Introduction to Sleep Medicine

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KEYWORDS

• Sleep medicine • Physiologic • Sleep regulation

KEY POINTS

- The sleep disturbances provoked by frequent awakening adversely affect all aspects of health.
- Sleep can be a sensitive marker, and serves as a bellwether of overall health.

HISTORY

Sleep Physiology

Sleep medicine's roots date back to Henri Peiron who published *Le Probleme Physiologique du Sommeil* in 1913.[1] Peiron considered sleep from a physiologic perspective and performed research supporting the hypnotoxin theory of sleep regulation. He induced sleepiness by injecting alert dogs with serum from sleep-deprived dogs. Approximately a decade and a half later, in 1929 the "father of electroencephalography," Johannes Berger,[2] demonstrated the difference between brain activity during wakefulness and sleep. That same year, Constantin Von Economo[3] proposed a sleep-regulatory hypothalamic brain site based on his clinical experience with patients suffering from encephalitis. The first continuous all-night sleep studies were performed in 1936-1937 by Loomis and colleagues[4] as part of an intellectual exploration at the Loomis's Tuxedo Park laboratory. The first sleep stage classification arose from their work. Their classification did not include a description of the sleep stage later illustrated by Aserinsky and Kleitmman[5] (1953) that was ultimately named rapid eye movement (REM) sleep. REM sleep fascinated many researchers because of its association with dreams, what Freud had regarded as the "royal road to the unconscious."[6]

Long before sleep medicine developed, circadian rhythm had been described in plants and animals. Jean Jacques d'Ortous de Mairan[7] demonstrated heliotrope leaf opening and closing independent of sunlight in 1729. After more than 2 centuries of experimentation, the term "biological clock" was coined in 1935 by Bunning[8] and conceptually framed as a part of the sleep-wake cycle. In 1972, Robert Y. Moore's work[9] established the circadian pacemaker in the suprachiasmatic nuclei (SCN), and soon after mapped the retinohypothalamic projection as the pathway linking light and darkness to the sleep-wake circadian rhythm.

Sleep Disorders

In 1945 Karl-Axel Ekbom coined the term "restless legs."[10] This sleep disorder had been initially described back in 1672 by Sir Thomas Willis, who noted that arm and leg movements were associated with sleep disturbances.[11] Although many descriptions of the restless legs syndrome (RLS) followed, it was Ekbom who provided a comprehensive report, clearly characterized the symptoms, differentiated it from other disorders, and estimated its prevalence. He also linked RLS to anemia. His work languished for many years but was revived in the past decade by Walters and Hening.[12]

Sleep apnea was described first by Gastaut and colleagues[13] (1965) in morbidly obese patients. The moniker "Pickwickian" was attached because

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Charles Dickens had described such individuals, including their excessive sleepiness, in his fictional work *The Pickwick Papers*. Over time, it was realized that sleep apnea also occurs in patients who are not morbidly obese, and in 1978 the book *Sleep Apnea Syndromes* was published.[14] Positive airway pressure therapy was developed by Sullivan and colleagues[15] and was found to be an effective treatment; commercially available devices became available in 1982.

A quite different sleep disorder associated with excessive sleepiness (ie, narcolepsy) had been described in the medical literature back in 1880 by Gelineau.[16] However, this disorder was also associated with cataplexy that was triggerable by emotion. Sleep paralysis and hallucinations during transition between sleep and waking were also features. The link between narcolepsy and REM sleep emerged in the 1960s, and in 1962 Bedrich Roth[17] penned the book *Narkolepsie und Hypersomnie*. The discovery of hypocretin as the genetic underpinning for this disorder was a landmark discovery.[18]

Nosology

1979 marked the birth of the first "official" diagnostic classification of sleep and arousal disorders, which was published in the fledgling journal *Sleep*.[19] This nosology represented the most complete cataloging of sleep disorders and rapidly became the standard. The nosology was reorganized and expanded in 1990 under Michael Thorpy's chairmanship, and the International Classification of Sleep Disorders (ICSD) resulted.[20] The year before marked the publication of the first edition of *Principles and Practice of Sleep Medicine* (edited by Meir Kryger, Thomas Roth, and William C. Dement), which became the de facto textbook of the field.[21] The second edition of ICSD was published in 2005 and **Table 1** shows is basic configuration.[22]

