

The Neurobiology of Sleep

Saper, Clifford B. MD, PhD, FAAN, FRCP. CONTINUUM: Lifelong Learning in Neurology. Volume 19(1) Sleep Disorders. February 2013: p 19–31.

Abstract

ABSTRACT:

Purpose of Review:

The basic circuitries that regulate wake-sleep cycles are described, along with how these are affected by different disease states and how those alterations lead to the clinical manifestations of those disorders.

Recent Findings:

The discovery of both sleep-promoting neurons in the ventrolateral preoptic nucleus and wake-promoting neurons, such as the lateral hypothalamic orexin (also called hypocretin) neurons, has allowed us to recognize that these two populations of neurons are mutually antagonistic (ie, inhibit each other) and form a “flip-flop switch,” a type of circuit that results in rapid and complete transition in behavioral state. The same principle applies to the circuitry controlling transitions between REM sleep and non-REM (NREM) sleep.

Summary:

The flip-flop switch circuitry of the wake-sleep regulatory system produces the typical sleep pattern seen in healthy adults, with consolidated waking during the day and alternation between NREM and REM sleep at night. Breakdown in this circuitry both results in and explains the manifestations of a variety of sleep disorders including insomnia, narcolepsy with cataplexy, and REM sleep behavior disorder.

Key Points

- von Economo was the first neurologist to recognize that specific brain lesions could identify brain circuitry controlling wake-sleep cycles.
- The ascending arousal system begins in the upper pons and contains two branches, one to the thalamus and the other through the hypothalamus and basal forebrain, both of which activate the cerebral cortex.
- Sleep-promoting neurons in the preoptic area, posterior lateral hypothalamus, and possibly the lower brainstem inhibit the neurons in the arousal areas during sleep.

- The mutual inhibition between the wake-promoting and sleep-promoting circuits produces a flip-flop switch, which ensures rapid and complete transitions between sleep and wakefulness.
- Sleep is divided into REM sleep, characterized by a fast EEG and muscle atonia, and non-REM sleep, during which the EEG is slow and high voltage, and muscle tone is present but low.
- Primary insomnia is associated with a state of coactivation of both arousal- and sleep-promoting systems, resulting in a different state in which the EEG simultaneously shows both the slowing of non-REM sleep and the fast frequencies associated with active wakefulness.
- REM sleep behavior disorder is due to a failure of atonia circuitry during REM sleep, allowing the patient to act out dreams, which often are violent.
- REM generator neurons in the upper pons are tonically inhibited by REM-off neurons in the lower midbrain, which gate the entry into REM sleep.
- Orexin neurons in the posterior lateral hypothalamus stabilize the sleep-wake and the REM switches.
- The loss of orexin neurons produces narcolepsy, which is characterized by state instability: falling asleep too often when awake, waking up too often when asleep, and falling into partial REM states such as atonia (cataplexy) or dreaming (hypnagogic or hypnopompic hallucinations).

Approach to and Evaluation of Sleep Disorders

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Abstract

ABSTRACT:

Purpose of Review:

This article provides a framework for the clinical assessment of patients with sleep-related complaints and outlines a systematic approach to a sleep-specific history and physical examination, subjective assessment tools, and diagnostic testing modalities.

Recent Findings:

Physical examination findings may suggest the presence of a sleep disorder, and obstructive sleep apnea in particular, but the clinical history remains the most important element of the assessment for most sleep problems. While nocturnal polysomnography in a sleep laboratory remains the gold standard for diagnosis of sleep-disordered breathing, out-of-center testing may be considered when the clinician has a high pretest suspicion for obstructive sleep apnea and the patient has no significant cardiopulmonary, neuromuscular, or other sleep disorders.

Summary:

Sleep-related symptoms are common in adult and pediatric patients. A comprehensive sleep history, physical examination with detailed evaluation of the head and neck, and judicious use of

sleep-specific questionnaires guide the decision to pursue diagnostic testing. Understanding of the benefits and limitations of various diagnostic modalities is important as the spectrum of testing options increases.

Key Points

- Information from the patient, medical record, and any available bed partner, friend, or family member can clarify the extent and consequences of the patient's sleep-related symptoms.
- The 3P framework of insomnia comprises predisposing, precipitating, and perpetuating factors. Discussion of all factors facilitates identification of potential treatment targets.
- Details of facial morphology, nasal airway patency, and oral airway crowding are key features of the sleep-specific examination.
- Classification of the patient's dentition helps to evaluate the position of the maxillary arch relative to the mandibular arch.
- The Epworth Sleepiness Scale, a patient-completed questionnaire, assesses the patient's subjective tendency to doze during sedentary situations in recent times, not only at the moment the questionnaire is completed.
- The Epworth Sleepiness Scale should not be used in lieu of diagnostic testing but may be a valuable component of ongoing clinical evaluation.
- A daily sleep diary helps to summarize a patient's sleep-wake schedule more accurately than memory often allows and can facilitate construction of personalized plans for management of circadian rhythm sleep disorders and insomnia.
- The complex classification of portable testing devices reflects the multitude of designs available to clinicians and will undoubtedly change as technology advances.
- Careful consideration should be given to the indications for out-of-center testing. Attended nocturnal polysomnography is indicated if a portable study yields a negative or technically inadequate result.
- The multiple sleep latency test is the gold standard for objective assessment of daytime sleepiness, but interpretation of the results must be made within the clinical context of the patient's history.
- In the multiple sleep latency test, the patient is instructed to try to sleep during each nap trial. In the maintenance of wakefulness test, the patient is instructed to try to remain awake during the nap trial.
- A baseline nocturnal polysomnogram is required before a multiple sleep latency test and considered, but not required, before a maintenance of wakefulness test.
- Actigraphy can be useful in evaluation and treatment of circadian rhythm sleep disorders and in management of insomnia.
- Neuroimaging is not routinely indicated in the clinical evaluation of sleep disorders and should be pursued on a case-by-case basis.
- Careful assimilation of the clinical history, the sleep-specific physical examination, patient questionnaires, and diagnostic test results leads to the most accurate assessment of patients with symptoms related to sleep or alertness.

