

Appendix A: Sleep-Related Medical and Neurological Disorders

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This section includes medical and neurological disorders that are not classified elsewhere but have specific sleep-related manifestations. Some of these disorders (e.g., sleep-related epilepsy and sleep-related headache) may be encountered during evaluation for other sleep disorders. In addition, some of these disorders are in the differential diagnosis of other sleep-wake disorders. For example, sleep-related epilepsy must be considered in the differential diagnosis of certain movement disorders and parasomnias. Sleep-related headaches may indicate the presence of sleep apnea. Sleep-related gastroesophageal reflux may either be a precipitant of a sleep apnea episode or be triggered by sleep apnea with aspiration pneumonia as its most serious consequence. Sleep-related myocardial ischemia is an important consideration because myocardial infarction has a predilection to occur in the early morning hours during the latter phase of the sleep period and may be precipitated by episodes of sleep apnea. In addition, sleep-related laryngospasm is a potentially life-threatening consequence of neurodegenerative diseases such as multiple system atrophy. Fatal familial insomnia, although rare, presents with severe insomnia and has well-understood neuropathology.

Fatal Familial Insomnia

Alternate Names

Fatal progressive insomnia with dysautonomia, familial thalamic degeneration of the anterior and dorsomedial thalamic nuclei, thalamic insomnia.

Essential Features

Fatal familial insomnia is a very rare, progressive disorder. Its clinical hallmark is *agrypnia excitata*, a condition characterized by increasing difficulty initiating and maintaining sleep and spontaneous lapses from quiet wakefulness into a sleep state (oneiric stupor). During oneiric stupor, peculiar motor behaviors mimic daily-life activities, such as dressing, combing the hair, washing, and manipulating nonexistent objects. If questioned, patients link these gestures to an oneiric scene.

Early cognitive impairment primarily affects attention and vigilance. Intellectual function remains intact until advanced stages of the disorder when a confusional state with impaired alertness makes testing impossible. The disorder then progresses to an unarousable coma and, finally, death.

Associated Features

Bronchopulmonary and other infections may also be present. There is a loss of the circadian rhythmicity of endocrine and catecholamine rhythms. Autonomic hyperactivity (e.g., pyrexia, salivation, hyperhidrosis, tachycardia, tachypnea, and dyspnea) is present. The disorder is associated with somatomotor disturbances, dysarthria, dysphagia, tremor, spontaneous and reflex myoclonus, dystonic posturing, ataxia, hallucinations, and an extensor plantar response.

Clinical and Pathologic Subtypes

Patients who are homozygous for FFI present with faster evolution of disease while heterozygous individuals have a slower progression. The homozygotes have more prominent insomnia, myoclonus, autonomic dysfunction, spatial disorientation, hallucinations, and weight loss. The heterozygotes exhibit earlier onset of ataxia, dysarthria, seizures, and bulbar symptoms.

Spontaneous fatal insomnia (sFI) is a third clinical variant. Patients tend to be younger and have no family history. The majority (74%) develop insomnia later in the disease course and although they share the same pathological features as FFI, they do not have the genetic mutation.

Demographics

Age of onset is usually in adulthood, between 36 and 62 years of age. The disorder is rare. There are no sex differences.

Predisposing and Precipitating Factors

Not known or applicable.

Familial Patterns

Fatal familial insomnia (FFI) is transmitted according to an autosomal dominant pattern. Patients harbor a missense GAC to AAC mutation at codon 178 of the prion protein gene *PRNP* located on chromosome 20. The mutation co-segregates with the methionine polymorphism at codon 129 of the same gene on

the mutated allele (D178N 129M). The clinical syndrome varies by the M129V genotype. Patients who are methionine homozygous at the 129 codon are younger and display a shorter disease course than those who are methionine-valine heterozygous at codon 129. The sporadic form has a different prion protein responsible for its pathogenesis. While the FFI prion is PrP^{TSE} type 2B, the sporadic form is PrP^{TSE} type 2A. The difference is in the over-representation of the diglycosylated form in the familial type and the monoglycosylated form in the sporadic type.

Onset, Course, and Complications

The disorder is always fatal, usually within eight to 72 months. The course is one of relentless worsening of symptoms. Patients may die after a short (less than 12 months) or long (12 to 72 months) disease course. The younger age at disease onset and, consequently, a lower rate of comorbidity may explain the generally more prolonged disease course in FFI than in other prion diseases. Complications include cardiovascular dysfunction leading to hypertension and tachycardia, respiratory failure, and infections (particularly of the lungs and bladder) that develop during the course of the disease, especially in the late stages. These complications represent the usual causes of death. Other frequent complications include skin ulcers when patients become bedridden, and aspiration of food due to severe dysphagia; the latter may require nasogastric or gastrostomy feeding. Patients also develop excessive salivation and lacrimation, a decrease in gut motility, and loss of sphincteric control. The latter leads to constipation and stool incontinence. Lastly, there is also difficulty controlling core body temperature as well as hyperhidrosis. The latter could be due to sweat gland hyperstimulation or a manifestation of episodic autonomic storm. The autonomic storm in FFI is a paroxysmal burst of sympathetic activity manifested as increased core body temperature, hypertension, tachycardia, hypersalivation, hyperhidrosis, and lacrimation. These may be followed by brief periods (a few minutes) of slow-wave sleep described by patients as restorative.

