cholinergic drive in REM sleep in contrast to the reduced monoaminergic drive of cortical function in waking in depressed patients. Behaviorally, the increased anterior paralimbic activation may represent increased affective responsivity in depressed patients, similar to the increased responsivity found in the amygdala in response to emotional stimuli. Increased activation of executive cortex may represent a cognitive response to a negative affective state. In general, these studies firmly link the REM sleep insomnia of depression to altered function in limbic, paralimbic and executive cortex.

26.5.3. *Depression: NREM sleep*

In healthy subjects, the most striking changes in brain function from waking to NREM sleep are declines in activity in heteromodal association cortex and in the thalamus. Depressed patients are thought to be 'hyper-aroused', a somewhat vague physiological notion that the central nervous system is in an overactivated state associated with generalized stress and is not able to demodulate itself following removal of stressful stimuli. One way this hyperarousal may manifest itself is a failure of cortical activity to decline normally from waking to NREM sleep. In this general model, two studies to date have assessed regional brain function during NREM sleep in depressed patients. Ho et al. (1996) assessed cerebral metabolism using the [18F] FDG PET method in ten depressed men and 12 healthy men during the first NREM period of the night. They found increased whole brain metabolism during NREM sleep in the depressed subjects. Regionally, these increases were most noticeable in the posterior cingulate, the amygdala, hippocampus, occipital and temporal cortex and the pons. Relative hypofrontality was noted in the patients. They also showed reduced relative metabolism in the anterior cingulate, caudate, and medial thalamus in relation to the controls. On the basis of the increased overall brain metabolism, they interpreted these findings to suggest that depressed patients have hyperarousal.

In order to further clarify the neurobiology of dysfunctional arousal in depression, Nofzinger et al. (2000) assessed the relationship between beta EEG power, an electrophysiological marker of arousal, and regional cerebral glucose metabolism during NREM sleep. Nine healthy subjects and 12 depressed patients

underwent concurrent EEG sleep studies and [18F]2-fluoro-2-deoxy-D-glucose ([18F]FDG) positron emission tomography (PET) scans during their first NREM period of sleep in order to generate hypotheses about specific brain structures that show a relationship between increased beta power and increased relative glucose metabolism. In both healthy and depressed subjects, beta power negatively correlated with subjective sleep quality. Regions that demonstrated significant correlations between beta power and relative cerebral glucose metabolism in both the healthy and depressed subjects included the ventromedial prefrontal cortex. Given functional links between this region and structures known to participate in arousal, they suggested that the ventromedial prefrontal cortex may have abnormally elevated function in depressed patients and that this elevation may thereby influence general cortical arousal in this disorder.

26.5.4. Depression: sleep deprivation

The notion of hyperarousal in paralimbic structures in depressed patients has received further support from an extensive literature describing the functional neuroanatomical correlates of the antidepressant response to sleep deprivation in depressed patients. These studies identify the anterior cingulate cortex as playing an important role in the response to sleep deprivation. Across studies, there is a general tendency for patients who have elevated baseline metabolism in the anterior cingulate cortex to have more favorable responses to sleep deprivation with normalization of this increased function following sleep deprivation (Ebert et al., 1991, 1994; Wu et al., 1992, 1999; Volk et al., 1997; Smith, et al., 1999, 2002).

26.5.5. Summary of functional neuroimaging findings during sleep in depression

These functional neuroimaging findings suggest that the alterations in REM and NREM sleep found in depressed patients may reflect abnormally increased function in limbic and paralimbic structures including the anterior cingulate cortex and reduced function in the prefrontal cortex. Future studies are needed to clarify the relationships between altered function in these structures and the behavioral changes in depressed patients as well as the altered neuropsychopharmacology in this disorder. Future studies are also needed to clarify whether the insomnias associated with other psychiatric disorders also reflect

altered function in brain structures that regulate mood and cognitive function.

26.6. Brain behavior model of psychiatric insomnia

Figure 26.1 provides a general conceptual model for understanding the psychiatric insomnias based on the EEG and functional neuroanatomic sleep studies in healthy subjects and in patients with psychiatric disorders. In this model there are three interconnected neural systems that interact in producing the insomnia complaints of psychiatric patients: an arousal system, an emotion system and a cognitive system. These three systems have anatomical and functional overlaps. The arousal system includes components of the ascending reticular activating system originating in the brainstem as well as the hypothalamic and basal forebrain structures previously implicated in the production of wake or sleep periods globally. The emotion system includes primary limbic and anterior paralimbic structures such as the amygdala, the hippocampus, the ventral striatum and components of the anterior cingulate and ventral prefrontal cortex. The cognitive system includes neocortical structures involved in attention, memory and goal-directed thinking. Psychiatric patients are proposed to have disturbances in systems that control emotional and cognitive behavior that are unique to the psychiatric

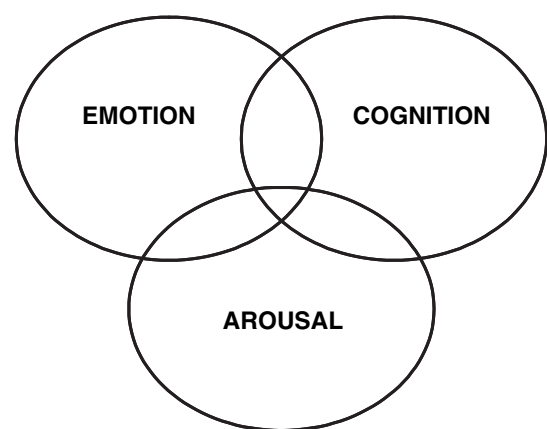


Fig. 26.1. Conceptual model for understanding psychiatric insomnias. Interacting neural systems in the development of insomnia. Arousal, ascending reticular activating system, hypothalamus/basal forebrain. Emotion, hippocampus, amygdala, ventral striatum, anterior cingulate cortex. Cognition, thalamocortical networks, especially prefrontal cortex.

disorder. These alterations interact with the arousal system in producing the generalized complaints of insomnia. More specific EEG alterations within NREM and REM sleep are thought to be subserved by limbic and paralimbic systems (most active in REM sleep) and by the prefrontal cortex (associated with slow-wave sleep abnormalities).

26.7. Summary

This review of the psychiatric insomnias demonstrates that disturbed sleep is among the more common symptoms of patients with psychiatric disorders. EEG sleep studies provided early evidence that these disruptions in sleep were associated with fundamental changes in the neurobiology of these patients. Recent functional neuroimaging studies provide evidence that these disruptions in sleep are related to altered function in brain structures that regulate arousal, emotional and cognitive behavior.

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CHAPTER 27

Circadian rhythm sleep disorders

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27.1. Introduction

All living organisms from single cells to humans display circadian rhythms in their physiology and behavior (Halberg, 1968). In mammals the circadian pacemaker is located in the specific brain region known as the suprachiasmatic nuclei (SCN) (Moore and Eichler, 1972; Stephan and Zucker, 1972; Ralph et al., 1990; Moore, 1997). The circadian pacemaker not only synchronizes biological processes to the external environment, but also maintains the temporal organization of these processes to each other. These self-sustaining endogenous circadian rhythms are genetically regulated and persist in the absence of external time cues with a period of approximately 24 hours (Dunlap, 1999; Hardin, 2000). In humans, light is the strongest synchronizing agent (*zeitgeber*), although non-photic agents such as the rest/activity state and social activity, also play a role in entrainment of circadian rhythms (Aschoff et al., 1971; Turek, 1989).

The cycle of wakefulness and sleep is one of the most obvious and prominent circadian rhythms in humans. Human sleep–wake behaviors are regulated by a complex interaction of endogenous circadian and homeostatic processes of sleep, as well as environmental factors. Evidence for a circadian process regulating sleep initiation and duration was first obtained in temporal isolation studies, suggesting a circadian rhythm of sleep propensity and wakefulness. In humans, daily variation in physiological sleep tendency, assessed by multiple sleep latency tests, reveals a biphasic circadian rhythm of sleep propensity. In

most individuals, there is a mid-day increase in sleep tendency occurring around 2–4 p.m., followed by a robust decrease in sleep tendency and increase in alertness that lasts through the early to mid-evening hours. The primary role of the circadian pacemaker is to promote wakefulness during the day, and thus, facilitate the consolidation of sleep during the nighttime hours (Wever, 1979; Czeisler et al., 1980; Zulley et al., 1981; Dijk and Czeisler, 1994). The timing, duration and architecture of sleep are regulated by this interaction between the homeostatic and circadian processes. Disruption of this complex interaction between the sleep homeostatic process and circadian rhythms results in serious consequences for sleep, performance and health.

27.2. Circadian rhythm sleep disorders

For optimal sleep, the desired sleep time should match the timing of the endogenous circadian rhythm of sleep propensity. Therefore, patterns of sleep disturbance may result from misalignment between the circadian timing system and the 24-hour physical environment and social schedules. These patterns arise when the physical environment is altered relative to the internal circadian timing system, such as in jet lag and shift work, or vice versa, such as in the primary circadian rhythm sleep disorders. In addition to physiological and environmental factors, maladaptive behaviors often influence the presentation and severity of circadian rhythm sleep disorders.

The essential feature of a circadian rhythm sleep disorder (CRSD) is a persistent or recurrent pattern of sleep disturbance due primarily to alterations of the circadian time-keeping system or a misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep. The circadian-related sleep disruption leads to insomnia or excessive daytime sleepiness with impairment in important areas of functioning and quality of life. In

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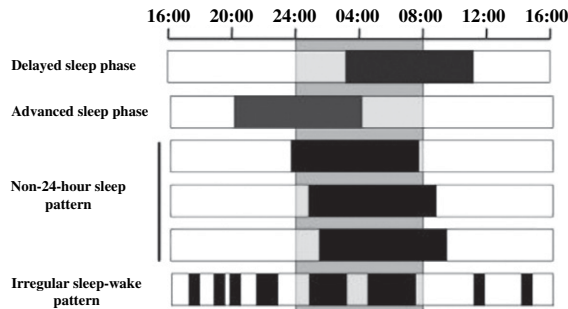


Fig. 27.1. Schematic representation of the primary circadian rhythm sleep disorders. Black bars represent patients' preferred sleep times.

this chapter, only the primary circadian rhythm sleep disorders: delayed sleep phase syndrome (DSPS), advanced sleep phase syndrome (ASPS), irregular sleep–wake pattern, and free-running sleep–wake disorder will be discussed. The general characteristics of these circadian sleep disorders are illustrated in Figure 27.1.

27.3. Circadian rhythm sleep phase disorders

Of the circadian sleep disorders, the most common are the circadian sleep phase disorders, delayed sleep phase syndrome and advanced sleep phase syndrome. In these conditions the timing of the major consolidated sleep period is delayed or advanced in relation to 24-hour clock time. The diagnoses of both DSPS and ASPS are largely based on published clinical criteria from the International Classification of Sleep Disorders (ICSD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR (Michael, 2000); DCSC, 1990). A diagnosis of DSPS or ASPS requires a complaint of inability to fall asleep or to remain asleep at the desired or conventional time. Diagnostic criteria also include an advanced or delayed sleep pattern that is stable and maintained for a minimum period of 3 months. This is to differentiate these conditions from altered phase relationships caused by acute responses to changing work schedules or traveling across time zones.