Chronic Insomnia

Neubauer, David N. MD. CONTINUUM: Lifelong Learning in Neurology. Volume 19(1) Sleep Disorders. February 2013: p 50–66.

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Abstract

ABSTRACT:

Purpose of Review:

This article provides an overview of current strategies for evaluating and treating patients who experience chronic insomnia.

Recent Findings:

The US Food and Drug Administration (FDA) has approved several medications for the treatment of insomnia that incorporate a variety of pharmacodynamics and pharmacokinetic properties, thus allowing the development of a customized therapeutic approach. FDA-approved medications include γ -aminobutyric acid-modulating benzodiazepine receptor agonists, a melatonin receptor agonist, and a histamine receptor agonist. Psychological and behavioral techniques combined as cognitive-behavioral therapy also have been shown to be effective in the treatment of chronic insomnia.

Summary:

Insomnia is the most common sleep disturbance and represents a chronic condition for many people. Difficulty falling asleep and maintaining sleep are highly prevalent problems in patients with neurologic disorders. Multiple factors typically contribute to insomnia. Accordingly, a rather broad approach to evaluating patients is warranted. Evidence-based guidelines support the use of cognitive and behavioral strategies and selected medications in the treatment of patients with chronic insomnia.

Key Points

- Poor sleep, whether due to inadequate quality or quantity, increases the risk for multiple chronic comorbid health conditions.
- Wellness promotion should include good quality sleep along with a healthy diet and exercise plan.
- The diagnosis of insomnia requires some degree of daytime impairment in addition to persistent difficulty falling asleep or remaining asleep.
- Insomnia currently is conceptualized as a disorder of the wake system resulting in round-the-clock hyperarousal.
- During the daytime most patients with chronic insomnia feel fatigued but not sleepy.
- Chronic insomnia associated with daytime consequences affects about one in 10 adults.
- Patients with chronic insomnia frequently have comorbid conditions associated with their sleep disturbance.
- Use a comprehensive approach in evaluating chronic insomnia; the etiology is multifactorial for most patients.
- Sleep logs and questionnaires completed by patients are very helpful in the insomnia evaluation process.
- Sleep laboratory studies are not routinely performed in the insomnia evaluation, but they are invaluable for selected patients with risk factors for comorbid sleep disorders.
- It is useful to establish clear goals with patients when treating their insomnia symptoms.
- Always consider the potential influences of sleep-disordered breathing and circadian rhythm sleep disorders when evaluating insomnia symptoms.

- Be sure to review the complete list of a patient's medications to identify possible sleep-disturbing effects.
- Strongly encourage healthy sleep habits for all patients. Primary treatment modalities may fail if patients have irregular bedtime hours or drink excessive caffeinated beverages.
- Psychological and behavioral strategies combined as cognitive-behavioral therapy for insomnia have been shown to be effective in numerous well-controlled studies.
- Insomnia medications approved by the US Food and Drug Administration include γ -aminobutyric acid response modulators, a melatonin receptor agonist, and a histamine H1 receptor antagonist.
- Benzodiazepine receptor agonist hypnotics all are allosteric modulators of γ -aminobutyric acid responses at the GABA_A receptor complex.
- In addition to immediate-release and extended-release pill and tablet formulations, benzodiazepine receptor agonist hypnotics are available in oral spray and sublingual dissolvable formulations.
- Low-dose doxepin is approved for the treatment of insomnia characterized by difficulty with sleep maintenance.
- Beware of the anticholinergic effects associated with over-the-counter antihistamines people often use as sleep aids.
- Melatonin, which is unregulated in the United States, may be beneficial in the treatment of certain circadian rhythm sleep disorders, especially in people with a phase-delay pattern.
- Currently the most promising novel pipeline compounds are orexin receptor antagonists.

Primary Hypersomnias of Central Origin

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Abstract

ABSTRACT:

Purpose of Review:

This review discusses the various causes of primary hypersomnias with emphasis on clinical recognition, diagnosis, and treatment options.

Recent Findings:

Narcolepsy is probably the most fascinating syndrome causing excessive daytime sleepiness. With increasing understanding of the hypocretin/orexin pathways and the neurotransmitters that subserve the role of wakefulness and sleep, newer therapeutic modalities with promising results are being investigated and opening new frontiers in the treatment of this rare but devastating disease.

Summary:

This article reviews the primary hypersomnias of central origin. Where possible, clinical cases that highlight and explain the clinical syndromes are included. Treatment modalities and future directions are also discussed to help the clinician identify and treat the underlying disorder.