Pathology and Pathophysiology

The pathological findings include severe bilateral loss of neurons, with reactive gliosis of the anterior and dorsomedial thalamic nuclei and severe neuronal loss and reactive astroglia in the inferior olives. Spongiform changes in cortical layers, most prominent in corticolimbic areas, have been described in cases with a prolonged course. Deposition of proteinase K-resistant prion protein type 2 in the grey matter but not the white matter occurs in familial and sporadic fatal insomnia. Both familial and sporadic fatal insomnia have been transmitted to transgenic animals by intracerebral inoculum of brain homogenates.

Objective Findings

In the early stages of FFI, periods of relaxed wakefulness alternate with episodes of electroencephalographic (EEG) desynchronization, rapid eye movement (REM) bursts, loss of antigravity

muscle tone, and irregular myoclonic activities associated with oneiric scenes. Sleep spindles, K complexes, and features of slow-wave sleep are progressively lost or absent throughout the course of the illness. Total sleep time is reduced. In the final stages of the disorder, the EEG becomes unreactive and progressively flattens until death occurs; it may display periodic spike discharges.

Single Photon Emission Computed Tomography (SPECT) imaging shows decreased blood flow perfusion in bilateral temporal lobes, basal ganglia, and thalami.

Cerebrospinal fluid (CSF) analysis may show elevated 14-3-3 protein (a non-specific marker of neuronal death) in FFI but is usually normal in sporadic FI.

Positron emission tomography (PET) with (18F)-2-fluorodeoxy-d-glucose shows thalamic hypometabolism from the early stages of the disease. Multisequence magnetic resonance spectroscopy can detect prion-induced gliosis in vivo. Circadian rhythms of body temperature, systemic blood pressure, heart and respiratory rate, and endocrine rhythms of growth hormone, prolactin, luteinizing hormone, follicle-stimulating hormone, and adrenocorticotrophic hormone may be lost. Serum catecholamine and cortisol values are elevated, with low or undetectable adrenocorticotrophic hormone levels.

Differential Diagnosis

REM sleep behavior disorder (RBD) is associated with behaviors that may resemble those seen during oneiric stupor of FFI. However, RBD is not associated with autonomic hyperactivity or a familial pattern.

Dementia, sporadic Creutzfeldt–Jakob disease (CJD), Morvan Syndrome, delirium tremens, Mulvihill-Smith syndrome, Whipple disease, Hashimoto encephalopathy, viral and autoimmune encephalitis, and schizophrenia must also be considered in the differential.

Unresolved Issues and Future Directions

Not applicable or known.

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Sleep-Related Epilepsy

Alternate Names

Nocturnal epilepsy, nocturnal seizures, sleep-related seizures.

Essential Features

A seizure is a transient occurrence of signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Seizures are classified as focal onset, generalized onset, and unknown onset. Epilepsy is defined as two unprovoked seizures >24 h apart, one unprovoked seizure and a probability of further seizure recurrence risk (at least 60%), or a diagnosis of a distinctive epilepsy syndrome. Epilepsy syndromes are defined as a cluster of features incorporating seizure types, EEG, and imaging features that tend to occur together. Sleep facilitates epileptic activity and seizures. Sleep-related epilepsies consist of three types of epileptic syndromes: focal onset, generalized onset, and unknown onset. Details are discussed in the Clinical and Pathologic Subtypes section below.

Associated Features

The different types of *Sleep-related Hypermotor Epilepsy (SHE)*, formerly known as Nocturnal Frontal Lobe Epilepsy (NFLE), may cause severe sleep disruption, affecting both the macrostructure and microstructure of sleep. This disruption, in turn, may result in poor sleep quality, daytime fatigue, and sleepiness in some patients. The movements may also be so severe that injuries can occur.

Neurocognitive impairment is present in almost all cases of *Continuous Spike Waves during NREM sleep (CSWS)*. Cognitive impairment, particularly in verbal IQ, has also been described in over half of SHE patients. People with *epilepsy with centrotemporal spikes* and related conditions may also demonstrate cognitive deficits.

Motor impairment in the form of a unilateral deficit is sometimes seen as an associated feature of CSWS. Those with SHE-specific genetic mutations are at higher risk.