27.3.1. Delayed sleep phase syndrome (delayed sleep phase type)

Delayed sleep phase syndrome (DSPS) was first described by Weitzman and colleagues, and is characterized by bedtimes and wake times that are delayed 3–6 hours relative to desired or conventional

sleep/wake times (Weitzman et al., 1981). The patient typically finds it difficult to fall asleep before 2–6 a.m. and wake up earlier than 10 a.m.–1 p.m. (Weitzman et al., 1981; Regestein and Monk, 1995). Affected individuals complain of difficulty falling asleep at a socially acceptable time, but once sleep ensues, sleep is reported to be normal. When allowed to follow their preferred schedule, circadian phase of sleep is delayed, but relatively stable. Patients with DSPS often report feeling most alert and active in the late evening and most sleepy in the morning. They typically score as 'evening' types on the Horne and Ostberg questionnaire of diurnal preference and are described as 'night' people, or 'owls' (Horne and Ostberg, 1976). Attempts to fall asleep earlier are usually unsuccessful. Sleep often is extended into the late morning when the individual has no obligations requiring an early wake time, such as on weekends and vacations.

27.3.1.1. Prevalence, course and associated features

DSPS is the most common primary circadian rhythm sleep disorder (Yamadera et al., 1996). Although the true prevalence of DSPS in the general population is unknown (Schrader et al., 1993; Ando et al., 1995), it is more common among adolescents and young adults, with a reported prevalence of 7–16% (Pelayo et al., 1988; Regestein and Monk, 1995). In sleep clinics, DSPS is estimated to account for 5–10% of the chronic insomnia patients (Weitzman et al., 1981). A positive family history may be present in approximately 40% of individuals with DSPS. In one family, DSPS phenotype was shown to segregate as an autosomal dominant trait (Ancoli-Israel et al., 2001). Recent reports of polymorphisms in the circadian clock genes, *hPer3* and *Clock* in DSPS suggest a genetic basis for DSPS (Ebisawa et al., 2001; Iwase et al., 2002; Archer et al., 2003; Hohjoh et al., 2003).

In general, individuals with DSPS seek treatment because enforced socially acceptable bed times and wake up times result in insomnia, excessive sleepiness and functional impairments, particularly during the morning hours (Regestein and Monk, 1995). Attempts to fall asleep earlier may result in prolonged sleep latency and promote the development of issues associated with conditioned insomnia. Individuals may use alcohol, sedative hypnotics and stimulants which may exacerbate their underlying sleep disorder. Social and behavioral factors play an important role in the development and maintenance of the delayed sleep pattern. Personal, social and occupational activities which continue into the late evening may perpetuate

and exacerbate the sleep phase delay. In adolescents, the role of school avoidance, social maladjustment and family dysfunction are often contributing factors.

27.3.1.2. *Pathophysiology*

The exact mechanisms responsible for DSPS are unknown. Based on the fundamental properties of the circadian timing system and sleep regulation, several mechanisms could account for a persistently altered phase relationship between the endogenous sleep/wake rhythm and the desired or conventional times for sleep and wake. First, the persistently delayed phase may be due to an unusually prolonged endogenous circadian period that is too long to make the required daily adjustments to maintain a 24-hour cycle at an appropriate time (Regestein and Monk, 1995). A second possibility is that it may be the result of changes in the entrainment mechanisms of the circadian clock to synchronizing agents, such as light. For example, the advance portion of the phase response curve to light may be abnormally small (Czeisler et al., 1981) or lack of exposure to light in the phase advance region (due to prolonged sleep in the morning) may explain the inability to advance the phase of sleep under normal light–dark cycles (Ozaki et al., 1996). Prolonged sleep and lack of bright light exposure in the early morning acts as a vicious cycle and perpetuates the already delayed schedule. There is evidence that individuals with long free-running periods have a reduced response to morning light (Rufiange et al., 2002), suggesting the possibility of an altered responsiveness to light in DSPS. Therefore, it is likely that not only changes in the free-running period but also entrainment mechanisms of the circadian system contribute to the alteration in the timing of sleep in DSPS.

Although it is commonly accepted that alterations in circadian timing underlie the pathophysiology of DSPS, there is increasing evidence that alterations in the homeostatic regulation of sleep may also play an important role (Uchiyama et al., 1999). Polysomnographic recordings of sleep in DSPS patients showed that sleep architecture was not disrupted after the initiation of sleep when the subject was allowed to sleep until their desired wake time (Weitzman et al., 1981; Thorpy et al., 1988; Alvarez et al., 1992; Uchiyama et al., 1992). However, following 24 hours of sleep deprivation, DSPS patients, when compared to controls, showed a decreased ability to compensate for sleep loss during the subjective day and the first hours of subjective night (Uchiyama et al., 1999, 2000).

These results suggest that poor sleep recovery not only contributes to daytime sleepiness, but also perpetuates the inability of patients with DSPS to advance their sleep phase.

27.3.1.3. *Polysomnographic and other laboratory findings*

Studies of sleep and wake will yield very different results depending on when they are performed. Recordings of sleep diaries and actigraphy over a period of at least 2 weeks demonstrate delayed sleep onset and sleep offset (Figure 27.2). Sleep onset is typically delayed until 1–6 a.m. and wake up time occurs in the late morning or afternoon. Daily demands and schedules may result in an earlier than desired wake up time during weekdays, but a delay in bedtime and wake up time is almost always seen during weekends and while on vacation. Polysomnographic (PSG) parameters of sleep architecture, when performed at the preferred (delayed) sleep times, are essentially normal for age (Weitzman et al., 1981; Thorpy et al., 1988; Alvarez et al., 1992; Uchiyama et al., 1992). However, if a conventional bedtime and wake up time is enforced, PSG recording will show prolonged sleep latency and decreased total sleep time.

Laboratory measures to determine the phase of circadian rhythms, such as core body temperature and plasma or salivary melatonin levels generally show the expected phase delay in the timing of circadian rhythms such as the nadir of the temperature rhythm (Figure 27.2) and dim light melatonin onset (DLMO). The Horne–Ostberg questionnaire is a useful tool to assess the chronotype of ‘eveningness’ and ‘morningness’ (Horne and Ostberg, 1977; Kerkhof, 1985). Individuals with DSPS score as definite evening types.

27.3.1.4. *Treatment*

Treatment approaches for DSPS include chronotherapy, timed bright light exposure in the morning and pharmacotherapy with hypnotics or melatonin. Chronotherapy is a treatment in which the circadian clock is reset by progressively delaying sleep times by approximately 3 hours per day until a final earlier bedtime schedule is achieved and maintained (Weitzman et al., 1981). While effective, the requirement for strict social and professional restrictions and the prolonged duration of treatment limit its practicality and acceptability in the clinical setting. Moreover, several DSPS patients following chronotherapy treatment developed non-24-hour sleep–wake syndrome (Oren and Wehr, 1992).

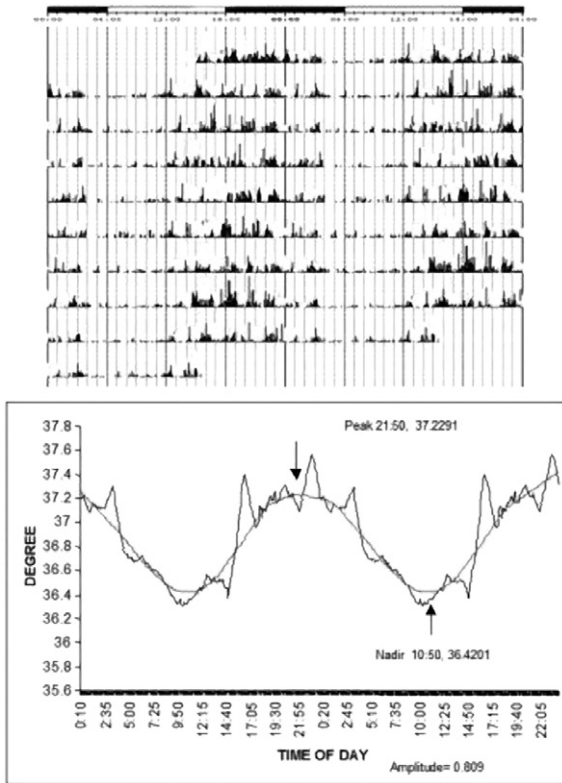


Fig. 27.2. Sleep/wake (as recorded by actigraphy) and core body temperature rhythm in a patient with delayed sleep phase syndrome. The upper panel is actigraphy data (double plotted) showing a stable and persistent delay in the phase of sleep onset (03:30–04:00) and offset (12:00). The lower panel shows the core body temperature rhythm showing a nadir or minimum at 10:50, which is approximately 5 hours delayed compared to an individual with a normal circadian phase.

One of the most widely used treatments for DSPS is timed bright light therapy (Chesson et al., 1999). Exposure to bright light at different times of the day can reset the human circadian clock (Lewy, 1983; Lewy et al., 1984; Czeisler et al., 1986, 1989). Exposure to bright light for 1–2 hours in the morning results in an advance of the phase of circadian rhythms, whereas evening light exposure causes phase delays. In one study, the combination of morning bright light exposure and evening light avoidance was effective in the treatment of DSPS (Rosenthal et al., 1990). After 2 weeks of receiving 2 hours of bright light of 2500 lux intensity each morning and restricted evening light, the body temperature rhythm advanced, reported sleep times were earlier, and subjects reported feeling more alert in the morning (Rosenthal

et al., 1990). However, in patients who are severely delayed, it may be difficult for them to awaken early enough for bright light exposure (Thorpy et al., 1988; Regestein and Monk, 1995). The need to awaken at an earlier time combined with the structuring of social and professional activities around the light exposure limit compliance with bright light therapy. Although timed bright light appears to have potential utility, the timing, intensity and duration of treatment remain to be defined. With the availability of units that emit light in the blue-green spectrum, the duration and intensity of phototherapy may be decreased and thus may improve its efficacy.

Due to the limitations of chronotherapy and phototherapy, melatonin, taken orally in the evening, has been increasingly investigated. Administration of the hormone melatonin at different times of the day can also reset the circadian clock in humans (Lewy et al., 1992). Several studies have demonstrated the potential effectiveness of melatonin administered in the evening (James et al., 1990; Dahlitz et al., 1991; Oldani et al., 1994; Nagtegaal et al., 1998). However, because the timing of administration and dose varied between studies, from a fixed time in the evening to a few hours before sleep time, a standardized approach for the timing of melatonin administration or dose is not available. Thus, the treatment of DSPS with melatonin remains somewhat empirical. There is agreement that treatment should be individualized to increase the chance of its success. Moreover, that success depends on many variables including severity of the disorder, co-morbid psychopathology, ability and willingness of the patient to comply with the treatment, school schedule, work obligations and social pressures (Thorpy et al., 1988; Ohta et al., 1992; Regestein and Monk, 1995). A summary of treatment approaches of DSPS is shown in Figure 27.3.