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Key Points

- Most whites and African Americans who have narcolepsy with cataplexy are positive for HLA-DQB1*0602, showing a strong association with this human leukocyte antigen type.
- Naps are usually refreshing and often recommended as part of the treatment plan for narcolepsy. Short daytime naps lasting about 30 minutes can result in the attenuation of the sleep drive for a few hours.
- Symptoms of subtle muscle weakness in cataplexy include slurring of speech, buckling of knees, jaw dropping, or even nodding of the head and should be specifically elicited during history taking.
- A rare sustained cataplectic episode, status cataplecticus, may occur following abrupt discontinuation of medications used to treat cataplexy. This is also referred to as rebound cataplexy.
- The presence of a sleep-onset REM period on an overnight sleep study of a patient with a history of excessive daytime sleepiness and muscle atonia that occurs in the setting of an emotional outburst may be suggestive of a diagnosis of narcolepsy with cataplexy.
- Hypocretin-1 and hypocretin-2 are the two peptides that result from the splitting of their precursor, preprohypocretin. Hypocretin-1 is implicated in human narcolepsy.
- A finding of low (less than 110 pg/mL) or undetectable CSF hypocretin levels will nearly always be seen in patients with true narcolepsy with cataplexy.
- Various medications treat the individual symptoms of narcolepsy with cataplexy, but sodium oxybate is favored over the others because of its effectiveness in treating the primary symptoms, including excessive daytime sleepiness and REM-related atonia (cataplexy), simultaneously.
- Idiopathic hypersomnia has an unknown etiology and is typified by symptoms of nonrefreshing sleep with difficulty waking up, which could either be in the morning or after a nap.
- Naps are usually not refreshing in patients with idiopathic hypersomnia, in contrast to patients with narcolepsy, who find scheduled naps very rewarding.
- Kleine-Levin syndrome consists of symptoms of hyperphagia, hypersomnia, and hypersexuality.
- Kleine-Levin syndrome is a clinical diagnosis, and the investigations are done merely to rule out other causes of hypersomnia.
- Most episodes of Kleine-Levin syndrome resolve spontaneously within a 30-day period, and the interepisode hiatus almost never surpasses 15 months.
- SPECT has demonstrated a reduced perfusion of the thalamus during an active Kleine-Levin syndrome episode that eventually reversed to normal as the symptoms resolved.
- Women with menstrual-related hypersomnia experience episodes of recurrent sleepiness coinciding with their menstrual cycles.
- Posttraumatic hypersomnia is prevalent and often missed as a cause of unexplained hypersomnia.

Sleep-Disordered Breathing

Panossian, Lori MD, MS; Daley, Joseph MD, PhD. CONTINUUM: Lifelong Learning in Neurology. Volume 19(1) Sleep Disorders. February 2013: p 86–103.

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Abstract

ABSTRACT:

Purpose of Review:

This article introduces readers to the clinical presentation, diagnosis, and treatment of sleep-disordered breathing and reviews the associated risk factors and health consequences.

Recent Findings:

Sleep-disordered breathing is associated with significant impairments in daytime alertness and cognitive function as well as adverse health outcomes. The initial treatment of choice is positive airway pressure. Improvements in technology and mask delivery systems have helped to make this treatment more comfortable and convenient for many patients.

Summary:

Sleep-disordered breathing, particularly in the form of obstructive sleep apnea, is highly prevalent in the general population and has important implications for neurology patients. Sleep-disordered breathing is characterized by repetitive periods of cessation in breathing, termed apneas, or reductions in the amplitude of a breath, known as *hypopneas*, that occur during sleep. These events are frequently associated with fragmentation of sleep, declines in oxygen saturation, and sympathetic nervous system activation with heart rate and blood pressure elevation. Obstructive sleep apnea, which represents cessation of airflow, develops because of factors such as anatomic obstruction of the upper airway related to obesity, excess tissue bulk in the pharynx, and changes in muscle tone and nerve activity during sleep. Central sleep apnea represents cessation of airflow along with absence or significant reduction in respiratory effort during sleep and is more commonly found in the setting of congestive heart failure, neurologic disorders, or cardiopulmonary disease.

Key Points

- An obstructive apnea is defined as cessation of airflow with continued respiratory effort due to complete upper airway occlusion.
- A hypopnea is a partial decrement in airflow with an associated physiologic consequence, either an arousal or oxygen desaturation, due to partial upper airway collapse.
- A mixed apnea is defined as a period of airflow cessation without respiratory effort followed by a period of resumed effort with continued decrements in airflow.
- Obstructive sleep apnea is a highly prevalent condition that occurs predominantly in middle-aged or older men and postmenopausal women.
- Obstructive sleep apnea is viewed as a primarily mechanical problem of the upper airway, with both neuronal and anatomic factors contributing to increased collapsibility.
- Symptoms suggestive of obstructive sleep apnea include snoring; witnessed apneas; arousals associated with choking, gasping, and diaphoretic awakenings from sleep; and excessive daytime sleepiness.
- Polysomnography is the diagnostic modality of choice for obstructive sleep apnea and other sleep disorders, although monitors with fewer channels have been validated in certain populations for obstructive sleep apnea detection.
- The apnea-hypopnea index is the measure used to define the severity of sleep apnea; 5 or greater is considered to be abnormal.

- Continuous positive airway pressure uses forced air to stent the airway open and reduce obstructive events.
- A central apnea is defined by cessation of airflow without evidence of respiratory effort.
- Central sleep apnea can be seen in a variety of conditions, including congestive heart failure, medullary lesions, and autonomic dysregulation.
- Successful treatment of central sleep apnea associated with heart failure is associated with improved cardiac function and survival.