From one-third to one-half of patients with sleep-related epilepsy also have occasional daytime attacks, although these are not necessarily of the same type as those occurring at night.

Clinical and Pathologic Subtypes

Clinical and EEG criteria are used to define a variety of sleep-related epilepsy subtypes. Sleep-related epilepsies can be subdivided into sleep-associated, sleep-accentuated, and those occurring upon awakening. Sleep-associated epileptic syndromes include SHE and CSWS. Sleep-accentuated seizures include the tonic seizures of Lennox Gastaut Syndrome and those with Landau-Kleffner Syndrome. The sleep-associated group also includes occipital lobe seizures (particularly those seen in Panayiotopoulos syndrome (PS)) and certain temporal lobe seizures. Epilepsies that occur upon awakening are primarily juvenile myoclonic epilepsy (JME), generalized tonic-clonic seizures on awakening, and self-limiting epilepsy with centrotemporal spikes (ECTS).

SHE often presents with hypermotor manifestations, dystonic posturing, and rarely with episodic wandering. The movements can be choreoathetoid, ballistic, and dystonic. Hypermotor manifestations are usually high amplitude, repetitive proximal/axial movements often resembling natural movements like rocking, bicycling, or kicking. Axial tonic seizures are also very common. However, there are paroxysmal stereotypic arousals without motor manifestations that fall on the clinical spectrum of SHE. There is usually some preservation of awareness and abrupt offset and onset of events. Most events last less than 2 minutes but occasionally can last longer.

ECTS can present with focal clonic facial twitching, often preceded by perioral numbness. These seizures are more often seen in drowsiness and sleep than wakefulness. The clinical course is often self-limited with disappearance of the seizures in adulthood. Some may be refractory to treatment due to underlying, unrecognized cortical malformation.

Panayiotopoulos syndrome (PS) is characterized by focal seizures marked by deviation of the eyes and vomiting. Sleep is the main precipitating factor, with most of the seizures occurring soon after sleep onset or in the early hours of the morning. There is frequent evolution to a secondary generalized seizure. The clinical evolution of the early-onset type is benign, whereas, in the late-onset type with visual seizures, the prognosis is uncertain.

CSWS (formerly known as electrical status epilepticus of sleep [ESES]) is defined by continuous and diffuse slow spike-and-wave complexes persisting through NREM sleep (at least 85% of the duration), as well as neuropsychological and motor impairment. Despite the continuous presence of epileptic spike-wave activity on EEG in sleep, there may be no associated visible sleep-related movement. However, clinical epileptic seizures are sometimes seen in the daytime.

CSWS, ECTS, PS, and related conditions such as Landau Kleffner Syndrome all result in various degrees of cognitive difficulties and have a shared genetic substrate.

JME is characterized by bilaterally synchronous myoclonic jerks activated by sleep deprivation and frequently occurs upon awakening. JME patients can also have rare generalized tonic-clonic seizures (GTC) and rare absence seizures.

Demographics

SHE is male predominant without a clearly established M/F ratio. JME is female predominant with F/M of 3:2, as is PS with F/M of 2:1. CSWS and ECTS have a slight male predominance.

Predisposing and Participating Factors

Stress, sleep deprivation, irregularities of the sleep-wake rhythm, other sleep pathologies, and stimulants or other drugs that modify sleep architecture may predispose an individual to seizures. Prenatal or perinatal problems, congenital hemiparesis, and prior encephalopathy may be antecedents of the syndrome of CSWS. OSA may exacerbate sleep-related seizures and complicate their treatment.

Familial Patterns

The genetic generalized epilepsies form the largest category of epilepsies that appear to be heritable but show no clear mendelian mode of transmission. Juvenile Myoclonic Epilepsy (JME) and genetic generalized epilepsy with adolescent onset appear to be genetically heterogeneous. Among the focal epilepsies, ECTS shows a familial pattern. A form of autosomal dominant SHE (ADSHE) with 70% to 80% penetrance has been reported, accounting for 14% of SHE cases. Although genetic heterogeneity has been reported, most ADSHE cases are due to a mutation in the genes coding for subunits of the neuronal nicotinic acetylcholine receptor (nAChR). Multiple mutations have been identified in CSWS and related syndromes, the majority resulting in channelopathies. Familial antecedents of epilepsy (including febrile convulsions) have been reported in 15% of cases.

Onset, Course, and Complications

Genetic generalized epilepsies and focal epilepsy may start at any age. The onset of self-limiting epilepsies of childhood with centrotemporal (ECTS) or occipital spikes (PS and other related occipital epilepsies) is between 4 and 12 years of age. The onset of SHE is generally from age 10 to 16, mainly before 20 years of age. The average age of recognition of CSWS is between 4 and 14 years, but the appearance of the first seizure is earlier, typically between two months and 12 years of age. Most patients with recurrent sleep-related epilepsy continue to have seizures restricted to sleep. In some cases, they may have seizures during both sleep and wakefulness. The prognosis is less favorable for focal epilepsies (excluding ECTS and

the early-onset type of PS) than for generalized epilepsies. At least 35% of the focal seizures confined to sleep are resistant to anti-seizure medications.