CROSSROADS

Sleep medicine, nearly 100 years now from its original conception, finds itself at an important crossroads. Sleep medicine is now recognized by the American Board of Medical Specialties (ABMS). In addition, the Accreditation Council for Graduate Medical Education (ACGME) accredits sleep medicine fellowship training programs. Thus, sleep medicine has unquestionably entered the mainstream of professional medicine. With this entrance, the forces and currents of the mainstream now control its destiny more than the ideas, wishes, and principles of its founders and proponents. Sleep medicine arose largely from a laboratory science and its traditional orientation focused on research, methodology, diagnostics, classification, and epidemiology. As the field has matured, more attention has been paid to therapeutics, disease management, and outcome assessment. Public health and economics, 2 major currents of the mainstream, now enter the picture. Sleep medicine must adapt to economic demands and prove its worth in terms of improving health if it is to survive. Much work is needed with respect to sleep disorders and functional disabilities, disease burden, and positive outcomes produced by therapeutic interventions.

Leading the way in this endeavor are research projects providing evidence that sleep disorders (and in particular sleep-related breathing disorders) are associated with major medical problems. The link between sleep apnea and hypertension, heart disease, and cerebrovascular disease raised awareness that sleep disorders are important.[23,24] The icing on the cake will be when successful treatment of sleep disorders is proven to reverse or reduce the burden of these illnesses. Another area of progress has been clear links between motor vehicle accidents and excessive sleepiness (and sleep disorders that produce excessive sleepiness). The relationship between sleep problems and workplace productivity (and on-the-job accidents) has grabbed the attention of regulators, safety officers, and corporate managers. We have begun to see regulations targeting hours of service, sleep disorder screening, and sleep disorder therapeutic compliance, especially in the transportation industry. Rules are likely to become stricter, more specific, and more strongly enforced in the future. Thus, sleep clinicians will be at another crossroads, the one intersecting patient advocacy and regulatory restrictions. This position may be an uncomfortable one for many of us. Clinicians intrinsically devote themselves to patient care and reflexively advocate for their patients. We now find ourselves in a regulatory role in order to promote public safety. Furthermore, motor vehicle regulations are determined on a state-by-state basis, and reporting laws may conflict with federal Health Insurance Portability and Accountability Act (HIPAA) Privacy Rules.

UNDERLYING DYSFUNCTION OF SLEEP GENERATOR, WAKE GENERATOR, AND COORDINATION OF SLEEP AND WAKE GENERATORS

Basic mechanisms coordinating and governing sleep and wakefulness include (1) homeostatic sleep drive, (2) circadian rhythms, and (3) autonomic nervous system balance.[25] Homeostatic

Table 1
Sleep diagnostic categories according to the international classification of sleep disorders, 2nd edition

I. INSOMNIA
1. Adjustment Insomnia
2. Psychophysiological Insomnia
3. Paradoxical Insomnia
4. Idiopathic Insomnia
5. Insomnia due to Mental Disorder
6. Inadequate Sleep Hygiene
7. Behavioral Insomnia of Childhood
8. Insomnia due to Drug or Substance
9. Insomnia due to Medical Condition
10. Insomnia Not Due to Substance or Known Physiological Condition, Unspecified (*Nonorganic Insomnia, NOS*)
11. Physiological (*Organic*) Insomnia, Unspecified

II. SLEEP RELATED BREATHING DISORDERS

A. Central Sleep Apnea Syndromes
1. Primary Central Sleep Apnea
2. Central Sleep Apnea Due to Cheyne Stokes Breathing Pattern
3. Central Sleep Apnea Due to High-Altitude Periodic Breathing
4. Central Sleep Apnea Due to Medical Condition Not Cheyne Stokes
5. Central Sleep Apnea Due to Drug or Substance
6. Primary Sleep Apnea of Infancy