27.3.2. Advanced sleep phase syndrome (advanced sleep phase type)

Advanced sleep phase syndrome (ASPS) is a sleep disorder in which there is a stable advance of the major sleep period, characterized by habitual and involuntary sleep onset and wake-up times that are several hours earlier relative to conventional and desired times (Figure 27.1). Individuals with ASPS usually report sleep onset of 6–9 p.m. and wake time of 2–5 a.m. (Moldofsky et al., 1986; Kamei et al., 1998). ASPS complaints include early-morning awakenings, sleep maintenance insomnia, and also of sleepiness in the

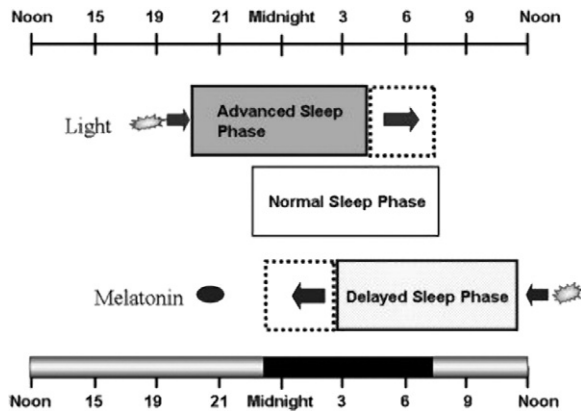


Fig. 27.3. Schematic representation of treatment approaches for ASPS and DSPS. Bright light exposure in the evening (usually 7–9 p.m., but exact timing will depend on timing of the phase of the individual's circadian phase) advances circadian rhythms which may be useful in patients with ASPS, whereas, light in the early morning (usually 6–8 a.m.; timing dependent on the individual's circadian phase) will delay circadian rhythms and therefore useful in patients with DSPS. Melatonin in the evening, approximately 5 hours before habitual sleep time has also been used in DSPS.

late afternoon or early evening. Individuals with ASPS typically consider themselves 'larks' and score as morning types on the Horne–Ostberg questionnaire (Horne and Ostberg, 1976).

27.3.2.1. Prevalence, course and associated features

The actual prevalence of ASPS is estimated to much lower than DSPS (Schrader et al., 1993; Ando et al., 1995; Baker and Zee, 2000). ASPS not associated with aging, is probably rare, with only a few reported cases (Moldofsky et al., 1986; Jones et al., 1999; Reid et al., 2001). ASPS is more common among middle-aged and older adults, with an estimated prevalence of 1% of middle-aged adults (Ando et al., 1995). Several familial cases of advanced sleep phase pattern have been identified (Jones et al., 1999; Reid et al., 2001). In all of the families, the trait segregated with an autosomal dominant mode of inheritance. A mutation in the circadian clock gene *hPer2* was localized in a large family with advanced sleep phase syndrome (Toh et al., 2001). In addition to genetic factors, the prevalence and the risk of developing an advanced sleep pattern clearly increase with age. However, it is not known whether the commonly seen age-associated advance in sleep and wake times is the same entity as ASPS in younger individuals.

27.3.2.2. Pathophysiology

Although the precise mechanisms underlying the pathophysiology of ASPS are unknown, it has been postulated that alteration in the interaction between the endogenous circadian rhythm and the sleep homeostatic processes that regulate sleep and wakefulness play an important role. Based on the principles of circadian rhythm regulation, several mechanisms, such as an unusually short endogenous circadian period, that is less than 24 hours (Jones et al., 1999), alterations in the ability of the circadian clock to phase delay due to a dominant phase advance region of the phase response curve to light, decreased exposure or weakened response to entraining agents such as light and physical activity (Ancoli-Israel and Kripke, 1991; Moore, 1999; Naylor et al., 2000) may result in an advanced sleep phase.

27.3.2.3. Polysomnographic and other laboratory findings

Sleep studies yield different results depending on when they are performed. Recording of sleep diaries and actigraphy over a period of at least 2 weeks can be useful and demonstrate sleep onset and sleep offset that are advanced relative to conventional times (Figure 27.2). Sleep onset is typically advanced 6–9 p.m., and wake times between 2–5 a.m. Polysomnography studies when performed at the preferred sleep times (advanced) are essentially normal for age. However, if conventional bedtime and wake times are enforced, the PSG recording may show decreased sleep latency, decreased total sleep time and moderately short REM sleep latency. Laboratory measures to determine the phase of circadian rhythms such as core body temperature and plasma or salivary melatonin levels generally show the expected phase advance in the timing of the nadir of the temperature rhythm and dim light melatonin onset (DLMO). However, wake up time may be more advanced relative to these circadian markers. The Horne–Ostberg questionnaire is a useful tool to assess the chronotype of 'eveningness' and 'morningness'. Individuals with advanced sleep phase score as definite morning types (Reid et al., 2001).

27.3.2.4. Treatment

Treatment approaches for ASPS may include chronotherapy, pharmacotherapy with hypnotics or melatonin and timed bright light exposure in the evening. Chronotherapy was one of the earliest treatment approaches proposed for ASPS (Moldofsky et al.,

1986). In this study, attempts to delay the sleep times of the ASPS patients were unsuccessful and only a 3-hour advance in sleep time every 2 days allowed the individual to shift to the desired later sleep schedule.

As with DSPS, the most commonly used treatment is timed bright light therapy for 2 hours in the evening, usually between 7–9 p.m. (Campbell et al., 1993; Lack and Schumacher, 1993; Lack and Wright, 1993). In these studies, bright light exposure improved sleep efficiency and delayed the phase of circadian rhythms, but patients had difficulty maintaining treatment (Campbell, 1999).

As noted earlier, melatonin has circadian phase re-setting properties and theoretically may be useful in delaying the phase of circadian rhythms and sleep in ASPS. However, there are very few data of its usefulness in the treatment of ASPS. Based on the phase response curve to melatonin, in order to delay circadian rhythms, the timing of melatonin administration should be in the early morning. The sedative effects of melatonin and the timing of administration may make melatonin impractical for the treatment of ASPS. A summary of the treatment approaches for ASPS is shown in Figure 27.3.

27.4. Free-running Type (Non-24 hour, Hypernycthermal Syndrome)

Free-running circadian rhythm sleep disorder is characterized by a steady daily drift of the major sleep period in which the intrinsic circadian pacemaker is free-running with a period that is usually longer than 24 hours (Figure 27.1). In individuals who attempt to maintain a conventional sleep and wake schedule, symptoms of insomnia and excessive daytime sleepiness occur periodically when the non-entrained circadian pacemaker is out of phase with desired sleep and wake times. When the timing of endogenous circadian rhythms is in phase with the desired and conventional sleep times, sleep is usually normal and some individuals adopt a sleep pattern in which their sleep times each day delay by 1–2 hours.

The diagnosis of a free-running circadian period requires that the periodic disturbances of sleep and wakefulness can be related to a free-running circadian rhythm of sleep and wake propensity (not entrained to the 24-hour physical environment) and associated impairment of social, occupational or other areas of functioning. The patient has periodic complaints that can switch from insomnia to early morning awakenings to excessive daytime sleepiness (DSM IV-TR).

The pattern should be present for at least 2 months and no other medical, mental or sleep disorder can be identified that better explains the altered sleep pattern (DSM IV-TR).

This circadian rhythm sleep disorder is most commonly seen in blind people who lack photic entrainment (Elliott et al., 1971). It has been rarely reported in sighted individuals living in normal society (Weber et al., 1980). It has been estimated that about 50% of the totally blind have free-running circadian rhythms (Sack et al., 1992) and that approximately 70% have complaints of chronic sleep disturbances (Miles et al., 1977; Martens et al., 1990).

Sleep studies yield different results depending on when the study is performed. Actigraphy and sleep logs recorded over 2–4 weeks may demonstrate the progressive drift in the timing of sleep and wake times and the lack of stable entrainment of the sleep–wake cycle to the 24-hour physical environment. During the time periods when sleep schedules are in synchrony with the endogenous circadian propensity for sleep and wake, actigraphy and polysomnography are usually normal for age, but sleep and wake times are typically delayed each day. Serial measurements of a circadian marker rhythm such as dim light melatonin onset (DLMO) or nadir of the core body temperature rhythm may be used to confirm the diagnosis by demonstrating a free-running circadian rhythm (Klein et al., 1993).

27.4.1. Pathophysiology

The intrinsic period of the human circadian pacemaker is near, but longer than, 24 hours and requires regular input from the environment to maintain synchrony to the 24-hour day (Czeisler et al., 1999). The light–dark cycle is probably the most important zeitgeber in humans. Therefore, in blind people, the lack of photic entrainment of the circadian pacemaker is the most likely cause of the free-running circadian rhythm of sleep and wake. However, not all blind people have free-running circadian rhythms. In these individuals, non-photic inputs such as social likely play a role in the entrainment of circadian rhythms. In addition, despite their lack of light perception, there is evidence that the circadian pacemaker of some blind individuals responds to bright light (Czeisler et al., 1999).

In sighted individuals the etiology is unclear. It has been postulated that individuals with free-running circadian sleep disorder may have an extremely pro-

longed endogenous circadian period that is beyond the range of entrainment to the normal 24-hour day (Uchiyama et al., 2002). In fact, it has been postulated that free-running circadian sleep disorder may be a severe form of DSPS (Regestein and Monk, 1995). Supporting this hypothesis are case reports of DSPS patients who developed a free-running pattern after chronotherapy (Oren and Wehr, 1992). Other possibilities include a decreased sensitivity of the circadian clock to light or alteration in the entrainment pathways, resulting in weakened entrainment or lack of entrainment of the endogenous circadian rhythm (McArthur et al., 1996). Non-24 hour sleep disorder has also been reported following brain injury (Boivin et al., 2003).

In blind people, timed exposure to non-photic circadian synchronizing agents such as melatonin and maintenance of regular schedules of sleep and work have been successful strategies for the treatment of free-running circadian sleep disorders. Melatonin, typically given 1 hour before bedtime, has shown to be effective (Sack et al., 2000). A recent study has shown that 10 mg of melatonin at night could entrain most blind individuals, and in some this entrainment could be maintained with a gradual reduction to just 0.5 mg at night (Lewy et al., 2001). Much less is known regarding the treatment in sighted individuals. Increasing the strength of the light–dark cycle with bright light exposure and/or melatonin to entrain circadian rhythms may be useful. There has been also been a case report of the successful treatment of free-running sleep and wake rhythms with flurazepam and vitamin B12 (Kamgar-Parsi et al., 1983).

27.5. Irregular Sleep–Wake Sleep Pattern (No Circadian Rhythm, grossly disturbed sleep wake rhythm, low amplitude circadian rhythm)

Irregular sleep–wake type is characterized by lack of a clearly defined circadian rhythm of sleep and wake. The sleep–wake pattern is temporally disorganized, so that sleep and wake periods are variable throughout the 24-hour period. Individuals with irregular sleep–wake pattern typically take multiple ‘naps’, usually three or more, throughout the day (Figure 27.1).

Diagnosis of irregular sleep–wake type requires a complaint of insomnia and/or excessive sleepiness associated with multiple irregular sleep bouts (at least three) during a 24-hour period. Total sleep time per 24-hour period is essentially normal for age (DSM IV-

TR 2000 and ICSD 1990). Continuous monitoring with polysomnography (at least a 24-hour recording) or actigraphy for a minimum of 2 weeks show disturbed or low-amplitude circadian rhythm with loss of the normal diurnal sleep–wake pattern. Actigraphy and polysomnography (for at least 24 hours) may aid in diagnosis by showing a disturbed or low-amplitude sleep–wake pattern without a distinct circadian rhythm. Poor sleep hygiene and voluntary maintenance of irregular sleep schedules as seen with shift work and frequent transmeridian travel can mimic irregular sleep–wake pattern.

The prevalence of irregular sleep–wake pattern in the general population is rare (Yamadera et al., 1996). It is most frequently seen in association with neurological dysfunction, such as head trauma and children with psychomotor retardation where a low-amplitude or irregular rhythm of sleep–wake pattern may be seen (Witting et al., 1990). An irregular sleep–wake pattern has been reported in patients with neurodegenerative disorders, such as dementia (Edgar et al., 1993; Hoogendijk et al., 1996).