JME usually starts in adolescence and is responsive to treatment with anti-seizure medications.

Definitive data on the natural history of SHE are not available, although a high prevalence of disorders of arousal (DOA) is documented in SHE patients. In SHE, bruxism, PLMD, and neck myoclonus tend to occur with higher frequency than controls, hence creating more significant diagnostic challenges. Adults with SHE and DOA are also more likely to have violent manifestations than are children.

CSWS resolves in many cases within three years after onset and in almost all cases by the mid-teen years. Despite normalization of the EEG and elimination of seizures, neuropsychological impairment may persist. Notably, there may be prolonged cognitive and motor impairment and a syndrome of acquired aphasia called Landau Kleffner. In addition, hyperkinesias, aggressiveness, and psychotic states may appear.

Certain epilepsy treatments such as Vagal Nerve Stimulation (VNS) may worsen central and obstructive apneas. Obstructive apneas and hypopneas occur during the ON phase of VNS. Anti-seizure medications can be associated with weight gain and thus worsen OSA. Lastly, nocturnal hypoxemia is a risk factor for Sudden Unexplained Death in Epilepsy (SUDEP).

JME patients tend to have a more delayed sleep-wake phase than those with other epilepsies.

Chronic insomnia is also more common in patients with epilepsy than in the general population and is multifactorial in etiology. Together with depression, it is one of the most prominent determinants of poor quality of life in this population.

Developmental Issues

See Onset, Course, and Complications for discussion of developmental factors.

Pathology and Pathophysiology

In idiopathic generalized epilepsy, genetic factors are contributory. Pathogenic markers, associated neurologic deficits, and characteristic brain imaging findings have not been identified. However, microdysgenesis has been described in some forms of idiopathic generalized epilepsy. SHE patients can also have cortical dysplasias or other structural abnormalities. Usually, these patients are more likely to have interictal discharges on EEG than those with ADSHE.

Sleep-related hypermotor seizures involve a large neuronal network. Some of their clinical expressions are possible consequences of the disinhibition of innate motor patterns produced by the central pattern generator. Recent reports derived from stereo-EEG studies suggest that in some cases, the seizures

(particularly nocturnal wanderings) may arise from temporal or insular regions (rather than frontal regions) with a secondary spread to the cingulate regions. They may sometimes mimic DOAs.

JME is associated with increased photosensitivity. This sensitivity is considered the underlying reason for the myoclonic jerks. In this regard, JME overlaps with reading epilepsy, the latter having more subtle myoclonus. JME patients also have hyperconnectivity in the sensorimotor and frontal cortices postulated to be the underlying mechanism for their frontal cognitive dysfunction.

Secondary bilateral synchrony is the mechanism generating CSWS. This hypothesis is supported by EEG, intracranial recordings, EEG with coherence computer-assisted analysis, and metabolic (positron emission tomography [PET] and single-photon emission computed tomography [SPECT]) studies. CSWS associated with Landau-Kleffner syndrome (acquired epileptic aphasia) is probably secondary to the disturbance of N3 sleep by CSWS, a stage critical for cortical plasticity. The damage can involve the thalamus as well as the cortex.

Objective Findings

Patients with suspected sleep-related epilepsy often require sleep laboratory evaluation (with video and a 10-20 system of 20 channel EEG monitoring) or long-term video EEG monitoring. However, EEGs may be unrevealing because the seizure foci may be too deep to capture with surface electrodes, or movement may obscure epileptiform activity. In the outpatient setting, sleep-deprived EEGs may increase yield for interictal epileptiform discharges. In the epilepsy monitoring unit (EMU), EEG recordings with sphenoidal leads may show epileptic activity over the mesiotemporal regions in focal epilepsies

The characteristic interictal epileptiform activity in idiopathic generalized epilepsies usually increases during NREM sleep and decreases during REM sleep and wakefulness. In addition, interictal epileptiform activity may be associated with phasic arousals. In awakening epilepsies such as JME, maximal epileptiform activity occurs during awakening from the major sleep period.

In focal epilepsies, the interictal epileptiform activity occurs in a localized distribution with an increase in spike frequency in stages N2 and N3 compared to REM sleep. REM sleep-related interictal abnormalities, despite their rarity, have better localizing value than those in NREM sleep. Most seizures, particularly focal epilepsies, are activated in transitional sleep and light NREM. Over 70% of sleep-related focal seizures occur in NREM sleep. Monitoring may also detect transient autonomic alterations in cardiac rhythm, blood pressure, and respiration during seizures. If epilepsy is suspected, a standard daytime 20-channel EEG (with partial or total sleep deprivation the night before, as indicated) should be performed. In addition, ambulatory 24-hour EEG recordings may be helpful to detect the distribution of interictal epileptiform activity during the sleep-wake cycle.