B. Obstructive Sleep Apnea Syndrome
7. Obstructive Sleep Apnea, Adult
8. Obstructive Sleep Apnea, Pediatric

C. Sleep Related Hypoventilation/Hypoxemic Syndrome
9. Sleep Related Nonobstructive Alveolar Hypoventilation, Idiopathic
10. Congenital Central Alveolar Hypoventilation Syndrome

D. Sleep Related Hypoventilation/Hypoxemia Due to Medical Condition
11. Sleep Related Hypoventilation/Hypoxemia Due to Pulmonary Parenchymal or Vascular Pathology
12. Sleep Related Hypoventilation/Hypoxemia Due to Lower Airway Obstruction
13. Sleep Related Hypoventilation/Hypoxemia Due to Neuromuscular & Chest Wall Disorders

E. Other Sleep Related Breathing Disorder
14. Sleep Apnea/Sleep Related Breathing Disorder, Unspecified.

III. HYPERSOMNIA OF CENTRAL ORIGIN NOT DUE TO A CIRCADIAN RHYTHM SLEEP DISORDER, SLEEP RELATED BREATHING DISORDER, OR OTHER CAUSE OF DISTURBED NOCTURNAL SLEEP.
1. Narcolepsy With Cataplexy
2. Narcolepsy Without Cataplexy
3. Narcolepsy Due to Medical Condition
4. Narcolepsy, Unspecified
5. Recurrent Hypersomnia
15. Kleine-Levin Syndrome
16. Menstrual-Related Hypersomnia
6. Idiopathic Hypersomnia With Long Sleep Time
7. Idiopathic Hypersomnia Without Long Sleep Time
8. Behaviorally Induced Insufficient Sleep Syndrome
9. Hypersomnia Due to Medical Condition
10. Hypersomnia due to Drug or Substance
11. Hypersomnia Not Due to Substance or Known Physiological Condition (*Nonorganic Hypersomnia, NOS*)
12. Physiological (Organic) Hypersomnia, Unspecified (*Organic Hypersomnia, NOS*)

IV. CIRCADIAN RHYTHM SLEEP DISORDERS
1. Circadian Rhythm Sleep Disorder, Delayed Sleep Phase Type
2. Circadian Rhythm Sleep Disorder, Advanced Sleep Phase Type
3. Circadian Rhythm Sleep Disorder, Irregular Sleep-Wake Type
4. Circadian Rhythm Sleep Disorder, Free Running Type
5. Circadian Rhythm Sleep Disorder, Jet Lag Type (*Jet Lag Disorder*)
6. Circadian Rhythm Sleep Disorder, Shift Work Type (*Shift Work Disorder*)
7. Circadian Rhythm Sleep Disorder Due to Medical Condition
8. Other Circadian Rhythm Sleep Disorder
9. Other Circadian Rhythm Sleep Disorder Due to Drug or Substance

V. PARASOMNIAS

A. Disorders of Arousal (From NREM Sleep)
1. Confusional Arousals
2. Sleepwalking
3. Sleep Terrors

B. Parasomnias Usually Associated with REM Sleep
4. REM sleep behavior disorder (including parasomnia overlap disorder and status dissociatus)
5. Recurrent Isolated Sleep Paralysis
6. Nightmare Disorder

C. Other Parasomnias
7. Sleep Related Dissociative Disorder
8. Sleep Enuresis
9. Sleep Related Groaning (Catathrenia)
10. Exploding Head Syndrome
11. Sleep Related Hallucinations
12. Sleep Related Eating Disorder
13. Parasomnia, Unspecified
14. Parasomnia Due to Drug or Substance
15. Parasomnia due to Medical Condition

VI. SLEEP RELATED MOVEMENT DISORDERS
1. Restless Legs Syndrome
2. Periodic Limb Movement Disorder
3. Sleep Related Leg Cramps
4. Sleep Related Bruxism
5. Sleep Related Rhythmic Movement
6. Sleep Related Movement Disorder, Unspecified
7. Sleep Related Movement Disorder Due to Drug of Substance.
8. Sleep Related Movement Disorder Due to Medical Condition