In certain populations, like the institutionalized elderly, lack of exposure to these external synchronizing agents such as light and social schedules may act as predisposing as well as precipitating factors in the development of irregular sleep–wake pattern (van Someren et al., 1996; Pollak and Stokes, 1997). Therefore both dysfunction of circadian regulation and weakened synchronizing agents likely contribute to the development and maintenance of irregular or arrhythmic sleep and wake patterns.

Treatment approaches have been aimed at increasing exposure to synchronizing agents, such as bright light and social and physical activity to enhance circadian rhythms and thus consolidate sleep and wake cycles in individuals with irregular sleep–wake pattern (Van Someren et al., 1999; Naylor et al., 2000; Ancoli-Israel et al., 2001). In the elderly with dementia, programs of structured activities and increased social interaction have been shown to consolidate sleep and wake (Okawa et al., 1991). Several studies have shown that increased light exposure during the day can improve circadian rhythms and consolidate sleep (Van Someren et al., 1999; Ancoli-Israel et al., 2002).

In one study, 45% of patients with irregular sleep cycles responded to treatment with bright light, chronotherapy, vitamin B12 and hypnotics (Yamadera et al., 1996). In children with psychomotor retardation, evening administration of melatonin may

improve sleep and wake patterns (Pillar et al., 2000). Despite the potential utility of the various pharmacological and behavioral interventions, treatment is often difficult and results variable.

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CHAPTER 28

Headaches and sleep disorders

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28.1. Introduction

Headache and sleep disturbances are among the most common neurologic complaints. The intermittent nature of both sleep and almost all headache syndromes suggests the possibilities that sleep might affect headaches and headaches affect sleep. In fact complex interactions do occur, although the mechanisms involved have not been well delineated to date. Several classifications of these relationships have been suggested (Sahota and Dexter, 1990; Jennum and Jensen, 2002; Dodick et al., 2003). A logical, empiric approach is to consider headache as the result of disturbed nocturnal sleep, headache resulting in a disturbance of nocturnal sleep, and headache syndromes intrinsically related to sleep by common anatomic, biochemical and physiologic mechanisms (Dodick et al., 2003). These relationships will be explored by considering specific headache syndromes and the complex topic of the possible association of headaches and sleep-disordered breathing.

28.2. Migraine

Migraine is characterized by recurrent unilateral, often pulsating, headaches, worsened by physical activity and associated with nausea, photophobia and phonophobia. The headaches may be preceded by sensory auras, usually visual, in which case the syndrome is referred to as migraine with aura. If auras are absent, the condition is named migraine without aura. Migraine is more common in women than in men and generally commences before the age of 30 years. A family history of the disorder is usually present.

Current concepts of migraine pathogenesis suggest that the syndrome occurs as a result of hypothalamic or limbic dysfunction, which activates the trigeminovascular system. The relationship between migraine and sleep is complex. Migraine may arise from sleep, possibly with greater frequency during or after rapid eye movement (REM) sleep. Paradoxically, the headaches may be relieved by sleep. Migraine may result in disturbance of sleep architecture, efficiency and continuity. There also appears to be a relationship between migraine and disorders of arousal such as sleep walking.

Migraine headaches may originate during the day or the night and in some patients sleep seems to precipitate attacks. Five patients with migraine without aura who reported that more than 75% of their naps would result in a headache were allowed to nap at 1 p.m. for up to 2 hours for 3–5 consecutive days (Dexter, 1979). Eight of 17 naps resulted in arousals associated with headaches, which only occurred if the patient had entered slow-wave or REM sleep. Four patients with a history of migraine without aura arising from nocturnal sleep were studied for a total of 29 nights (Dexter, 1979). Migraine was common in the morning following nights with higher quantities of slow-wave or REM sleep. Three patients with nocturnal headaches due to migraine without aura underwent polysomnography (PSG) (Dexter and Weitzman, 1970). Six headaches arose from REM sleep, and two within 9 minutes of termination of REM sleep.

Sleep may help migraine resolve. Fifty-six percent of 50 patients with migraine reported their headaches resolving after a night's sleep and 28% following a daytime nap lasting 30 minutes to 6 hours (Blau, 1982). In a series of 310 patients attending an acute headache clinic, those who slept during an attack (the majority with the help of a sedative) recovered more quickly than those who did not (Wilkinson et al., 1978).

Migraine may result in disturbances of sleep. A questionnaire study of 164 children aged 5–14 years

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compared to 893 controls showed that patients with migraine had decreased sleep duration, increased sleep latency, poorer sleep quality and more sleep interruptions. Children with migraine reported more sleepiness during the day (Bruni et al., 1997). In a PSG study of 26 patients with migraine complicated by chronic daily headaches from ergot or analgesic abuse, withdrawal of medication resulted in fewer headaches. Total sleep time increased, sleep efficiency rose and the number of nocturnal arousals fell (Hering-Hanit et al., 2000).

A consistent link between migraine and sleepwalking has been noted in several studies. Thirty percent of 60 children with migraine had a history of sleep walking compared to less than 7% of 162 children with other headaches, seizures or other neurologic disorders (Barabas et al., 1983). In a study of 150 adults with migraine, 22% reported a history of sleep walking compared to 7% of 150 controls with allergies (Pradalier et al., 1987). Sleep walking was reported in 55% of 100 migraine patients compared to 16% of controls with neurologic disease (Dexter, 1986). Sleepwalking was found to be more frequent in children with migraine with aura (13%) compared to controls, but not in children with migraine without aura (3%) (Bruni et al., 1997). A history of rhythmic movement disorder was also more frequent in the group with migraine compared to controls (Bruni et al., 1997).

The mechanisms for these intriguing associations between sleep and migraine have not been determined; electrical activity of the serotonergic raphe nuclei decreases in sleep and ceases during REM sleep. Serotonin is depleted during migraine attacks and this may be a possible mechanism whereby sleep predisposes to headache episodes (Silberstein, 1994). Various lines of evidence also suggest that the anterior hypothalamus may play a role in migraine pathogenesis. It has been speculated that the suprachiasmatic nuclei may be involved, producing a possible link between the disorder and circadian abnormalities (Zurak, 1997; Dodick et al., 2003).

28.3. Tension-type headache

Tension-type headaches are usually bilateral, non-pulsating headaches not associated with nausea, photophobia, sonophobia or autonomic hyperactivity. They may be occipital, frontal or generalized and often have a dull, pressure-like quality. Despite being the most common type of headache, few studies of sleep and tension-type headaches have been performed.

An ambulatory PSG study without respiratory monitoring of ten patients with tension-type headaches, ten with migraine and ten with mixed tension-vascular headaches has been reported (Drake et al., 1990). The groups with tension type or mixed headaches showed decreased total sleep time, increased sleep latency and increased wake time after sleep onset. Slow-wave sleep time was reduced in the tension-type headache group. A questionnaire study of 119 children with tension-type headaches compared to 893 controls revealed decreased sleep duration, increased sleep latency, poor sleep interrupted by awakenings and a history of falling asleep in school in the headache group (Bruni et al., 1997). Minimal data are available on accompanying sleep disorders of patients with tension-type headaches. Five patients complaining of nocturnal or early morning tension-type headaches underwent PSG; two were found to have OSAS (Paiva et al., 1995).

28.4. Cluster headache

Cluster headaches consist of excruciating bouts of unilateral face or head pain usually lasting 1–2 hours and recurring about one to three times a day. Autonomic accompaniments include unilateral nasal congestion, conjunctival injection, miosis and ptosis, but nausea is uncommon. Episodic cluster headaches occur in bouts lasting several months and then remit for months to years, while chronic cluster headaches continue for several years without remission. The disorder occurs more commonly in men and associated factors include tobacco and alcohol use. The pathogenesis of cluster headache involves activation of the parasympathetic and trigeminovascular systems.

More than 50% of patients with cluster headaches report that they occur either frequently or entirely during the night (Kudrow et al., 1984). PSG studies have shown that episodic cluster headaches appear to be frequently associated with REM sleep. Both patients studied in one report had headaches arising from REM sleep (Manzoni et al., 1981), while nine headaches recorded from three patients with episodic clusters all either arose from REM sleep or within 5 minutes of termination of a REM sleep period (Dexter and Weitzman, 1970). In contrast, 25 attacks from nine patients with chronic cluster headache were recorded by PSG (Pfaffenrath et al., 1986). Twelve percent of headaches arose from wakefulness, 16% from stage 1, 44% from stage 2 and 8% from stage 3 NREM sleep. Only 20% arose from REM sleep.

A relationship exists between cluster headaches and sleep-disordered breathing. Cluster headaches associated with REM-sleep-related obstructive sleep apnea syndrome (OSAS) resolved in one patient with the use of bilevel positive airway pressure (Buckle et al., 1993). In an uncontrolled study of 25 patients with predominantly episodic cluster headache, 80% had an apnea-hypnea index (AHI) >5 per hour (Chervin et al., 2000). PSG on five patients with episodic and five with chronic cluster headaches selected without attention to sleep symptoms revealed an AHI of >5 per hour in all the patients in the episodic group and one in the chronic group (Kudrow et al., 1984). Oxyhemoglobin desaturation preceded headache onset in 57% of the recorded attacks in the group with sleep-disordered breathing. Fifty-three percent of all attacks were associated with REM sleep, equally in the groups with and without sleep apnea. Sixteen patients underwent PSG during headache clusters and were compared to 29 age- and body-mass-index-matched controls (Nobre et al., 2003). Thirty-one percent of the patients had AHI greater than 5 per hour, compared to 10% of the controls ($P = 0.08$). Two headache attacks were recorded during the study, both occurring out of REM sleep at times of oxyhemoglobin desaturation. Cluster headaches improved in two patients treated with nasal continuous positive airway pressure.

The data suggest that both the state of REM sleep and sleep-disordered breathing may be separate factors that can trigger attacks in patients susceptible to cluster headaches. In support of hypoxemia being a precipitating factor is the excellent effect of high-flow oxygen in terminating attacks. It has been postulated that there may be abnormal chemoreceptor sensitivity in the carotid bodies in cluster headache patients and that hypoxemia might then result in a hyperactive chemoreceptor response (Kudrow, 1983). Clinically, a history of snoring, observed apneas and excessive daytime sleepiness should be elicited from all cluster headache patients and PSG performed if there is a sufficiently strong suspicion of sleep-disordered breathing.

Melatonin has been used as a prophylactic agent for the prevention of cluster headaches. In a double-blind parallel trial, 20 patients received either 3 mg melatonin or placebo for 2 weeks (Leone et al., 1996). Headache frequency significantly fell in the group treated with melatonin with 50% of the patients responding. Another patient with cluster headaches and delayed sleep phase syndrome reported resolution of the headaches with 5 mg melatonin taken 5 hours

before dim light melatonin onset (Nagtegaal et al., 1998). These observations might suggest a circadian factor in cluster headache pathogenesis but there are other perhaps more likely explanations for the efficacy of melatonin (Nagtegaal et al., 1998; Dodick et al., 2003). Melatonin inhibits the synthesis of prostaglandin E₂ which activates sterile perivascular inflammation in the trigeminovascular system. It raises the threshold of gamma aminobutyric acid mediated central pain pathways and modulates cerebral arterial tone.