In addition to NREM sleep facilitating discharge propagation, seizures in JME and ECTS follow a circadian pattern suggesting a role for core clock genes in epileptogenesis.

Nocturnal 20-channel EEG vPSG is the standard test for SHE. Most seizures appear during NREM sleep, with preponderance in stage N2 sleep (greater than 60%). They emerge from REM sleep only rarely. Video-polysomnographic (vPSG) analysis confirms that the motor pattern of SHE resembles that noted in orbital and mesial frontal seizures. In some cases, the motor attacks may show a periodicity (every 20 seconds to two minutes), particularly in the case of shorter seizures with fewer hypermotor features. Since the discharges originate deep in cortical areas and are not visible using scalp EEG, the EEG during the attacks is uninformative in almost half of the cases. Recordings using intracranial or depth electrodes confirm the paroxysms during or preceding the motor components. The ictal and interictal sleep EEG is abnormal in 50% of subjects; specifically, focal epileptic abnormalities are seen, predominantly in the anterior regions. The video recording of the different types of attacks in SHE permits categorization of the seizures and characterization of the main features. Not all SHE is of frontal lobe origin; however, frontal SHE seizures are shorter in duration than extra-frontal ones, and they progress more rapidly to hypermotor manifestations. In addition, postictal confusion and emotional symptoms tend to occur more often with extra-frontal SHE than frontal epilepsy.

During CSWS, diffuse spike waves at 2.0 to 2.5 Hz occur in bursts, with or without clinical manifestations. The discharges are continuous and occupy 85- 100% of NREM sleep stages. Abnormalities arise as soon as the patients fall asleep and disappear abruptly on awakening. REM sleep is typically preserved, and the frequency of spike-wave discharges during REM significantly decreases, but the frontal predominance of the infrequent bursts may become more prominent. In general, EEG patterns during REM sleep are similar to those in the awake records. The percentages of NREM and REM sleep are normal. However, the presence of almost continuous spike-wave discharges makes the recognition of normal NREM sleep EEG elements (such as K complexes, spindles, or vertex sharp transients) difficult.

Daytime sleep EEG is usually diagnostic for JME, PS, and ECTS with an accuracy of about 90%.

Differential Diagnosis

Disorders of arousal (DOA) SHE may be mistaken for a disorder of arousal from NREM sleep, primarily because of a shared mechanism and shared genetics of the motor symptomatology between the two conditions. Ictal and interictal EEGs are often normal because the focus for the epileptic discharge may be deep in the brain. Disorders of arousal arise predominantly out of stage N3 sleep and never out of REM sleep, while SHE tends to arise primarily from N2 sleep, although it may occur with lower frequency in other stages. The manifestations of DOA are not stereotyped, often have a sustained autonomic component, and are frequently seen during the first part of the night. Disorders of arousal tend to disappear or decrease in frequency after adolescence. In the clinical setting, a thorough history eliciting the differentiating symptomatology between SHE and NREM parasomnias can be helpful in making a diagnosis. VPSG is often useful to identify event distribution per sleep stage and the clinical features of the events.

Sleep talking, bruxism, neck myoclonus, and rhythmic movement disorders can be differentiated from nocturnal seizures by history and vPSG recordings.

Benign neonatal sleep myoclonus may be confused with clonic or myoclonic seizures during sleep.

REM sleep behavior disorder occurs primarily in individuals over 60 years of age and is differentiated from SHE primarily by vPSG recording.

Periodic limb movement disorder, sleep starts, and propriospinal myoclonus at sleep onset do not show EEG epileptiform activity and belong in the category of movement disorders during sleep.

Jerks, dyskinesias, or arousals on resumption of breathing in patients with OSA also enter into the differential diagnosis of sleep-related epilepsy. Rare cases of *anoxic syncope* with some clonic jerks at the end of a prolonged (longer than two minutes) obstructive event have been described.

Unresolved Issues and Further Directions

Greater coherence with the evolving classification systems of the International League Against Epilepsy and the American Epilepsy Society is a desirable goal for future editions of the ICSD.

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Sleep-related Headaches

Alternate Names

Various (see Clinical and Pathologic Subtypes).

Essential Features

Sleep-related headaches are a group of cephalalgias of varying severity and duration that occur during sleep or upon awakening from sleep, or have other sleep-related associations. It is a heterogenous group of different headache entities. The characteristics of specific subtypes of sleep-related headaches are discussed below in the Clinical and Pathologic Subtypes section.