VII. ISOLATED SYMPTOMS, APPARENTLY NORMAL VARIANTS, AND UNRESOLVED ISSUES.
1. Long Sleeper
2. Short Sleeper
3. Snoring
4. Sleep Talking
5. Sleep Starts (*Hypnic Jerk*)
6. Benign Sleep Myoclonus of Infancy
7. Hypnagogic Foot Tremor and Alternating Leg Muscle Activation during sleep.
8. Propriospinal Cyclones at Sleep Onset
9. Excessive Fragmentary Myoclonus

VIII. OTHER SLEEP DISORDERS
1. Other physiological (Organic) Sleep Disorders
2. Other Sleep disorder Not Due to Substance or Known Physiological Conditions.
3. Environmental Sleep Disorder

regulation of sleepiness parallels that for thirst, hunger, and sex. Sleepiness increases as a function of the duration of prior wakefulness. Homeostatic process is thought to be mediated hypothalamically. The hypnotoxin theory represents an early mechanistic approach to explaining sleep homeostasis. An alternative theory, one in which neurotransmitters are depleted during wakefulness and must be replenished by sleep, has also been proposed. Of course, both are correct at some level. However, homeostasis is inadequate to explain our sleep-wake behaviors. Most individuals reach peak alertness in the late evening, just before they become sleepy. Why someone would reach peak alertness at 8 PM after being awake all day contradicts the homeostatic prediction. Thus another factor must be involved to regulate the sleep-wake cycle, and this is the circadian rhythm. As previously mentioned, the sleep-wake circadian rhythm is regulated by the suprachiasmatic nucleus and it provides a wakefulness stimulus to offset accumulating homeostatic drive for sleep. When SCN activation declines, homeostatic drive asserts itself and the individual becomes very sleepy. Autonomic activation provides a mechanism to override the usual dynamics of the sleep-wake process. Increasing sympathetic activation can reduce sleepiness, at least temporarily. Thus, noradrenergic (and dopaminergic) responses to emergency situations protect the individual from being at the mercy of their sleep-wake cycle; it allows wakefulness to supersede sleep for a period of time so that life-threatening situations can sometimes be averted.

NORMAL SLEEP

Because sleep is conceptualized as something done by the brain, the traditional measurement approach involves recording electroencephalographic (EEG) activity. An assortment of fairly unique EEG events occur during sleep (**Fig. 1**), and these can be used to classify sleep into stages. Electrooculographic (EOG) and electromyographic (EMG) activity were added to further differentiate specific sleep categories and characterize their features. Systems for sleep staging were developed to summarize sleep patterns in an attempt to find commonalities between individuals and to characterize a normal sleep pattern. An assortment of early sleep stage systems finally gave way to establishment of the standardized manual in 1968.[26] This scoring system remained the standard for 39 years, ultimately being updated by the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events (2007).[27]

EEG activity recorded from central, occipital, and frontal derivations, EOG activity from the right and left eyes' outer canthi, and EMG recorded from the submentalis are summarized for each 30 seconds of recording (or epoch). Sleep stage scoring involves dividing the recording into epochs and classifying each as W (wake) or sleep stage N1, N2, N3, and R (REM). Stages 1, 2, or 3 are collectively referred to as non-REM (NREM) sleep.[28] EEG, EOG, and EMG characteristics vary for wakefulness and the different sleep stages. N1 is characterized by low-voltage mixed-frequency EEG without K-complexes, spindles, or rapid eye movements, and less than 15 seconds of alpha EEG activity. Vertex sharp waves may be present. N2 sleep is characterized by sleep spindles or K-complexes but less than 5 seconds of high-amplitude delta EEG activity (slow waves) per epoch. N3 sleep is scored if more than 5 seconds of slow-wave activity occurs. REM sleep is characterized by low-voltage mixed-frequency EEG activity (but devoid of spindles or K-complexes) accompanied by rapid eye movements and nearly absent submentalis EMG activity.