28.5. Chronic paroxysmal hemicrania

This headache occurs predominantly in women and may be a variant of cluster headache. Attacks are also unilateral but last a shorter period (10–20 minutes) and may recur more frequently over the course of a day. A classic diagnostic feature differentiating them from cluster headaches is their dramatic response to treatment with indomethacin. The pathogenesis is uncertain.

A PSG study in a single patient with chronic paroxysmal hemicrania has been reported (Kayed et al., 1978). Over four nights, 18 attacks were recorded with 17 occurring out of REM sleep. No respiratory monitoring was performed.

28.6. Hypnic headaches

Hypnic headaches are headaches occurring in middle-aged or older patients that result in awakening from sleep at a fairly constant time (Raskin, 1988; Morales-Asin et al., 1998). Eighty-four percent of a series of 19 patients were women and the average age of onset was 60.5 years (range 40–73) (Dodick et al., 1998). The headaches are usually bilateral, but may be unilateral in a third of patients (Gould and Silberstein, 1997; Dodick et al., 1998). They are most frequently frontal but may be diffuse. They generally last 30–60 minutes but can be present for more than 2 hours. A minority of patients will have nausea but no other autonomic symptoms or photophobia. Other headache types may be present in up to a half of patients, most commonly migraine without aura (Dodick et al., 1998). Hypnic headaches differ from cluster headache and chronic paroxysmal hemicrania with respect to their duration, location, lack of association with autonomic symptoms and occurrence only at night.

PSG studies have been reported in seven patients with hypnic headaches with the typical headache

occurring during the study in four of these. In three the headache arose out of REM sleep (Dodick, 2000; Evers et al., 2003), including one patient who had four headaches over three nights of PSG (Evers et al., 2003). In one patient the headache arose from stage 3 non-rapid eye movement (NREM) sleep (Arjona et al., 2000). One of these patients had severe obstructive sleep apnea syndrome with a mean oxyhemoglobin saturation of 69.5% in REM sleep out of which the headache arose. Treatment with nasal CPAP resulted in resolution of the headaches (Dodick, 2000). Another patient had a few episodes of 'decreased oxygenation' to a minimum of 85%, but the headache occurred at a time of normal oxyhemoglobin saturation (Evers et al., 2003). The other five patients studied did not have significant sleep-disordered breathing. Thus, similar to other headache syndromes such as migraine, cluster headache and chronic paroxysmal hemicrania, hypnic headaches have a predilection for REM sleep. However, REM sleep is not essential for their occurrence. Some hypnic headaches may be related to hypoxemia from obstructive sleep apnea syndrome, but the majority of patients studied to date appear to have an idiopathic headache syndrome.

Various forms of treatment have been used successfully in hypnic headache, but no controlled trials have been reported. Caffeine before bed in the form of a cup of coffee or 40–60 mg tablet was helpful in four of six patients (Dodick et al., 1998). Indomethacin can be effective (Ivanetz et al., 1998) but may induce daytime headaches (Dodick et al., 2000). Lithium (Vieira-Dias and Esperanca, 2001), flunarizine (Raskin, 1988) and atenolol (Dodick et al., 1998) have also been used prophylactically.

28.7. Sleep deprivation headaches

Can headaches be caused by sleep deprivation? There is a single study of 25 subjects, selected by the investigator from colleagues, students and acquaintances, who answered affirmatively to the question whether they experienced headache on missing sleep (Blau, 1990). The total number of subjects questioned is not stated. Seventy-six percent were women. Sleep loss reported to cause headache varied between 1 hour on a single night and more than 3 hours on three successive nights. The majority of headaches were frontal, described as an ache or dull heavy pain. The pain persisted for variable times, ranging from 1 hour to all day unless sleep was obtained or over-the-counter analgesics ingested. Eight-four percent experienced

other additional headaches, including 32% with migraine. The mechanism by which sleep deprivation can cause headaches is undetermined.

28.8. Headaches and Sleep-Disordered Breathing

As discussed above, there appears to be a relationship in some patients between cluster or hypnic headache and sleep-disordered breathing. It has long been believed that early morning headache in general is a symptom of obstructive sleep apnea syndrome. This dogma has been investigated in a number of studies comparing patients with snoring and sleep apnea syndrome to control groups consisting of normal subjects, snorers and those with other sleep disorders.

In a population-based study of 3323 men, headache was more common in self-reported snorers than in non-snorers with an odds ratio of 1.5 (95% confidence intervals (CI) 1.3–1.8) (Jennum et al., 1994). In a similar study, the odds ratio of having early morning headache in heavy snorers compared to controls was 7.9 (CI 3.5–18) in men and 5.8 (CI 3–11) in women (Ulfberg et al., 1996). Early morning headache appeared more frequent in elderly women who snored compared to those who did not (Thoman, 1997). Habitual snoring was more frequent in a group of 206 chronic daily headache patients compared to 507 patients with infrequent headaches (Scher et al., 2003). A retrospective study of 304 patients with OSAS revealed early morning headaches in 18%, but in only 6% of 65 normal controls (Aldrich and Chauncey, 1990). In a prospective study, early morning tension-type headaches were reported in the sleep laboratory by 25% of patients with OSAS compared to 3% of normal controls (Goder et al., 2003).

When, however, patients with OSAS are compared to control groups of patients with snoring or other sleep disorders, the results are strikingly different. The frequency of early morning headache was statistically identical in 164 patients with AHI of 15 or higher (19%) and 148 snorers with AHI less than 15 (16%) (Neau et al., 2002). In a study of 72 patients with OSA, 28 with periodic limb movements of sleep and 42 with psychophysiologic insomnia, about a quarter of each group reported early morning headache (Poceta and Dalessio, 1995). The percentage of 152 OSAS patients reporting tension-type headaches on waking in the sleep laboratory was not statistically different from the percentage of 280 patients with other sleep disorders (Goder et al., 2003).

One retrospective study has shown different results. An interviewer blinded to the patients' sleep disorders obtained a detailed headache history from 80 consecutive patients with OSAS and 22 patients with periodic limb movement disorder. Similar percentages of patients in the two groups gave histories of migraine and tension-type headaches (Loh et al., 1999). However, 29% of the OSAS group and none of the control group described awakening headaches not classifiable into specific diagnostic criteria of the International Headache Society. These headaches lasted less than 30 minutes in 39% of patients and were either holocephalic or occurred in the frontal or occipital regions. Taking into the account the nature of the headache may have resulted in different results from other studies.

Uncontrolled studies of treatment of OSAS suggest that headaches may improve in some patients. Seven of 14 patients with OSAS reported moderate or marked improvement in their early morning headaches (Poceta and Dalessio, 1995). Seventy-one percent of 36 patients treated for OSAS reported relief or marked improvement in headaches after a few weeks (Neau et al., 2002). Marked improvement in awakening headaches was reported by 80% of 29 patients with OSAS (Loh et al., 1999). No data are available regarding relief of headaches in patients with sleep disorders other than OSAS.

A number of hypotheses have been suggested to explain the occurrence of headaches in patients with sleep-disordered breathing. These include hypoxemia, vasodilatation related to hypercapnia, transient increase in intracranial pressure, disturbances of cerebral autoregulation and bruxism (Neau et al., 2002). However, studies have failed to establish a relationship between severity of sleep-disordered breathing and morning headaches. In a study of 212 patients with various grades of sleep-disordered breathing, multivariate analysis showed no differences between AHI or mean nocturnal oxyhemoglobin saturation in patients with and without headache, but a significant increase in a depression index in the headache group (Neau et al., 2002). Of 161 patients with moderate or severe OSA, there was no difference between the AHI and the minimum oxyhemoglobin saturation in the groups with and without frequent headaches (Aldrich and Chauncey, 1990). Twenty-nine patients with OSAS who reported waking with headaches were compared to 87 without early morning headaches (Greenough et al., 2002). The only significant differences were that headaches were more common in

women and the percentage of REM sleep was lower in the headache group. There was no difference between AHI, time spent with oxyhemoglobin saturation below 90% or depression scale scores in the two groups. Thirteen patients with OSAS reported early morning headache on only one of two nights spent in a sleep laboratory. The AHI and mean oxyhemoglobin saturation were not significantly different on the two nights, but sleep latency was prolonged, and sleep efficiency, total sleep time and percentage REM sleep lower on the night preceding the headache (Goder et al., 2003).

Thus it appears that headaches may be more associated with sleep fragmentation and emotional factors than disturbed respiratory function. This explanation would also explain the high frequency of headaches found in sleep disorders other than OSAS. It does not rule out the possibility that hypoxemia or hypercapnia may be an important causative factor in specific headache types such as cluster headache. Whatever the pathogenesis, it is certainly worthwhile for clinicians to question patients with early morning headache about the presence of snoring, arousals from snoring, observed apneas and daytime sleepiness. If there is a strong suspicion of OSAS, a PSG should be performed.

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CHAPTER 29

Sleep and autonomic nervous system dysfunction

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29.1. Introduction

The autonomic nervous system (ANS), through its complex central and peripheral circuits, controls vital involuntary functions of the body, such as circulation, respiration, thermoregulation, neuroendocrine secretion, gastrointestinal and genitourinary functions. The autonomic nervous system (ANS) and sleep are closely related along anatomical, physiological and neurochemical lines. In the past, it was commonly assumed that autonomic regulation remained unchanged across behavioral states; the concept of a state-dependent regulation of the ANS has been addressed only recently. A major confirmation of this link between ANS and sleep is the demonstration of dynamic and synchronous fluctuations in sleep phases and autonomic functions. Sleep and the ANS are, in fact, interdependent on each other by virtue of common controls, neurobiological substrates and functions. It is important, for example, to emphasize that changes in state during sleep are coordinated principally by the pons, basal forebrain areas and other subcortical structures, and the main neurotransmitters involved are noradrenaline (norepinephrine), serotonin and acetylcholine. The same neuronal populations that produce and distribute these neurotransmitters constitute the central representation of the sympathetic and parasympathetic nervous systems. The central autonomic network (CAN), through its ascending and descending connections between the hypothalamic-limbic region and the nucleus tractus solitarius (NTS) in the medulla, orchestrates the sympathetic and parasympathetic divisions of the ANS (Benarroch, 1997). Sleep-promoting neurons, which are scattered in the vicinity of the

central autonomic network (CAN) and its connections (e.g. preoptic–anterior hypothalamic (POAH) region and NTS) along with cholinergic ‘REM-on’ and catecholaminergic ‘REM-off’ cells in the ponto–mesencephalic junction and pons, control non-rapid eye movement (NREM) and rapid eye movement (REM) sleep cycles. Sleep induces profound changes in the functions of the ANS, and disorders of the ANS adversely affect vital functions during sleep, including circulation and respiration.

NREM sleep is characterized by electrocortical synchronization, reduced muscle tone and stable parasympathetic predominance. In this phase, there is a tonic decrease in arterial pressure and heart rate as a result of parasympathetic activation and sympathetic inhibition. Hypotension reflects a decrease in cardiac output and in peripheral resistance. A moderate reduction of cardiac output results primarily from a decrease in heart rate, reflecting increased parasympathetic activity. The decrease in total peripheral resistance is largely from a reduction in sympathetic vasomotor tone, resulting in skin, muscle and visceral vasodilation. The combination of lower arterial pressure, heart rate and sympathetic nerve activity indicates that NREM sleep is accompanied by downward resetting and increased sensitivity of the baroreceptor reflex. The increase in baroreceptor reflex gain during NREM sleep contributes to the decreased variability of arterial pressure typical of this stage (Conway et al., 1983; Mancia, 1993). In NREM sleep, sympathetic activity may be transiently increased by arousal stimuli, coinciding with the appearance of K complexes in the electroencephalogram. This is associated with increased heart rate and respiration.