Associated Features

Individual features associated with specific sleep-related headache types are discussed in the following section.

Clinical and Pathologic Subtypes

Most sleep-related headaches are daytime headache conditions that also may occur during sleep. These include primary headaches such as migraine, cluster headache, and chronic paroxysmal hemicrania. Other primary headaches occur solely with sleep; for example, hypnic headaches. Headaches secondary to other medical, neurological, psychiatric, and sleep disorders may also occur during sleep.

Migraines

Migraines are recurrent headaches of unilateral, moderate to severe pain intensity with a duration of four to 72 hours. Diagnostic criteria require at least five headache episodes. Pain is typically unilateral and pulsating, and aggravated by routine physical activity. Migraines must be associated with either nausea/vomiting or photophobia/phonophobia. Migraine headaches are classified by the presence or

absence of aura. If present, an aura precedes the migraine and consists of transient neurologic symptoms, typically a visual scintillating scotoma, usually 4-60 minutes in duration. The aura may continue or even begin during the headache phase in some patients. The other primary type of migraine is without aura. This type has the same features as previously listed. Migraine headaches may have other signs of neurological dysfunction, including paresthesias, weakness, aphasia, vertigo, tinnitus, dysarthria, decreased hearing, diplopia, ataxia, and impaired level of consciousness. A syndrome of familial hemiplegic migraine is well described. The hemiplegia is reversible and associated with fully reversible visual, sensory, or speech and language symptoms.

Migraines occur during wakefulness or sleep; approximately 50% of migraine attacks occur between 4:00 a.m. and 9:00 a.m. Migraines do not have a fixed association with a particular sleep stage and may arise from NREM or REM sleep.

Trigeminal autonomic cephalgias

Trigeminal autonomic cephalgias (TACs) are primary headaches associated with cranial parasympathetic autonomic symptoms. These associated symptoms are lateralized and ipsilateral to the headache. They include conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, or eyelid edema. The main TACs are cluster headaches and paroxysmal hemicranias.

Cluster headaches are severe, unilateral, periorbital, or temporal headaches that start quickly and peak within 10 to 15 minutes. They have a relatively shorter duration, lasting 15-180 minutes (mean, 60 minutes). The headache frequencies are from every other day up to eight times per day during cluster periods. One or more cranial autonomic features must accompany attacks of cluster headaches. Most patients with cluster headaches have one cluster period per year, though this can vary from patient to patient. Cluster headaches tend to occur at the same hour each day, with 75% of cluster episodes reported to occur between 9:00 p.m. and 10:00 a.m. Cluster headaches are more common among men. Unlike migraines, in which the patient wants to remain still, patients with a cluster headache will be restless during an episode. A strong predilection for attacks to occur during sleep is well recognized, and these attacks are strongly related to REM sleep.

Paroxysmal hemicranias closely resemble cluster headaches and consist of severe unilateral orbital, supraorbital, or temporal pain associated with one or more cranial autonomic features. Diagnostic criteria require at least 20 attacks associated with one or more cranial parasympathetic autonomic symptoms or restlessness. The attacks are short (2-30 minutes) and occur at least five times per day. A defining feature of paroxysmal hemicrania is exquisite sensitivity to indomethacin. Attacks are also strongly associated with REM sleep.

Hypnic headaches

Hypnic headaches occur only during sleep and are uncommon. They awaken the patient from sleep with a generalized or lateralized headache that lasts 15 minutes to 4 hours with a frequency of at least ten times per month for at least three months. Hypnic headaches do not have cranial autonomic features or restlessness. Onset is typically after the age of 50, although similar headaches are described rarely in

younger individuals, including children. Isolated nausea, photophobia, or phonophobia may be present. They may occur one to three times during the night, with many patients reporting that the headaches occur at the same time of the night - giving rise to the term "alarm clock" headache. The headaches tend to occur during REM sleep; however, they have also been reported to occur during stage N3 sleep. A positive therapeutic response to lithium, indomethacin, and caffeine has been reported in many patients.

Secondary Headaches

Secondary Headaches are due to other medical (e.g., hypertension), neurologic (e.g., brain tumors, arteriovenous malformations, cerebral venous thrombosis, or trauma), and psychiatric (e.g., depression) conditions, as well as other sleep disorders (e.g., OSA). They give rise to headaches that may occur during sleep or upon awakening from sleep.

Patients with increased intracranial pressure (due, for example, to a brain tumor, hematoma, arteriovenous malformations, or cerebral venous thrombosis) may complain of headache that begins in the morning or following recumbence and improves after the patient is up for 30 to 60 minutes. Nausea, vomiting, signs of focal neurological deficits, and papilledema may be present. The headache may worsen with bending, sneezing, or other activities that may cause a further increase in intracranial pressure.