A healthy young adult will sleep 85% to 95% of their time in bed. Sleep onset should occur within 15 to 20 minutes after retiring, and nocturnal awakenings should be brief. N2 sleep typically occupies approximately half the night's sleep, with N3 accounting for 10% to 20%, N1 for 1% to 5%, and REM sleep for 20% to 25%. Inconsequential differences in stage distributions are found between young adult men and women, but these can increase with advancing age. NREM and REM repeat in 90- to 120-minute long cycles and **Fig. 2** shows a typical night for a healthy young adult. Sleep architecture can be generalized as beginning with NREM sleep, having slow-wave activity predominate in the first third of the night, having REM sleep predominate in the latter half of the night, and containing 4 to 6 individual REM sleep episodes that successively lengthen during the sleep period.[29]

PRESENTATIONS: INSOMNIA, HYPERSOMNIA, AND PARASOMNIA

Patients with sleep disorders often present with multiple nighttime symptoms and related daytime consequences. The main categories of presenting complaints include insomnia, excessive sleepiness, and unusual or unwanted behaviors occurring during sleep or arising from sleep (parasomnias). Insomnia in adults may include: difficulty falling sleep, difficulty maintaining sleep, and/or early morning awakening. By contrast, in pediatrics the insomnia may present as bedtime

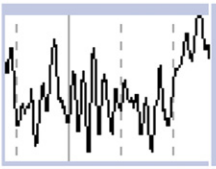
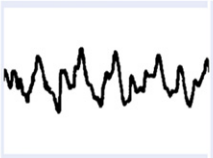
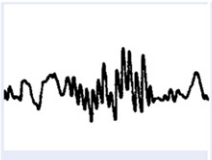
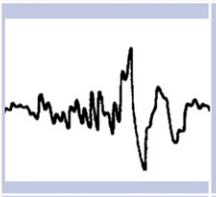
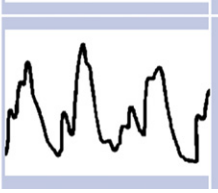
EEG Activity	Sample	Definition
Alpha activity		8-13 Hz rhythm, usually most prominent in occipital derivations. Used as a marker to differentiate sleep from wakefulness and to detect CNS arousals.
Theta activity		4-8 Hz waves typically prominent in central & temporal derivations. Saw-tooth activity (shown in figure) is a variant seen during REM sleep.
Vertex sharp waves		A sharply contoured, negative-going bursts that stand out from the background activity. Vertex sharp waves typically most prominent in central derivations placed near the midline
Sleep spindle		A phasic burst of 11-16 Hz activity, prominent in central derivations, typically lasting for 0.5 - 1.5 seconds.
K complex		An EEG event consisting of a well delineated negative sharp wave immediately followed by a positive component standing out from the background EEG with total duration ≥0.5 seconds, usually maximal in amplitude over the frontal regions.
Slow waves		High amplitude (≥75μvolts), low frequency (≤ 2 Hz) variant of delta (1-4 Hz) activity that are the defining characteristic of stage N3 sleep.

Fig. 1. EEG waveforms characterizing sleep and wakefulness.

resistance and/or inability to sleep independently. According to the latest classification of sleep disorders, diagnosis of insomnia should be considered if the aforementioned complaints are associated with daytime consequences, including: daytime sleepiness, fatigue, or malaise; impaired attention, concentration, or memory; social or vocational dysfunction or poor school

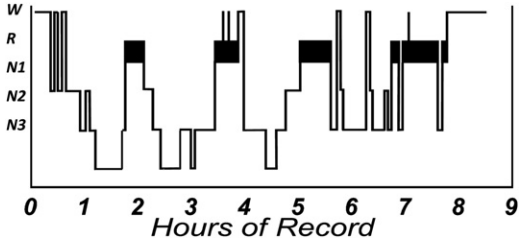


Fig. 2. Sleep Stage Histogram for a Normal, Young Adult Subject.

performance; mood disturbance or irritability; daytime sleepiness; motivation, energy, or initiative reduction; proneness for errors or accidents at work or while driving; tension headaches or gastrointestinal symptoms in response to sleep loss; and concerns or worries about sleep. Insomnia may be primary, but usually there are identifiable causes. Other comorbid conditions include medical or mental illnesses, other sleep disorders, or medications or drugs that produce or perpetuate the sleeplessness problem.