In contrast to NREM sleep, REM sleep is characterized by electrocortical desynchronization, muscle atonia and phasic motor autonomic changes. Marked phasic fluctuations of sympathetic and parasympathetic activity and impairment of baroreflex responses and thermoregulation also occur in REM sleep.

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During tonic REM sleep, there is a marked bradycardia along with decreased peripheral resistance, resulting in a decrease in arterial pressure below levels observed in NREM sleep. The decrease in arterial pressure observed during REM is interrupted by large transient increases in arterial pressure and in heart rate during bursts of rapid eye movements and muscle twitches (phasic REM); variability of these cardiovascular parameters is an important feature of REM sleep which results from phasic inhibition of parasympathetic activity and phasic increases in sympathetic discharge.

Because of the close relationship between the cardiovascular and respiratory systems, the variations of the former during sleep–wake cycle implicate related modifications to the latter. The integration of the cardiorespiratory system during sleep is achieved at several levels in the neuraxis; it is essentially linked to the ANS and is important in preserving functional homeostasis during sleep. In NREM sleep, respiration is controlled by an automatic system driven by chemical stimuli. The core of this automatic system is composed of various neuron groups in the medulla; a neural subgroup produces consistent respiratory activity and is relatively insensitive to non-respiratory influences. There is another subgroup that is affected greatly by NREM sleep and by various non-respiratory influences. Medullary respiratory neurons exhibit extremely variable behavior in REM sleep, and this factor largely accounts for the irregular breathing of that state. It is also known that medullary respiratory activity in REM sleep is influenced by at least one type of phasic REM sleep event, the pontine–geniculate–occipital (PGO) wave, a finding clearly indicating non-respiratory and state-specific influences on the respiratory system during REM sleep. Some studies, however, show that the central respiratory drive, although erratic, is often increased in REM sleep.

Other factors have mutually important implications in ANS activity and the sleep–wake cycle, the most important being thermoregulation and endocrine circadian rhythm. The regulation of body temperature is controlled by the ANS, which uses several sources of information to generate specific thermoregulatory responses (e.g. sweating, shivering and skin vasomotor adjustments). The characteristics of thermoregulatory control vary significantly between sleep phases and wake and with time of day, being modulated by the circadian system and by sleep control mechanisms. Body temperature is regulated at a lower level during NREM sleep than during wakefulness; NREM sleep, in fact, is characterized by downward resetting

of the thermostat, and a decrease in body temperature and metabolism. Decreases in rectal temperature or increases in skin temperature have been reported routinely at the onset of sleep in adult humans sleeping in neutral or cool environments.

In animal studies, thermoregulatory responses to changes in peripheral or core body temperature show qualitatively different responses in NREM compared to REM sleep; during NREM sleep, thermoregulation mechanisms are operative and the ambient thermal load variations are balanced. This homeothermy is controlled by hypothalamic-preoptic integrative controls that drive subordinate brainstem and spinal somatic and visceral mechanisms. In contrast, transition from NREM sleep to REM sleep is characterized by a disruption of ongoing thermoregulation. In this phase, there is a marked inhibition of thermoregulation, and the changes in body temperature occur passively in relation to the environmental heat load. The result is that the temperature of the body changes according to its thermal inertia, as one would expect in a poikilothermic organism (Parmeggiani et al., 1971; Walker et al., 1983).

On the other hand, thermal environment and body temperature are important determinants of sleep architecture, and they have a prominent influence on both the amount and distribution of arousal states. The environmental temperature effects on sleep are more prominent during the light phase compared with the dark phase of the diurnal cycle. These data emphasize the importance of considering time-of-day in the relationship between temperature and sleep.

Moreover there are important relationships between the duration of sleep, REM sleep propensity and body temperature. In humans, the duration of sleep has also been related to changes in body temperature. In addition to the variations in environmental temperature and thermoregulatory responses associated with different stages of sleep and wake, there are daily cycles in the properties of the thermoregulatory system and consequent changes in body temperature that are independent of arousal states; they are under control of the circadian system, which also influences the organization of vigilance states. With regard to the relationships between sleep, the ANS and hormonal secretions, many biological, physiological and biochemical rhythms are regulated by the integration of inputs from the circadian clock and the sleep–wake cycle. Indeed, it can be argued that the entire temporal organization of an organism represents the combined effect of various regulatory systems.

In mammals, the suprachiasmatic nucleus in the anterior hypothalamus serves as the central neural pacemaker of the circadian timing system, and the discovery of its functional role sets the stage for understanding how a central circadian pacemaker is driving the daily fluctuations in a whole array of physiological functions. There is growing evidence that hormones have a regulatory influence on circadian rhythms and the sleep–wake cycle. Melatonin levels are highest during night sleep (Shanan and Czeiler, 1991); cortisol is low at the time of habitual sleep onset, but then it is high at the habitual morning wake time (Weitzman et al., 1983). Sleep opposes the circadian variations of thyroid-stimulating hormone (TSH), inhibiting the endogenous circadian rhythm of TSH release, which would otherwise peak in the middle of the night. That nocturnal peak is blunted by sleep, so that TSH levels reach the highest level just before sleep onset and are suppressed during sleep episodes. In contrast, the levels of growth hormone, prolactin and parathyroid hormone show prominent sleep-related increases. Moreover ultradian variations in the release of renin are closely related to the NREM–REM sleep cycle; increased relative delta power (S3–S4 stages of NREM sleep) is associated with increased levels of plasma renin activity. The aim of this chapter is to summarize the main autonomic abnormalities in sleep disorders, which are relevant to understanding the pathophysiological mechanisms of the diseases or to clinical practice.

29.2. Clinical neurophysiological techniques for the study of sleep and autonomic function

The first step is the clinical diagnosis; it should be directed at diagnosing the primary or secondary autonomic failure and its causes as well as assessment of sleep disturbances in all patients. It is very important to obtain a history documenting characteristic clinical manifestations of autonomic dysfunction, and the physician's attention should be directed to the possibility of sleep disorders and particularly sleep-related breathing disorders. The diagnosis of sleep disorders begins with a detailed history of sleep habits, sleep hygiene and subjective sleep complaints. It is often advisable to interview the bed partner to obtain an adequate history, particularly with regard to events occurring during sleep. Laboratory investigations should be an extension of the history and physical examination. For the assessment of sleep disorders and respiratory or cardiovascular dysfunction during sleep, the gold

standard is represented by an overnight polysomnographic study. This examination should include simultaneous recordings of EEG, electromyogram (EMG), electro-oculogram (EOG), electrocardiogram (ECG), respiratory monitoring (oro-nasal flow and thoracic and abdominal effort), snoring, body position and oxygen saturation by pulse oxymetry. Inclusion of video-polysomnography (PSG) study may be needed in some patients to diagnose movement disorders during sleep, such as REM-sleep behavior disorder and various other parasomnias or sleep-related behaviors, including nocturnal seizures. Particularly important in patients with suspected autonomic dysfunction during sleep is monitoring of additional autonomic parameters, such as continuous monitoring of blood pressure, plethysmogram and body core temperature.

Among the methods used to measure systemic arterial blood pressure, automatic self-inflating arm cuff sphygmomanometers are generally too 'invasive' to be used routinely in the sleep laboratory, because the patient may arouse when the cuff inflates. A considerable advance has been the non-invasive technique to measure finger arterial blood pressure, using a sophisticated system, which provides beat-to-beat pressure. This obviates the need for invasive intra-arterial (radial or brachial artery) catheterization, which previously was the only reliable means of obtaining continuous blood pressure measurements.

The Finapres (FINGER Arterial PRESSure) provides a reliable measure of change in blood pressure, especially when there are rapid responses. Finapres is based on the vascular unloading technique first described by the Czech physiologist Jan Peñáz. The finger arteries are clamped at a fixed diameter, although intra-arterial pressure changes continuously, by applying an external pulsating pressure via an inflatable bladder mounted in a finger cuff and a fast-acting servo system. Finapres uses the physiological criteria of Karel Wesseling for the setpoint criteria determination; the diameter at which the finger arteries are clamped is determined from an infrared plethysmograph mounted in the finger cuff such that transmural pressure is zero and intra-arterial and cuff pressure are equal both in shape and in level at all times. Finapres was commercially available through the US company Ohmeda but is now no longer in production. Its successor, Portapres, an advanced ambulatory non-invasive blood pressure monitor, is still available. Using the same patented methods as applied in Finapres, the arterial blood pressure waveform is measured continuously in the finger. Portapres

enables 24-hour ambulatory measurements and through the software package, Beatscope, for the analysis of arterial pressure waveforms, it is also possible to obtain the computation of beat-to-beat hemodynamic data, such as stroke volume and cardiac output. In healthy young men, continuous, non-invasive, beat-to-beat finger blood pressure monitoring induced modest reductions in sleep efficiency of similar magnitude to those observed previously with non-invasive ambulatory blood pressure monitoring (Van de Borne et al., 1993).

Choosing how to assess ANS function in the awake state mainly depends on the clinical presentation of the dysfunction (Box 29.1). In clinical practice, the main methods of autonomic investigation are based on assessment of cardiovascular functions, which can identify a deficit and also determine its location and severity. These methods are the most commonly used because they are non-invasive and easy to perform and interpret. In contrast to many neurophysiologic tests, which were introduced directly from the basic to the clinical laboratory with little validation, autonomic tests have been used extensively in clinical trials, so that detailed information is available regarding sensitivity, specificity, reproducibility and confounding variables (Low, 1996).

- (1) The head-up tilt test is the postural stimulus most commonly used with concomitant measurement of arterial pressure (AP) and heart rate (HR). In some cases, postural hypotension may be initially masked by food intake, physical exercise or a warm environment. Further tests will help to determine the severity of impaired autonomic control of the cardiovascular system. Basal measurements should be performed with the subject lying supine in a quiet room and as comfortable as possible. Several readings, over at least a 5–10-min interval, may be needed to determine the stability (or lability) of supine blood pressure. Postural change can be induced using either a manual or electrically operated tilt table (usually up to 65°), or by having the subject initially sit and then stand, or stand directly. A tilt table is advantageous, especially in subjects who have neurological disabilities, severe postural hypotension, or both, as it also enables rapid return to the horizontal if symptoms occur. Measurements of brachial blood pressure and heart rate during head-up tilt ideally should be continuous for a period of 10 min, as this also enables blood

Box 29.1

Outline of investigation in autonomic failure

Cardiovascular	Head-up tilt (65°); standing; Valsalva manoeuvre
Physiological	Pressor stimuli-isometric exercise, cutaneous cold
Mental arithmetic	Heart rate responses – deep breathing, hyperventilation Standing, head-up tilt, 30:15 ratio Liquid meal challenge Exercise testing Carotid sinus massage
Biochemical	Plasma noradrenaline- supine and head-up tilt or standing; Urinary catecholamine; plasma renin activity and aldosterone
Pharmacological	Noradrenaline (norepinephrine)- α - adrenoceptors – vascular Isoprenaline- β -adrenoceptors- vascular and cardiac Tyramine-pressor and noradrenaline response Edrophonium noradrenaline response Atropine parasympathetic cardiac blockade
Sudomotor	Central regulation thermoregulatory sweat test Sweat gland response intradermal acetylcholine, quantitative Sudomotor axon reflex test (Q-SART), localized sweat test Sympathetic skin response
Gastrointestinal	Barium studies, videocinefluoroscopy, endoscopy, gastric Emptying studies
Renal function and day and night urine volumes and sodium/potassium excretion	
Urinary tract	Urodynamic studies, intravenous urography, ultrasound Examination, sphincter electromyography
Sexual function	Penile plethysmography Intracavernosal papaverine
Respiratory	Laryngoscopy Sleep studies to assess apnoea/ oxygen desaturation
Eye	Schirmer's test Pupil function – pharmacological and physiological

collection for measurements of catecholamines and other vasoactive hormones released during postural change. It is important with Finapres recordings that the hand is at heart level; this is more reliably and comfortably maintained with an adjustable sling, especially during maneuvers that cause arm movement.