Complex Nocturnal Behaviors: Nocturnal Seizures and Parasomnias

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Abstract

ABSTRACT:

Purpose of Review:

This article summarizes the clinical and electrophysiologic manifestations of nocturnal seizures, particularly nocturnal frontal lobe epilepsy (NFLE), parasomnias, and other disorders presenting with complex behaviors in sleep. The evaluation and treatment of patients with complex nocturnal behaviors can be challenging. While the differential diagnosis of sleep-related movements, including physiologic and pathologic phenomena, is extensive, the focus of evaluation in patients with complex nocturnal behaviors distinguishes between nocturnal seizures and parasomnias.

Recent Findings:

Seizures in NFLE have a wide range of complexity and severity, overlapping considerably with the disorders of arousal from non-REM (NREM) sleep. Video polysomnography with EEG (VPSG-EEG) has identified key clinical features useful in differentiating these disorders. A dysfunctional arousal mechanism involving the cholinergic system is involved in the pathophysiology of the autosomal dominant form of NFLE and NREM parasomnias. The high prevalence of parasomnias in NFLE families further confounds their distinction. VPSG-EEG combines PSG with comprehensive EEG to evaluate unexplained nocturnal behaviors when epileptic seizures are suspected. This procedure provides improved detection of interictal and ictal EEG abnormalities and time-synchronized correlation of clinical and neurophysiologic phenomena.

Summary:

The diagnosis of complex nocturnal behaviors is among the most difficult to establish in sleep medicine clinics and laboratories. VPSG-EEG is indicated in the evaluation of patients with complex nocturnal behaviors when routine EEG is nondiagnostic. Ongoing research is necessary

to fully elucidate the pathophysiology of these disorders, which share a host of clinical manifestations.

Key Points

- Sleep is an important modulator of EEG abnormalities and seizures in patients with epilepsy; non-REM sleep activates and REM sleep inhibits epileptic discharges and seizures.
- The differential diagnosis of complex nocturnal behaviors includes nocturnal seizures, non-REM arousal disorders, REM sleep behavior disorder, and other parasomnias such as sleep-related dissociative disorders.
- Seizures in nocturnal frontal lobe epilepsy consist of hypermotor activity involving complex movements of the trunk and proximal extremities that are repetitive, high amplitude, and high velocity and asymmetric tonic seizures having dystonic, dyskinetic, and repetitive proximal movements that are highly stereotyped and frequent, often with preserved consciousness.
- Sudden, brief, and asymmetric tonic posturing of one or more extremities, commonly with both sides affected simultaneously, suggests early activation of the supplementary sensorimotor area.
- Autosomal dominant nocturnal frontal lobe epilepsy is associated with mutations in the transmembrane region of the neuronal nicotinic acetylcholine receptor alpha-4 subunit (*CHRNA4*), beta-2 subunit (*CHRN2*), and alpha-2 subunit (*CHRNA2*) and corticotrophin-releasing hormone.
- While sleep-related complex motor seizures have been considered pathognomonic for nocturnal frontal lobe epilepsy, extrafrontal origin is observed in up to 30% of patients, most often from the temporal and insular regions but also from the posterior cortex.
- Parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousals from sleep and involve complex, seemingly purposeful, goal-directed behaviors without consciousness.
- Arousal disorders can be precipitated by sleep deprivation and recovery from sleep deprivation due to slow-wave sleep rebound; mental and physical stress; fever; menses; environmental stimuli; sleep disorder-producing arousals, including sleep apnea and periodic limb movements; neurologic and psychiatric comorbid conditions; alcohol; and medications, particularly psychotropic drugs.
- The non-REM parasomnias include confusional arousals, sleep terrors, and sleepwalking, classified as distinct entities but in reality representing a spectrum of behaviors produced by a faulty arousal system.
- The presenting complaint in REM sleep behavior disorder is recurrent dream-enacting behaviors, including vocalizations and motor activity in relation to altered dream mentation. Sleep-related injuries to the affected person or bed partner occur in approximately one-third of cases.
- REM sleep behavior disorder usually emerges later in life, typically after age 50, and has a striking male predominance. The condition is frequently associated with the α -synucleinopathies, which include Parkinson disease, dementia with Lewy bodies, and multiple system atrophy.
- Activation of common pattern generators is responsible for the overlapping semiology of nocturnal seizures and arousal disorders.
- Video polysomnogram-EEG has several advantages over routine polysomnogram, including the improved ability to identify interictal and ictal EEG abnormalities and correlate clinical behaviors with neurophysiologic parameters.

- Complex nocturnal behaviors can be differentiated by the state from which episodes emerge. Nocturnal seizures typically arise from light non-REM sleep often during sleep-wake transitions, while arousal disorders arise from slow-wave sleep preferentially during the first third of the sleep period, and REM sleep behavior disorder episodes present from REM sleep preferentially during the last third of the sleep period.
- REM sleep behavior disorder is the only parasomnia that requires diagnostic confirmation by polysomnography. The pathognomonic polysomnographic finding in patients with clinical suspicion of REM sleep behavior disorder is REM sleep without atonia.

Circadian Rhythm Abnormalities

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Abstract

ABSTRACT:

Purpose:

This article reviews the recent advances in understanding of the fundamental properties of circadian rhythms and discusses the clinical features, diagnosis, and treatment of circadian rhythm sleep disorders (CRSDs).