Excessive sleepiness (ES) is a very common symptom among patients with sleep disorders.[30] Patients with ES usually struggle to stay awake and may fall asleep in various inappropriate (and sometimes dangerous) situations (eg, while driving an automobile). ES naturally arises from acute or chronic sleep deprivation. Sleepiness can result from not scheduling an adequate amount of time for sleep, a mismatch between circadian rhythm and the timing of sleep (eg, jet lag), frequent sleep interruptions due to environmental factors (eg, environmental noise), and/or disease-related sleep disturbances (eg, obstructive sleep apnea or periodic limb movements). ES may also result from primary dysfunction of sleep mechanisms (eg, brain injury or neurodegenerative diseases). Finally, in some cases the specific cause of the ES is not clear (eg, idiopathic hypersomnia).

Parasomnias are undesirable behaviors, physical events, or experiences that occur during entry into sleep, within sleep, or during arousal from sleep. Parasomnias encompass a wide assortment of abnormal sleep-related movements, behaviors, emotions, perceptions, dreaming, and autonomic nervous system functioning. Examples include nightmares, sleep walking, sleep bruxism, sleep terrors, and exploding head syndrome.

DIAGNOSTIC WORKUP

As with any illness, initial workup of sleep disorders relies heavily on eliciting a detailed history and performing a comprehensive physical examination (where indicated). One differentiating point in the workup of sleep disorders is the importance of interviewing the bed partner. A detailed history focuses on first identifying the major sleep complaint, establishing the timeline of its development, and identifying factors or circumstances that aggravate or improve the complaint. Furthermore, the interviewer should identify other associated symptoms that may help to narrow the differential diagnoses.

As part of comprehensive workup of sleep complaints, the detailed sleep pattern of the patient should be explored. The bedtime and wake time during weekdays and weekends, the subject's latency to fall asleep, number and duration of naps, effect of naps (refreshing or not), and details of work (and specifically shift work) constitute important information. In addition, use of stimulants (eg, quantity and timing of caffeinated beverages), alcohol, and timing of physical exercise can help to identify poor sleep hygiene that may contribute to sleep complaints.

Regarding insomnia, the onset of insomnia and the circumstance(s) that initiated the insomnia are important. In many cases, a major event such as the loss of a job or the death of a significant person initiates the insomnia. However, in most cases the insomnia resolves in less than 3 months. In some individuals, the insomnia will continue beyond this initial period. Identifying the sleep pattern, not only during adult life but also from the time that the patient may remember, will help to identify the tendency for developing prolonged insomnia in response to stressors. Identifying the habits that are developed and may feed into prolongation of this insomnia is very important. For example, an individual may start feeling tense when trying to fall asleep and ruminate about not being able to sleep (psychophysiologic insomnia). Development of psychophysiologic insomnia can perpetuate the initial phase of stressor-induced adjustment insomnia, and thus prolong the insomnia beyond the initial 3 months. The consequence of insomnia also should be explored, as difficulty falling asleep or maintaining sleep without any daytime consequences will not be considered insomnia. The interviewer should also explore the various behaviors that may not be conducive to sleep, as these are important as regards the proper initiation of sleep. Such behaviors can include reading or watching TV in bed or any other activities that may result in central nervous system stimulation close to bedtime.

Regarding parasomnias, detailed description of the events will be helpful in narrowing down the differential diagnosis. NREM parasomnias mostly happen at the earlier stages of sleep and closer to sleep onset. By contrast, REM-related parasomnias often occur late in the night when REM periods increase in duration and intensity.

Physical examination may help to identify factors associated with some of the sleep disorders. The most important findings are related to sleep-related breathing disorders, and include obesity, large tongue, upper airway abnormalities including crowded upper airways, large tonsils (especially in children), long uvula and soft palate, and large tongue. Facial abnormalities including mandibular retrognathia and micrognathia may predispose to a small airway and increase the risk of obstructive sleep apnea. Features of

endocrine disorders such as hypothyroidism and acromegaly may be seen in some patients with obstructive sleep apnea. However, lack of the aforementioned findings does not rule out clinically significant obstructive sleep apnea.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis for insomnia includes disorders of circadian rhythm disturbances, conditions that cause sleep disruption such as restless leg syndrome, a variety of chronic medical conditions that may interrupt sleep (eg, chronic obstructive pulmonary disease and congestive heart failure), and environmental factors that may disturb sleep (eg, noise, high temperature, light, or even a bed partner that snores). Use of medications, stimulants (eg, caffeinated beverages), alcohol, and recreational drugs may also cause insomnia. Psychiatric conditions (eg, mood disorders and posttraumatic stress disorder) are commonly associated with insomnia. Many comorbid forms of insomnia may result in a maladaptive behavior presenting as psychophysiological insomnia. Unfortunately, insomnia sometimes has no identifiable causal or exacerbating factors (ie, idiopathic insomnia).