- (2) The changes in blood pressure and heart rate during the Valsalva maneuver, when intrathoracic pressure ideally is raised to 40 mmHg, provide a further assessment of the baroreflex pathways. To perform this, the subject blows with an open glottis into a disposable syringe connected to the mercury column of a sphygmomanometer and maintains a forced expiratory pressure of up to 40 mmHg for 12–15 seconds. This may be difficult in some subjects, in whom levels between 20–40 mmHg often suffice to induce the necessary changes.

Normally, with the rise in intrathoracic pressure, the venous return falls along with blood pressure. On releasing intrathoracic pressure, there is a blood pressure overshoot because of persistence of sympathetic activity. Baroreflex activation then results in a secondary fall in heart rate to below basal levels. In sympathetic vasoconstrictor failure, the Valsalva maneuver results in a continuous fall in blood pressure with no stabilization; following release, there is no blood pressure overshoot. Thus there is no compensatory bradycardia. If the afferent and vagal efferent components of the baroreflex pathways are intact, heart rate rises while the blood pressure falls. In diabetics with a proliferative retinopathy, some feel that there may be a risk of intraocular haemorrhage, because of the pressure transients. The continuous measurement of heart rate with an electrocardiograph (ECG) often suffices in obtaining relevant information. However, the Finapres is of particular value in this test, as it will identify a lack of fall in blood pressure, indicating that intrathoracic pressure was not elevated adequately.

There are various measurements and derived ratios of heart rate during the different phases of the Valsalva maneuver. A commonly used ratio (the Valsalva ratio) relates to the changes in heart rate in response to the variations in blood pressure. Typically, when intrathoracic pressure is elevated (phase II), the blood pressure falls and heart rate rises. While in the first 30 seconds after release of intrathoracic pressure (phase IV), the

heart rate should fall in response to the rise in blood pressure. The Valsalva ratio is the derivative of the maximum rise and fall in these two phases (phase II + phase IV) and should normally be greater than 1. It is equal to or less than 1 in the presence of autonomic failure.

The position of the patient (lying or sitting) and the time of day when the Valsalva maneuver is performed may influence the response. The responses also need to be considered in relation to factors known to affect heart rate, such as drug therapy and the myocardial state. Analysis of the continuous blood pressure and heart rate record during the Valsalva often provides valuable information on the baroreflex. When the blood pressure falls, a rise in heart rate in response to the rise in intrathoracic pressure suggests that the afferent and vagal efferent pathways are operative. Recovery of the blood pressure while intrathoracic pressure is maintained often occurs in normal subjects, but not in those with sympathetic vasoconstrictor failure, when blood pressure usually falls inexorably. With release of intrathoracic pressure in such patients, there is only a slow return to the baseline without the overshoot, consistent with the lack of sympathetic vasoconstrictor function. These form the characteristic blood pressure features of a 'blocked' Valsalva maneuver.

- (3) Pressor stimuli raise blood pressure by stimulating sympathetic efferent pathways in a variety of ways. With isometric exercise or cutaneous cold, there is activation of peripheral receptors. There is also an important cerebral component, especially with isometric exercise. Other stimuli, such as sudden noise or mental arithmetic, are dependent predominantly on cerebral stimulation. Isometric exercise is performed by using either a dynamometer or a partially inflated sphygmomanometer cuff, and sustaining handgrip for 3–5 minutes, usually at a third of the maximum voluntary contraction pressure. The cold pressor (cutaneous cold) test consists of immersing the hand for up to 2 min in ice slush, usually just below 4°C. Cortical arousal is performed by sudden noise, mental arithmetic (subtraction or addition of 7 or 17) or a variety of more complex tasks. These stimuli normally elevate blood pressure and heart rate. In patients with central or efferent sympathetic lesions, the responses to these stimuli are impaired or absent. Responses to isometric exercise, cutaneous cold and mental arithmetic can be

obtained within a short period of time and often provide valuable information in a wide range of disorders. The most useful responses probably are those induced by isometric exercise and cutaneous cold. It should be noted that factors independent of the ANS may affect the responses; thus, disordered muscle function may influence the pressor response during isometric exercise, and the presence of a sensory deficit may limit the response to cutaneous cold. The sensitivity, specificity and reproducibility of these tests have been studied. The results obtained during isometric exercise with handgrip compare favorably with tilt-table tests. With the cold pressor test, systolic blood pressure was the more reliable measurement; reproducibility, however, was lower when testing was repeated over the same day, or over 3 consecutive days, presumably because of habituation or anticipation. The responses to mental arithmetic can vary; they may be reduced when the stimulus is too trivial, as in those who are highly numerate, or when they cannot be performed adequately, as in those with dementia.

- (4) Spectral analytical techniques may be used to study short- and long-term cardiovascular changes. These are being increasingly utilized, although largely in a research setting. The use of such techniques to study heart rate changes as a measure of cardiac autonomic function during sleep has been of value, especially in certain neuropsychiatric disorders. In narcolepsy, there are changes related to impairment of the sleep-wake cycle. In panic disorders, sympathetic overactivity occurs only in the day and not at night, thus excluding an intrinsic defect in autonomic regulation.
- (5) Skin and muscle sympathetic fiber activity can be recorded directly by inserting a microelectrode through the skin into the peroneal and median nerves (microneurography). This method is useful to clarify the many mechanisms pathophysiologically linked to a hyperactive sympathetic system but is of little clinical use in investigating autonomic failure when sympathetic activity is progressively reduced.
- (6) Pharmacological tests will determine the degree of sensitivity of alpha-adrenergic [noradrenaline (norepinephrine) infusion], beta-adrenergic (isoprenaline infusion) and cardiac muscarinic vascular receptors (atropine infusion). Pressor response

to raised plasma noradrenaline (norepinephrine; NA) levels on infusion of tyramine will indicate the reserves of NA in the peripheral sympathetic terminal.

7. Measurement of arterial pressure (AP) and heart rate (HR) circadian rhythms is especially useful to check for the nocturnal supine hypertension (non-dipper behavior) characteristic of patients with autonomic failure and/or obstructive sleep apnea.

29.3. Specific diseases

Many neurological and general medical disorders are associated with autonomic failure, and many of the afflicted patients have sleep disturbances. Box 29.2 lists disorders of primary and secondary autonomic failure which are associated with sleep dysfunction.

Box 29.3 lists primary sleep disorders that may have autonomic deficits. Some of these conditions may show mild autonomic changes whereas others may include clinically relevant ANS dysfunction.

29.3.1. *Fatal familial insomnia*

Fatal familial insomnia is a rare prion disease characterized by major sleep and autonomic disturbances. Postmortem brain studies have demonstrated severe loss of neurons, particularly in the anteroventral and dorsomedial thalamic nuclei (Lugaresi et al., 1986). Positron emission tomography (PET) studies have shown that severe thalamic hypometabolism is present at the onset of insomnia and dysautonomia, suggesting that damage to the medial thalamus is the biological cause of symptoms (Cortelli et al., 1997). The autonomic symptoms include sexual impotence, sphincter impairment, and increased tearing, salivation, sweating and increased core body temperature. Polysomnographic examination in the later stages shows total absence of sleep patterns and only short episodes of REM sleep without muscle atonia associated with enacted dreams (Sforza et al., 1995). Moreover, polygraphic analysis has shown consistent elevation of blood pressure and heart rate in fatal familial insomnia (FFI) patients. Correlation with electroencephalography (EEG) tracing showed that in those cases in which short episodes of NREM sleep still appeared, blood pressure and heart rate fall abruptly, thus displaying normal state-dependent behavior. An imbalanced autonomic control with

Box 29.2**Primary and secondary autonomic failure associated with sleep dysfunction****Neurodegenerative and prion diseases**

Multiple system atrophy
 Primary Parkinson disease
 Shy–Drager syndrome
 Progressive supranuclear palsy
 Fatal familial insomnia
 Cerebellar degeneration
 Alzheimer disease

Central nervous system lesions and other neurological disorders

Hypothalamic tumors
 Brainstem lesions
 Stroke
 Epilepsy
 Multiple sclerosis
 Headache

Neuromuscular disease

Myasthenia gravis
 Myotonic dystrophy
 Amyotrophic lateral sclerosis

Peripheral nervous system disease

Autonomic neuropathies

General medical disorders

Cardiac arrhythmias and myocardial infarction
 Bronchial asthma
 Chronic renal failure
 Chronic fatigue syndrome
 AIDS

preserved parasympathetic activity and a higher background and stimulated sympathetic activity was the conclusion derived from the autonomic tests in FFI patients. There is much evidence of sympathetic overactivity, such as elevated noradrenaline (norepinephrine) plasma levels at rest, increasing further under orthostatic stress, exaggerated blood pressure responses to physiologic stimuli (postural changes, Valsalva maneuver, isometric handgrip), absent blood pressure response to noradrenaline (norepinephrine) infusion, increased heart rate response to atropine and diminished depressor and sedative effects of clonidine (Benarroch and Stotz-Potter, 1998).

Box 29.3**Sleep disorders associated with clinically relevant autonomic nervous system dysfunctions**

Obstructive sleep apnea syndrome
 Ondine's curse
 Sleep terrors and other parasomnias
 REM sleep behavior disorder (RBD)

29.3.2. Obstructive sleep apnea syndrome

There are reports of alterations of both sympathetic and parasympathetic divisions of the ANS in patients with obstructive sleep apnea syndrome (OSAS). Many studies have emphasized hyperactivity of the sympathetic nervous system causing increased plasma noradrenaline (norepinephrine) levels and urinary catecholamine secretions, which are attributed to hypoxemia associated with apneic episodes. Enhanced muscle sympathetic nervous activity (MSNA) during wakefulness and sleep in patients with OSAS has been clearly documented (Watanabe et al., 1992; Hedner et al., 1995). The pathogenic hypothesis for this is that tonic activation of excitatory chemoreflex afferents may contribute to increased efferent sympathetic activity to muscle circulation in OSAS patients.

Studies of heart rate variability using spectral analysis show sympathetic activation [increased low-frequency (LF) components and increased LF/high-frequency (HF) ratio] during sleep apnea. Also, studies of circadian rhythms of autonomic activity and heart rate variability show that the mean HF (parasympathetic activity index) from morning to noon is lower in OSAS than in controls. The mean LF/HF ratio (sympathetic activity index) is higher in OSAS patients. These findings suggest that sleep-disordered breathing associated with severe oxygen desaturation influences heart rate variability not only during sleep but also during wakefulness.