Recent Findings:

Recent evidence strongly points to the ubiquitous influence of circadian timing in nearly all physiologic functions. Thus, in addition to the prominent sleep and wake disturbances, circadian rhythm disorders are associated with cognitive impairment, mood disturbances, and increased risk of cardiometabolic disorders. The recent availability of biomarkers of circadian timing in clinical practice has improved our ability to identify and treat these CRSDs.

Summary:

Circadian rhythms are endogenous rhythms with a periodicity of approximately 24 hours. These rhythms are synchronized to the physical environment by social and work schedules by various photic and nonphotic stimuli. CRSDs result from a misalignment between the timing of the circadian rhythm and the external environment (eg, jet lag and shift work) or a dysfunction of the circadian clock or its afferent and efferent pathways (eg, delayed sleep-phase, advanced sleep-phase, non-24-hour, and irregular sleep-wake rhythm disorders). The most common symptoms of these disorders are difficulties with sleep onset and/or sleep maintenance and excessive sleepiness that are associated with impaired social and occupational functioning. Effective treatment for most of the CRSDs requires a multimodal approach to accelerate circadian realignment with timed exposure to light, avoidance of bright light at inappropriate times, and adherence to scheduled sleep and wake times. In addition, pharmacologic agents are recommended for some of the CRSDs. For delayed sleep-phase, non-24-hour, and shift work disorders, timed low-dose melatonin can help advance or entrain circadian rhythms; and for shift work disorder, wakeenhancing agents such as caffeine, modafinil, and armodafinil are options for the management of excessive sleepiness.

Key Points

- Circadian rhythms are physiologic and behavioral cycles with a recurring periodicity of approximately 24 hours, generated by the endogenous biological pacemaker, the suprachiasmatic nucleus, located in the anterior hypothalamus.
- Circadian rhythms are synchronized with the earth's rotation by daily adjustments in the timing of the suprachiasmatic nucleus, following the exposure to stimuli that signal the time of day. These stimuli are known as “zeitgebers” (German for “time-giver”), of which light is the most important and potent stimulus. The magnitude and direction of the change in phase depends on when within the circadian system the light pulse is presented.
- Delayed sleep-phase disorder is characterized by chronic or recurrent inability to fall asleep and wake up at socially acceptable times, resulting in symptoms of difficulty falling asleep and excessive daytime sleepiness, particularly in the morning.
- Diagnosis of delayed sleep-phase disorder is made by careful history and well-kept sleep diaries with or without actigraphy for a minimum of 7 days (preferably 14 days).
- Bright light (full spectrum or blue enriched) in the morning for 2 hours shortly after the minimum of the core body temperature rhythm (typically occurring 2 to 3 hours before natural wake-up time) has been shown to successfully advance circadian rhythms in patients with delayed sleep-phase disorder.
- Patients with advanced sleep-phase disorder typically present with symptoms of daytime sleepiness (most prominent in the late afternoon or early evening hours) sleep maintenance difficulty, and early morning awakening.
- Practical therapeutic approaches for advanced sleep-phase disorder include timed light exposure in the evening and avoiding light in early morning hours. Melatonin or hypnotics may be beneficial for sleep-maintenance insomnia.
- Creating a cognitively enriched environment with structured social and physical activity during the day is an important therapeutic modality for patients with irregular sleep-wake rhythm disorder, especially if combined with a healthy bedtime routine and a nocturnal environment conducive to sleep.
- Non-24-hour sleep-wake disorder is characterized by a chronic or recurrent pattern of sleep and wake cycles that are not synchronized to the 24-hour environment. Typically a consistent daily drift (usually to later and later times) of sleep-onset and wake-up times occurs.
- In blind patients with non-24-hour sleep-wake disorder, melatonin is the therapeutic mainstay together with strong structured behavioral and social cues such as timing of meals, planned activities, and regular physical exercise. This same approach is recommended for sighted persons, with the additional option of bright light exposure in the morning shortly after awakening.
- Internal desynchronization of physiologic rhythms resulting from time-zone changes is responsible for most of the symptoms of jet-lag disorder. The severity of jet lag depends on several variables, including the number of time zones crossed and the direction of travel.
- Nonpharmacologic treatment approaches are important in the management of jet-lag disorder. Strategic exposure and avoidance of exposure to light have been utilized as an effective treatment approach.
- Based on the American Academy of Sleep Medicine practice parameters, timed melatonin administration is recommended as treatment for jet-lag disorder.
- Night shift workers and rotating shift workers get less sleep than day workers or evening shift workers.

- Shift work disorder is accompanied by significant social and economic burdens in the form of accidents, lost days of work, poorer performance, and increased health care use.
- For night shift workers, bright light exposure ranging from 1000 lux to 10,000 lux either in 3- to 6-hour blocks or in 20-minute to 1-hour blocks (ending 2 hours before the end of the shift) has been shown to accelerate circadian adaptation to night work and improve both alertness and performance.

Sleep and Comorbid Neurologic Disorders

Watson, Nathaniel F. MD, MSc; Viola-Saltzman, Mari DO. CONTINUUM: Lifelong Learning in Neurology. Volume 19(1) Sleep Disorders. February 2013: p 148–169.

Abstract

ABSTRACT:

Purpose of Review:

An understanding of the impact of sleep on neurologic disorders, and the impact of neurologic disorders on sleep, provides fresh opportunities for neurologists to improve the quality of life and functioning of their patients.