Differential diagnosis of excessive daytime sleepiness revolves around the adequacy and integrity of sleep. Disorders that result in sleep interruptions often present as ES. The interrupting factors can be environmental (eg, noise), respiratory events and snoring, leg movement, chest pain or dyspnea, waking up for frequent urination, or waking up because of reflux. The second category of causal factors for excessive daytime sleepiness is inadequate sleep time, which includes various forms of insomnia including circadian rhythm disorders and insufficient sleep because of lifestyle or work load. The third category of disorders presenting with ES includes disease patients who sleep for an adequate amount of time but remain sleepy. These conditions include disorders such as organic hypersomnia, including stroke. Use of recreational drugs also may also produce hypersomnia.

The differential diagnosis for parasomnias mainly includes NREM and REM parasomnias. Common parasomnias include nocturia, bruxism, and leg cramps. Some parasomnias are secondary to sleep-related breathing disorders while others can be drug induced. The major differential diagnosis for parasomnias involving prominent sleep-related behaviors (especially if injurious) is epilepsy. A detailed history and an extensive nocturnal EEG recording may help to differentiate seizure from other parasomnias.

ASSESSMENT

In the Office

Various diagnostic tests can help to narrow the differential diagnoses or confirm the diagnosis. Use of history and a focused physical examination should guide selection of subsequent diagnostic testing. Questionnaires and psychometric instruments can also provide valuable information. A good starting point is to determine the patient's sleep-wake schedule, especially if the chief complaint is insomnia or ES. Self-reported bedtimes and rising times (both on weekdays and weekends), possibly augmented by a sleep diary, can provide invaluable data. In a typical sleep diary, a patient not only tracks retiring and waking times, but also document how long it takes to fall asleep, how many hours thought to be slept, how many awakenings occurred, overall sleep quality (refreshingness), the use of stimulants (eg, caffeinated beverages), use and timing of medications (that may affect sleep), naps, and exercise times and frequency. The sleep diary will help obtain an overall picture of a patient's sleep-wake cycle and identify possible factors that may negatively affect sleep duration and quality. These self-reported data can be validated using objective measures obtained with actigraphy (see section on home testing). It is also standard procedure to administer a sleepiness questionnaire (eg, the Epworth Sleepiness Scale), a mood-screening instrument (eg, Zung Depression Scale or Beck Depression Inventory), possibly an anxiety scale, and some sort of generalized questionnaire on sleep problems. Because so many patients are referred for assessment of possible sleep-related breathing disorders, indexing the symptoms of sleep-disordered breathing and estimating severity with a validated instrument is strongly recommended (eg, the STOP-BANG questionnaire, Berlin Questionnaire, or Multivariable Apnea Prediction Scale).

Blood, urine, and other fluids drawn to further investigate possible sleep and fatigue issues also provide ancillary diagnostic information. Clinical laboratory testing for ferritin levels (for patients with possible RLS), thyroid function tests for patients with fatigue, urinalysis for drug screening, and HLA typing represent some of the analyses ordered at the sleep center.