Normotensive OSAS patients have higher heart rates and noradrenaline (norepinephrine) plasma levels (than controls) at rest. They also have higher blood pressure responses to head-up tilt with a significantly lower respiratory arrhythmia and Valsalva ratios associated with a greater decrease in heart rate induced by the cold face test. These data suggest sympathetic overactivity associated with a blunting of reflexes dependent on baroreceptor or pulmonary

afferents and normal or increased cardiac vagal efferent activity (Cortelli et al., 1994).

Moreover, there is evidence of a depression of spontaneous baroreceptor reflex sensitivity in severe OSAS patients; this baroreflex dysfunction may be involved in sympathetic activation during sleep (Parati et al., 1997). These alterations of circadian autonomic rhythms in OSAS patients could contribute to an increase in cardiac and cerebrovascular disease. Early investigators recognized hypertension as a clinical feature of sleep apnea, but until recently the link between sleep apnea and hypertension was uncertain because of the many confounding factors (obesity, age, and alcohol ingestion). However, there is now much epidemiological evidence supporting a direct contribution of sleep apnea to hypertension (Pepperell et al., 2002). Moreover, in a population of essential hypertensive patients, the non-dipper condition appeared to be closely linked to the presence of nocturnal obstructive sleep apnea (Portaluppi et al., 1997). Many hypotheses have been advanced to explain how sleep apnea leads to daytime blood pressure elevation. According to many authors, the most important causative factors are the effect of episodic hypoxemia and hypercapnia on chemoreceptors and sympathetic activity; the modification of the cardiovascular system (including fluid balance) in response to marked fluctuations in intrathoracic pressure during obstructive apneas; the generalized stress from sleep disruption (the arousal effect); and other metabolic or endocrine factors. However, the common mechanism shared by hypertension and OSAS is activation of the sympathetic system (Fletcher, 2003).

A number of cardiac arrhythmias resulting from changes in the ANS have been associated with obstructive sleep apnea. The most common is brady-tachyarrhythmia (relative bradycardia during obstruction and relative tachycardia on resumption of normal breathing). The other dysrhythmias include sinus bradycardia, sinus pauses lasting for 2–13 seconds, second-degree heart block, ventricular ectopic beats and ventricular tachycardia. Although ventricular arrhythmias seem to be closely related to the degree of desaturation, the precise causes of dysrhythmias in OSAS patients remain controversial. As previously described, OSAS, particularly if untreated, may lead to serious consequences related to nocturnal hemodynamic alterations and excessive daytime sleepiness. In fact, OSAS is an important risk factor for hypertension, cardiac arrhythmias, myocardial infarction, congestive cardiac failure and stroke.

Moreover, reduction of diurnal vigilance may increase the risk of car or work accidents.

29.3.3. *Ondine's curse*

This term describes a disease process in which there is a breathing abnormality characterized by hypoventilation during sleep and to varying degrees, also during wakefulness. This condition is, in fact, a failure of the autonomic control of breathing. During sleep, the pattern of breathing is often reduced tidal volume rather than frank apnea, but in severely decompensated patients, the onset of sleep can be associated with complete central apnea (Commare et al., 1993).

In this condition, hypoxic and hypercapnic ventilatory responses are impaired (Marcus et al., 1991). To describe patients without an identified cause of hypoventilation, the terms 'primary alveolar hypoventilation' or 'congenital central hypoventilation syndrome' (CCHS) are used. There is an association of CCHS with ganglioblastoma and Hirschsprung's disease (congenital megacolon due to absence of ganglion cells in the myenteric plexus) (Masumoto et al., 2002). The term 'secondary alveolar hypoventilation' identifies the same syndrome of sleep-related breathing alteration, but in this form, there is a clear neural cause (brainstem tumor, brainstem damage from encephalitis, or neuropathy affecting the respiratory motor nerves).

29.3.4. *Parasomnias*

Parasomnias are abnormal movements or behaviors intruding into sleep without substantially disturbing sleep architecture. Some of the parasomnias, particularly sleep terrors and REM sleep behavior disorder (RBD), are associated with autonomic dysfunction.

29.3.4.1. *Sleep terrors*

This parasomnia is classified as a disorder of arousal. The clinical onset is generally between 5 and 7 years of age, and familial cases are common. Sleep terror or pavor nocturnus generally arises out of S3–S4 NREM sleep phases during the first one-third of sleep. Episodes of sleep terror are characterized by intense autonomic manifestations, such as tachycardia, tachypnea, excessive sweating, pupillary dilation, flushing of the skin and reduced skin resistance. There is a correlation between the amount of prior NREM sleep (S3–S4 phases) and autonomic intensity as measured by the degree of tachycardia (Broughton, 1999).

29.3.4.2. REM sleep behavior disorder (RBD)

RBD is a sleep parasomnia characterized by dream-enacting behavior (which may be violent) during REM sleep, often causing injuries to the patient or bed partner. The polysomnographic examination shows loss of REM-related muscle atonia associated with a variety of abnormal motor activities during sleep.

This condition may be either idiopathic or secondary to a neurologic illness or medication; it can precede, by several years, the onset of some degenerative diseases [Parkinson's disease (PD), multiple system atrophy (MSA)] associated with autonomic failure (Olson et al., 2000). Evaluation of cardiac autonomic function has shown that autonomic dysfunction can be detected earlier during sleep than during wakefulness. In fact, the tonic and phasic heart rate variability appear reduced in RBD patients during sleep. Moreover, in RBD patients, tachycardia does not accompany the abnormal movements during REM sleep, indicating impairment of the sympathetic nervous system (Ferini-Strambi et al., 1996, Mahowald and Schenck, 1994).

29.4. Research studies in normal subjects and patients

Many experimental models have been developed to study the anatomy and functional roles of structures which regulate wakefulness and sleep. Experimental lesions and evidence from use of a variety of drugs suggest that serotonin is involved in the induction and maintenance of slow-wave sleep. Slow-wave sleep is generally considered a prerequisite for REM, so an alteration of brain serotonin levels will also affect REM sleep. Behavioral arousal occurs after lesions to the raphe nucleus (serotonergic nucleus), and a gradual reduction of slow-wave and REM sleep is produced by the injection of parachlorophenylalanine, which depletes the brain of serotonin. Noradrenaline (norepinephrine) is predominantly involved in the waking mechanism and in the REM suppression system. Acetylcholine is involved in wakefulness, slow-wave sleep and REM sleep. The injection of acetylcholine into the brainstem is followed by slow-wave sleep, but sometimes REM episodes occur. Atropine abolishes REM sleep.

The two aminergic neuronal subgroups (in the locus coeruleus and raphe nuclei) are most active in wakefulness, become progressively less active in NREM sleep and virtually cease firing in REM sleep.

On the other hand, the cholinergic neurons (in the dorsolateral tegmental and pedunclopontine nuclei) are active in both wakefulness and REM sleep. Consequently, in wakefulness, both systems are active. In NREM sleep, both systems are less active; in REM sleep, the cholinergic system acts alone.

Interesting changes occur in the regulation of breathing and cardiovascular functions at the transition from wakefulness to sleep, both in physiologic and pathologic conditions. The transition is characterized by inactivation of the 'wakefulness' – telencephalic control mechanism. At this moment, a breathing instability appears associated with respiratory and circulatory periodic phenomena. Under normal physiological conditions, the breathing pattern becomes regular with deep NREM sleep, when it is completely driven by the automatic medullary control mechanism. In REM sleep, a profound alteration occurs in this automatic control; in this sleep state, ventilation in humans and animals is very irregular, with the average frequency being increased or decreased with respect to the NREM sleep.

Moreover, in normal human subjects, hypotension and bradycardia appear during NREM sleep and become increasingly more pronounced as sleep progresses from stage I to stage IV (Parmeggiani, 1987). Sympathetic nerve activity, as recorded in skeletal muscle and skin, is decreased by more than half from wakefulness to stage IV of NREM sleep (Somers et al., 1993). In conclusion, in NREM sleep the changes in visceral regulation are consistent with somatic quiescence, as is the functional prevalence of parasympathetic activity, and the lowering of metabolic heat production and body temperature (vasodilatation of heat exchangers, sweating). In these phases of mammalian sleep, all somatic and visceral regulatory responses to endogenous and exogenous disturbances may be activated to maintain homeostasis. In contrast, REM sleep is characterized by the disintegration of a homeostatic physiological equilibrium, and it is difficult to establish a rational foundation of the observed functional phenomena. The leading regulatory structures of REM sleep are rhombencephalic, as shown by the occurrence of REM sleep phenomenology in brainstem preparations. In general, it may be assumed that a critical integrative instability develops during REM, as a result of the impaired homeostatic function of higher levels of integration.

Another important element for experimental study is the influence of external and internal temperature on wake-sleep modulation. Parmeggiani and col-

leagues (1969) first showed in cats that total sleep time is maximal within the thermoneutral zone and decreases above and below it. Moreover, the NREM to REM sleep ratio increases as ambient temperature deviates from thermoneutrality, which is due primarily to a reduction in the number of epochs of REM sleep. In particular, some studies have shown that in a cold environment, there is an increase in wakefulness, sleep latency, and movement time. The decrease in sleep time is due mostly to decreased REM sleep and stage II NREM sleep (Buguet et al., 1976). According to other authors, the decrease of stage II NREM sleep, when tested at a cold (21°C) vs neutral (29°C) ambient temperature, is greater than REM variations (Palca et al., 1986). Warm environments also cause increased wakefulness and reduce both REM and NREM sleep during the night. Then, when subjects are exposed to a range of ambient temperatures, it becomes evident that total sleep time, NREM sleep and REM sleep are maximum at thermoneutrality (29°C) (Hakell et al., 1981). On the other hand, body temperature also has a profound effect on the paradoxical sleep cycle. In a 'pontine' cat, the normal body temperature is about 39.5°C. If it is allowed to fall to around 30°C, the duration of each paradoxical sleep period is increased from 6 minutes to about 20 minutes.

In a temporal isolation experiment, subjects slept longer when they went to sleep at, or shortly after, the peak of the circadian temperature oscillation. Those who went to sleep during the temperature trough slept less. All subjects awoke during the rising phase of the temperature cycle and went to bed most often shortly after the circadian temperature trough (when alertness was decreased).

Another example of the effect of body temperature on sleep comes from studies of fever. In 1968, Karacan reported that fever had specific effects on nocturnal sleep, including an increase in wakefulness and stage I NREM sleep and dramatic decreases in both REM and stage IV NREM sleep. However, subsequent studies on the effects of putative pyrogens on sleep yielded controversial data; in most cases, the sleep and temperature effects were temporally displaced, dose-dependent and dependent upon the site and mode of injection and time of day (Walters et al., 1989; Opp et al., 1991).

29.5. Future advances and applications

Current works and past studies on the neurobiology of sleep and the ANS demonstrate that nocturnal and cir-

cadian evaluations are of expanding interest for both researchers and clinicians. For example, the link between hypertension and OSAS is epidemiologically well known, but the analyses of nocturnal variations of autonomic control, sympathetic and parasympathetic tone are still needed to elucidate the mechanisms of this relationship and to help prevent subsequent cardiovascular and cerebrovascular diseases. In clinical practice, the examination of autonomic functions and dysfunctions during sleep provides important information for correct diagnosis and treatment. This is true in the case of sleep-related breathing disorders associated with neurodegenerative diseases and in the treatment of neurogenic orthostatic hypotension.

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