Recent Findings:

Sleep-disordered breathing (SDB) is a risk factor for cerebrovascular disease and should be considered in all TIA and stroke patients. Sleep disorders can amplify nociception and worsen headache disorders; and some headaches, including those related to SDB and hypnic headache, are sleep specific. REM sleep behavior disorder may be an early sign of neurodegenerative disease. Focal lesions of almost any etiology (eg, multiple sclerosis and CNS malignancies) in the hypothalamus, basal forebrain, or brainstem may result in sleep disturbance, sleepiness, and insomnia. Sleep-related hypoventilation and fatigue are common in neuromuscular disease. SDB and epilepsy are mutually facilitatory, and poor sleep can exacerbate epilepsy.

Summary:

Continued surveillance for sleep disorders by neurologists is rewarded by new treatment avenues in their patients with the possibility of improved clinical outcomes.

Key Points

- Sleep-disordered breathing is a term that encompasses all breathing disturbances in sleep, including obstructive sleep apnea, central sleep apnea, Cheyne-Stokes respirations, and upper airway resistance syndrome.
- Sleep-disordered breathing is an independent risk factor for stroke.
- Sleep-disordered breathing should be considered in all stroke and TIA patients.
- Cervical dystonia is associated with reduced sleep quality and sleepiness, even when compared to patients with other focal movement disorders.

- Sleep disturbance is present in nearly 90% of patients with Huntington disease, with most rating it a significantly important factor in overall health impairment.
- Sleep is impaired in 20% to 50% of children and young adults with Tourette syndrome.
- Obstructive sleep apnea is a common cause for headache upon awakening, particularly if it dissipates during the course of the day.
- Bruxism should be considered as a potential cause for headache upon waking.
- Patients with cluster headache have an eightfold increased risk of obstructive sleep apnea when compared to age- and sex-matched controls.
- Hypnic headache is sleep specific, occurring relative to REM sleep at a consistent time of the night.
- Epilepsy and sleep-disordered breathing are mutually facilitatory, with higher rates of each disorder observed in patients with the other disorder when compared to the general population.
- One in five patients with epilepsy has seizures exclusively during sleep.
- Most sleep-related seizures occur out of non-REM sleep, most often non-REM sleep stage N2.
- Nocturnal frontal lobe epilepsy can be difficult to distinguish from parasomnias, with stereotypia, minimal postevent confusion, and shorter duration providing clues that the event was epileptic in nature.
- Medication side effects should always be considered as a cause of sleepiness in a patient with epilepsy.
- When approaching a sleep problem in a patient with neurodegenerative disease, medication side effects should always be considered as a causative factor, particularly with cholinergic, antipsychotic, and sedative hypnotic medications.
- Sundowning is common in patients with neurodegenerative diseases; treatment is best focused on nonpharmacologic measures, such as improved sleep hygiene and a consistent daytime schedule, that include light exposure and regular physical activity.
- REM sleep behavior disorder can herald preclinical synucleinopathies, and as such patients with REM sleep behavior disorder should be followed for signs and symptoms of these diseases over time.
- Indicators of sleep-disordered breathing in patients with neuromuscular disorders include disrupted nocturnal sleep, daytime sleepiness and fatigue, morning headache, and trouble concentrating.
- Objective tests indicating nocturnal hypoventilation in neuromuscular disease include daytime PaCO₂ greater than 45 mm Hg, nocturnal oximetry showing oxygen saturation of 88% or less for 5 consecutive minutes, nocturnal PaCO₂ of greater than 55 mm Hg for 10 minutes or more or a 10 mm Hg or greater increase in PaCO₂ during sleep (compared to wake) to a value exceeding 50 mm Hg for 10 minutes or more, maximal inspiratory pressure of less than 60-cm water, and forced vital capacity of less than 50% predicted.
- When treating patients with neuromuscular disorders with bilevel positive airway pressure, improving ventilation is often more important than relieving airway obstruction, and wide pressure-support windows may be necessary.
- Multiple sclerosis lesions in brain areas subserving sleep onset, alertness, and REM sleep paralysis can precipitate insomnia, sleepiness, and REM sleep behavior disorder.
- Insomnia is common in multiple sclerosis and likely due to many disease-related factors, such as pain, spasticity, bladder dysfunction, depression, anxiety, and medication side effects.
- Sellar or suprasellar malignancies can indirectly cause sleep-disordered breathing by endocrinologic dysfunction causing obesity.

- Secondary narcolepsy can occur from treatment of CNS malignancies with surgical resection or radiation therapy in the perihypothalamic region.

Sleep-Related Movement Disorders

Silber, Michael H. MBChB, FAAN. CONTINUUM: Lifelong Learning in Neurology. Volume 19(1) Sleep Disorders. February 2013: p 170–184.

Abstract

ABSTRACT:

Purpose of Review:

This article reviews the sleep-related movement disorders, including restless legs syndrome (RLS; Willis-Ekbom disease), periodic limb movement disorder, rhythmic movement disorders, sleep-related bruxism, and sleep-related leg cramps.

Recent Findings:

The prevalence of clinically significant RLS is 1.5% to 3.0%. The pathophysiology of RLS may involve abnormal iron transport across the blood-brain barrier and down-regulation of putaminal D2 receptors. The availability of the rotigotine patch provides an additional form of dopaminergic therapy for RLS. Calcium channel alpha-2-delta ligands (gabapentin, gabapentin enacarbil, and pregabalin) provide alternative therapies for RLS especially in patients with augmentation, impulse control disorders, or hypersomnia induced by dopamine agonists. Long-term use of opioid medication is safe and effective for refractory cases of RLS.