Demographics

The exact prevalence of sleep-related headaches is not known. One study from a headache clinic suggested that 17% of all headache patients complain of nocturnal or early morning headaches, and roughly half of these were related to an identifiable sleep disorder. However, many primary headache disorders can occur during sleep as well. Sleep-related migraines have been reported to increase in frequency with age.

Predisposing and Precipitating Factors

Primary headaches have several predisposing factors that vary from patient to patient. Stress and sleep disturbance are the most common triggers of migraines. Sleep deprivation or a sudden change in sleep patterns may trigger a migraine. Additionally, relaxation, changes in weather and barometric pressure, hypoglycemia, specific foods (e.g., chocolate, monosodium glutamate (MSG)), and alcohol trigger migraine headaches in some individuals. Alcohol can also predispose to cluster headaches and paroxysmal hemicrania. OSA and attendant hypoxia can be a trigger for cluster headaches. However, sleep apnea may also predispose a person to other types of headaches and may independently lead to morning headaches.

Familial Patterns

There is a positive family history of migraine in up to 80% of patients with this disorder. Familial hemiplegic migraine is inherited in an autosomal dominant pattern with various genetic mutations identified on chromosomes 1 and 19.

Cluster headache does not have as strong a familial disposition as migraine headache, but first-degree relatives of probands with cluster headache are seven times more likely to develop cluster headaches. This is especially true among female patients. Concordance rates in monozygotic twins are 100%.

The inheritance patterns of hypnic headaches are not known.

Onset, Course, and Complications

Sleep-related headaches tend to decrease in frequency with age, while some patients may experience spontaneous remission that lasts from months to years. Pregnancy has a variable effect on these headaches.

Migraine headaches usually start in the second or third decade of life, with slightly earlier onset in men than women. Most women experience a decrease in severity and frequency of migraine headaches during pregnancy. Migraines tend to decrease with age and, in women, may stop after menopause.

The mean age of onset of cluster headache is 28 years. Cluster headaches occur in only 0.3% of pregnancies. Cluster headaches, as the name suggests, generally occur in clusters separated by pain-free intervals lasting months to a couple of years. They also tend to decrease with age.

Paroxysmal hemicrania has a wide range of onset, from childhood to the elderly.

Most patients with hypnic headaches are elderly, with the age of onset from 40 to 82 years.

Secondary headaches, for example, those due to brain tumors, are more prevalent in the elderly, most occurring from the fifth decade to late life. Headaches in patients with brain tumors are related to increased intracranial pressure and tend to improve with treatment of the primary lesion and a decrease in intracranial pressure. Most patients with OSA report improvement of the headache after treatment of the apnea.

Sleep-related headaches can cause sleep disruption and insomnia with decreased sleep efficiency. Cluster headaches occurring regularly in sleep can also lead to transient situational insomnia that may resolve after the remission or the treatment of the cluster headache. Depending on the etiology of the sleep-related headache (e.g., brain tumor), other complications may occur.

Developmental Issues

See Onset, Course, and Complications for discussion of developmental factors.

Pathology and Pathophysiology

Pain sensation originates in part in the blood vessels and the trigeminal nerve. Cerebral arteries and dural sinuses are innervated with a-delta and c-fibers which transmit pain. The trigeminal ganglion, superior and inferior ganglia of the glossopharyngeal and vagus nerves, and C1–C3 dorsal root ganglia have inputs to the trigeminal nucleus caudalis (TNC), a brainstem nucleus. These pathways mediate pain and temperature sensation in the head and neck. The TNC has afferents to the ventral posteromedial thalamus (VPM) and then to the somatosensory cortex. TNC also has input to the limbic system and hypothalamus. Collaterals from the TNC synapse on the nucleus of the solitary tract (NTS). The parabrachial nucleus (PBN) serves as a sensory hub for pain (among other sensory inputs) and has widespread connections to other brain regions that modulate pain, arousal, and sleep.

An understanding of the mechanisms that underlie the relationship between sleep and headache is incomplete. In migraine, hypoactivity of arousal systems during REM sleep and reduced cyclic alternating patterns in NREM sleep may indicate disturbances in the serotonergic pathways connecting subcortical arousal systems in the basal forebrain, hypothalamus, and brainstem.

In cluster headache patients, MRI and positron emission tomography (PET) scans suggest changes in the posterior hypothalamus. In vivo studies of cluster headaches show activation of the trigeminovascular system.

Paroxysmal hemicrania functional studies also show activation of the trigeminal and autonomic pathways. Vasodilatation from hypoxia and hypercapnia are potential factors in the genesis of secondary headaches in OSA. The alterations in blood gases can result in the stimulation of trigeminal nociceptors in the cranial vasculature.