In the Laboratory

Attended laboratory sleep studies (also called polysomnography) are commonly used to diagnose sleep-related breathing disorders and to determine therapeutic positive airway pressure needed to eliminate breathing pathophysiologies.[31] Laboratory polysomnography, synchronized with video recording, is also indicated to diagnose other sleep disorders and to differentiate parasomnias from

sleep-related seizure.[32,33] The Multiple Sleep Latency Test (MSLT) is a procedure primarily used to confirm narcolepsy. In addition, it provides objective documentation of sleepiness. MSLT provides 4 or 5 nap opportunities, scheduled at 2-hour intervals throughout the day, beginning approximately 2 hours after rising from a prior night's laboratory sleep study. During each test session, polysomnographic parameters are recorded while the patient attempts to relax and not resist falling asleep. Maintenance of Wakefulness Testing (MWT) also provides patients with test sessions scheduled at 2-hour intervals; however, the patient is instructed to resist falling asleep. The success, partial success, or failure at remaining awake provides objective measures of the patient's ability to overcome drowsiness in a nonstimulating environment. Four 40-minute test sessions are recorded while EEG, EOG, and submentalis EMG parameters are recorded. The Suggested Immobilization Test (SIT) is used for the diagnosis of RLS. During a SIT procedure, the patient semi-reclines in bed with legs outstretched and eyes open for 60 minutes before bedtime. The patient is instructed not to move but to remain awake. Polysomnographic recordings, including leg EMG derivations, are made concurrently to determine whether abnormal muscle activity and/or irresistible movements occur.

Home Testing

As previously mentioned, actigraphy can be used to augment sleep diaries. A wristwatch-like device records movement using accelerometers.[31] Data are stored in memory for several days or weeks. Actigraphs commonly also monitor light levels using a photosensor. Information about a patient's sleep schedule, rest-activity cycle, and circadian patterns can be deduced from data collected.

Home sleep testing (HST) includes measures used principally to confirm sleep-disordered breathing in symptomatic patients.[34] Cardiopulmonary recorders with oximetry represent the most common configuration. HST is a confirmation technique only; it does not rule out sleep-related breathing disorders because it is prone to artifact and is less sensitive than laboratory polysomnography. Nonetheless, in patients with severe sleep apnea, HST clearly documents the pathophysiology, and treatment can thus proceed.

SLEEP'S PRESUMED FUNCTIONS IN RELATION TO NEUROREHABILITATION AND RELEVANT SLEEP DISORDERS

In Macbeth, Shakespeare muses on "Sleep that knits up the ravelled sleeve of care, the death of each day's life, sore labor's bath, balm of hurt minds, great nature's second course, chief nourisher in life's feast."[35] Although scientific disagreements invariably arise when colleagues discuss the "function of sleep," all generally agree with Shakespeare that sleep is essentially a restorative process. The healing power of sleep and its necessity to rejuvenate or recharge us after a long day's activity seems incontrovertible. Research focused on the underlying biology finds sleep critical for both somatic and psychological restoration as well as being responsive to changing demands placed on the body and mind.

Sleep-related breathing disorders are especially relevant to rehabilitation. The sleep disturbances provoked by frequent awakening adversely affects all aspects of health.[23] Increased blood pressure, autonomic dysregulation, possible insulin resistance, neuroendocrine imbalances, cardiac afterload, and cerebrovascular insult can all result from sleep apnea. Some sleep disorders are also associated with alterations in cytokines and inflammatory markers. Furthermore, consequent hypoxemia (especially in patients with comorbid lung disease) compromises the individual further by precipitating cardiac arrhythmia and lowering seizure threshold. A wide assortment of conditions increases the risk for sleep-disordered breathing, especially spinal injury and neurodegenerative disorders. Neurodegenerative disorders also increase the risk for RLS and the parasomnia REM sleep behavior disorder (which can also be prodromal for Parkinson disease).[36]

Sleep can also provide prognostic indications. Patients with cerebrovascular infarcts in whom sleep spindles do not return after several days usually have a poor outcome. By contrast, overall improvement in sleep quality usually signals good recovery. Sudden adverse changes in sleep and sleep-related phenomena are seldom good omens. If a patient suddenly begins to have vivid dreams, this usually indicates that a sleep disturbance is awakening them from REM sleep (if one does not awaken, dreams are not remembered).[37] The disturbance can arise from a failure of the dream process to defuse dream anxieties (possibly from being overwhelmed) or simply from an awakening caused by a breathing disorder (that often adversely affects REM more than NREM sleep). Sleep can be a sensitive marker because it is fragile, but also because it is resilient. In a sense, sleep serves as a bellwether of overall health.

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