Summary:

RLS is a common disorder causing considerable morbidity. Accurate diagnosis and appropriate investigations are essential. Many effective therapies are available, but the side effects of each class of medication should be considered in determining optimal treatment. Periodic limb movements of sleep, bruxism, and rhythmic movement disorders are sleep-related phenomena often accompanying other sleep disorders and only sometimes requiring primary therapy. Sleep-related leg cramps are generally idiopathic. Management is challenging with few effective therapies.

Key Points

- Restless legs syndrome that is prominent enough to occur at least twice a week and cause moderate or severe distress has a prevalence of 1.5% to 3.0%.
- Restless legs syndrome is diagnosed clinically and requires a history of an uncontrollable urge to move the legs while at rest that is worse in the evening or night and is relieved by movement such as walking.
- Mimickers of restless legs syndrome, especially sleep-related leg cramps relieved by stretching or massaging the affected muscle and positional discomfort relieved by changing position rather than walking, must be excluded.

- More than 50% of patients with restless legs syndrome have a family history of the disorder that is usually inherited in an autosomal dominant pattern. Multiple loci and several polymorphisms associated with restless legs syndrome have been identified.
- Low intracerebral iron, especially in the basal ganglia, possibly related to abnormalities in iron transport across the blood-brain barrier, may underlie restless legs syndrome. Restless legs syndrome is also associated with abnormalities in the dopamine system, possibly due to down-regulation of D2 receptors.
- Restless legs syndrome has profound effects on quality of life, equivalent to those caused by other chronic medical illnesses, and is associated with insomnia, depression, and anxiety.
- An association may exist between restless legs syndrome and vascular disease, but more research is needed to better define the degree and nature of the relationship before basing therapeutic decisions on concern for vascular risk.
- Serum ferritin should be measured in patients with chronic persistent restless legs syndrome.
- Oral iron replacement should be administered with vitamin C if serum ferritin levels are abnormally low and should be considered if levels are low normal (<50 μ /L).
- Nonergot dopamine agonists (ropinirole, pramipexole, and rotigotine transdermal patch) are highly effective treatments for restless legs syndrome but are associated with augmentation (worsening of restless legs syndrome earlier in the day), impulse control disorders, and hypersomnia.
- Impulse control disorders, including pathologic gambling and compulsive shopping, occur in 6% to 17% of patients taking dopamine agonists for restless legs syndrome and may only manifest 9 months or longer after starting treatment.
- Calcium channel alpha-2-delta ligands (gabapentin, pregabalin, and gabapentin enacarbil) are all effective in restless legs syndrome but can cause dizziness, unsteadiness, hypersomnia, and weight gain.
- High-potency opioids, such as oxycodone, hydrocodone, and methadone, are highly effective for refractory restless legs syndrome but are addictive and may exacerbate sleep apnea. In most patients they can be used for prolonged periods with no tolerance and continued effectiveness.
- Periodic limb movements of sleep occur in 80% to 88% of patients with restless legs syndrome and are also frequent in narcolepsy, REM sleep behavior disorder, obstructive sleep apnea, and normal people 60 years of age or older.
- In the absence of restless legs syndrome, periodic limb movements of sleep are generally nonspecific epiphenomena that accompany fragmented sleep with arousals and only rarely require treatment as a specific disorder.
- Sleep-related bruxism occurs in 8% of people, with highest prevalence in young adults. It can cause tooth damage and jaw discomfort but does not usually result in disrupted sleep.
- Rhythmic movement disorder, including head banging and body rocking, is common in infancy and early childhood but may persist into adulthood.
- Insomnia accompanying rhythmic movement disorder should be treated, but specific treatment for the movements is only needed if risk of bodily injury or severe disruption to sleep of a bed partner exists.
- Nocturnal leg cramps are usually idiopathic, and treatment is difficult; quinine should generally not be used because of serious potential side effects, including thrombocytopenia and cardiac arrhythmias.

Sleep Disorders in Children

Hoban, Timothy F. MD. CONTINUUM: Lifelong Learning in Neurology. Volume 19(1) Sleep Disorders. February 2013: p 185–198.

Abstract

ABSTRACT:

Purpose of Review:

The purpose of this review is to examine how sleep disorders in children are affected by age and comorbid medical influences, and to discuss current understanding of how the clinical manifestations, pathophysiology, and treatment of common childhood sleep disorders differ from those of the adult population.

Recent Findings:

Recently established age-specific norms are required for accurate interpretation of polysomnograms and multiple sleep latency tests in children.

Summary:

Sleep disorders such as insomnia, obstructive sleep apnea, and excessive daytime somnolence are common in both children and adults, but the clinical manifestations and underlying pathophysiology of these disorders vary substantially with age. For example, the bedtime struggles of a temperamental toddler are associated with different symptoms and causative factors compared to psychophysiologic insomnia affecting a middle-aged person. Similarly, a 6-year-old child with obstructive sleep apnea is more likely to exhibit daytime inattention and hyperactivity as a referable daytime symptom than the clear-cut lethargy or sleepiness that most affected adults experience. This review will examine how insomnia, excessive sleepiness, and obstructive sleep apnea differ in children compared to adults.

Key Points

- The symptoms, pathophysiology, and treatments for some sleep disorders are substantially different for children compared to adults.
- Ten percent of children do not achieve consolidated nighttime sleep by 1 year of age.
- Sleep-onset association disorder is one of the most common underlying or contributing causes for insomnia and night waking in infants and younger children.
- Many families try extinction-based interventions for only a few nights, encounter an “extinction burst” of temporarily worse symptoms, and abandon the technique before it has had time to be effective.
- Delayed sleep phase is an extremely common cause or contributing factor to insomnia in adolescent or older preadolescent children. When present, medication treatment alone is unlikely to be effective.
- “Sleeping in late” on weekend and non-school days can reduce the effectiveness of other interventions for delayed sleep phase.

- Obstructive sleep apnea is underdiagnosed in children in part because the lack of observed respiratory pauses and obvious daytime sleepiness in most affected children limit parent and medical practitioner recognition that the condition might be present.
- Although obesity represents a risk factor for childhood obstructive sleep apnea, children with low or normal body weight can have substantial obstructive sleep apnea, particularly when underlying adenotonsillar hypertrophy is present.
- Of children undergoing adenotonsillectomy for treatment of obstructive sleep apnea, 50% to 75% may still have some degree of obstructive sleep apnea postoperatively (usually milder).
- Continuous positive airway pressure is considered a first-line treatment for obstructive sleep apnea in children.
- Nasal steroids and rapid maxillary expansion represent promising alternative techniques for treatment of childhood obstructive sleep apnea.
- Some pediatric studies suggest that mild obstructive sleep apnea is more likely to be associated with symptoms suggestive of attention deficit hyperactivity disorder than more severe forms are.
- The presence of significant sleepiness in a child with snoring is concerning for the presence of severe underlying obstructive sleep apnea.
- Chronically insufficient nighttime sleep represents a very common cause of sleepiness and poor academic performance in children.

Sleep and Fatigue Countermeasures for the Neurology Resident and Physician

Avidan, Alon Y. MD, MPH, FAASM. CONTINUUM: Lifelong Learning in Neurology. Volume 19(1) Sleep Disorders. February 2013: p 204–222.

Abstract

ABSTRACT:

Purpose of Review:

Fragmented sleep, prolonged work hours, misalignment of sleep-wake cycles, and an expectation to make medical decisions when alertness levels are reduced are pervasive in neurology residency training. Sleep loss in residency training can lead to cognitive and psychosocial impairment and accidents, compromise patient care, and reduce the trainee's quality of life. Neurology residents experience levels of hypersomnolence similar to residents in surgical specialties and have comparable subjective levels of sleepiness as persons with pathologic sleep disorders such as narcolepsy and obstructive sleep apnea. Over the past 2 decades, work-hour limitations were established to alleviate fatigue and sleepiness. However, the implementation of work-hour limitations alone does not guarantee alleviation of fatigue and may be insufficient without additional key measures to prevent, counteract, and control sleepiness when it strikes. This article provides effective strategies to combat sleepiness, such as modification of the on-call structure (night float), power naps, and caffeine, in neurologists in training and those who are at risk for excessive sleepiness.

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Recent Findings:

Despite two specific work-hour restrictions set by the Accreditation Council for Graduate Medical Education, the most recent in July 2011, little data exist about the efficacy of work-hour restrictions alone in improving fatigue and sleepiness. Curtailed work hours, while appearing attractive on the surface, have important financial, educational, and patient care imperfections and fail to address the core issue—sleepiness.

Summary:

Historically, sleepiness and fatigue place both residents and patients at risk. Excessive sleepiness in residency training occurs because of sleep deprivation and a spectrum of other factors, such as mood disorders or even the anxiety of anticipating being woken up. An effective model to counteract sleep deprivation and its consequences is a multiplayer approach that uniquely targets and addresses the needs of all the stakeholders. A sleep medicine perspective is proposed along with other interventions to prevent adverse consequences.

Key Points

- Historically, residents have faced sleep loss and fatigue related to long working hours at the hospital. Recent regulations restrict on-duty scheduling in an effort to reduce sleepiness and improve safety.
- While data regarding ACGME work-hour stipulations among neurology trainees seem to trend toward improved quality of life in trainees, this comes at the cost of degradation of education opportunities and patient care.
- Subjective sleepiness in residents is alarming as it is similar to that found in cohorts of sleep patients—particularly those with narcolepsy and sleep apnea—who exhibit pathologic levels of hypersomnolence.
- Causes of hypersomnolence in residents are most likely circadian factors leading to diminished alertness during the nighttime; insufficient sleep; interrupted and fragmented sleep when on call; and comorbid medical, psychiatric, and primary sleep disorders.
- Consequences of sleep loss in residency training include disturbances in neurocognitive and psychomotor functioning as well as reduced satisfaction with work experience, increased stress, weight gain, pregnancy-related complications, and increased risk of accidents inside and outside the hospital.
- In neurology residencies, implementation of a night-float system may be operationally difficult, and data about its efficacy in improving sleepiness are equivocal.
- The only reliable way to counteract and reverse the physiologic need for sleep is to sleep.
- Countermeasures for sleep and fatigue in residency training consist of a number of interventions focusing on strategies to improve alertness, such as strategically placed 15- to 20-minute short naps (also known as power naps), caffeine intake, and light exposure.
- In neurology residencies, integration of a standardized sleep medicine curriculum, including teaching modules on fatigue countermeasures, may assist residents in managing excessive sleepiness when it occurs.
- The Swiss cheese model attempts to intercept sleepiness-related errors by supporting the integration of a comprehensive multifaceted approach, including the use of alerting techniques such as power naps, sleep education, and operational measures to curtail work hours.