Objective Findings

Polysomnographic aspects of sleep-related headaches are not well-defined. Migraine headaches occur in association with REM sleep or stage N3 sleep. An excess of stage N3 sleep has been reported in patients with migraines. An increased percentage of N2 and a decreased percentage of N3 sleep have been described among children with migraines. Cyclic alternating pattern (CAP) is reduced during NREM sleep among migraine subjects.

Fifty percent of cluster headaches and most chronic paroxysmal hemicrania are associated with REM sleep. Cluster headache patients have a decreased frequency of EEG arousals per hour of sleep, a longer REM latency, and a lower percentage of REM sleep. Hypnic headache occurs during any stage of sleep, although some studies have suggested an association with REM sleep. OSA and hypoxia during sleep may aggravate other sleep-related headaches or be an independent cause of headaches. Many sleep-related headaches have some relationship with REM sleep, but there are no defining or pathognomonic polysomnographic aspects of individual headache syndromes.

There is conflicting information on MRI and functional MRI findings among primary and secondary headache syndromes. For example, there is a gray matter volume decrease in the posterior hypothalamus in patients with hypnic headaches. An older study suggested increased gray matter in the posterior hypothalamus in cluster headaches. Neuroimaging studies (computed tomography or magnetic resonance imaging head scans or angiography) may be performed to rule out structural, vascular, or infectious disease processes that cause headaches.

Differential Diagnosis

Sleep-related headaches are a heterogeneous group of different headache entities that commonly occur during sleep. They need to be differentiated from other headache conditions that are not sleep-related. These include tension-type headaches and headaches associated with paranasal sinus inflammation, tooth infection, ear infection, febrile illness, benign intracranial hypertension, intracranial hypotension, vasculitis, vasculopathy (atrial/venous stroke and aneurysms), head trauma, alcohol intoxication, or bruxism.

Tension-type headaches are bilateral headaches with a band-like tightening sensation around the head.

Giant cell arteritis may present with lateralized or bilateral headache with tenderness over the temporal area in patients older than 50 years. Polymyalgia rheumatica and visual problems, including loss of vision, often accompany the condition.

Exploding head syndrome is in the differential diagnosis of headaches because it is associated with sleep. Patients report a loud, painless auditory shock occurring at sleep-onset

New daily persistent headaches are a subset of headaches with a clearly remembered onset. These headaches become consistent within 24 hours and must last for at least three months. It is a rare disorder and affects 0.03% to 0.1% of the general population, more commonly children and adolescents. These headaches may have migrainous features, but the distinct onset will often allow a clinical distinction from migraine headaches. Thirty percent of subjects reported insomnia symptoms.

Other types of trigeminal autonomic cephalalgias. These include short-lasting unilateral neuralgiform headache attacks, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms. These headache syndromes are similar to other trigeminal autonomic cephalalgias and have unilateral pain and cranial autonomic features. However, the distribution of these headaches in wakefulness and sleep is not known.

Unresolved Issues and Further Directions

Not applicable or known.

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Sleep-related Laryngospasm

Alternate Names

Stridor, laryngeal dysfunction

Essential Features

Sleep-related laryngospasm is a disorder in which tracheal muscle dysfunction or paratracheal soft tissue swelling causes stridor or interruption of airflow, with associated awakening from sleep. Patients may have total or near-total cessation of airflow while asleep and suddenly arouse. This brief respiratory blockage (lasting an estimated five to 45 seconds) is often followed by a period of stridor that lasts several minutes and gradually evolves to normal breathing. Episodes are associated with panic and fear of suffocation; cyanosis may be observed. In some cases of laryngospasm during sleep, patients have frequent laryngeal stridor (which may be difficult for families to differentiate from snoring), associated tachypnea, wheezing, and intermittent upper airway blockage.

Associated Features

Fear and panic upon awakening often accompany events and may, at times, lead to insomnia. This anxiety can give rise to intense hypnophobia. In some cases of sleep-related laryngospasm, gastroesophageal reflux has been identified as a putative precipitating factor. Less commonly, sleep-related laryngospasm has been related to underlying OSA. Occasionally, NREM and REM parasomnia can be seen, especially *in Anti-IgLON5* disease. In addition, daytime stridor can be present with laryngeal tumor or multiple system atrophy (MSA).

Clinical and Pathophysiological Subtypes

Sleep-related laryngospasm may be associated with MSA, a neurodegenerative disorder.

Demographics

Prevalence data do not exist. The typical age of onset is unknown, although affected individuals are typically older when the condition is due to multiple system atrophy. Prevalence of stridor in MSA varies from 12-42%.

Predisposing and Precipitating Factors

Sleep-related laryngospasm may be associated with gastroesophageal reflux. Laryngeal dysfunction seen in other disorders, including laryngeal tumors and multiple system atrophy, may cause sleep-related stridor and intermittent laryngospasm. Precipitating factors include hypnotic or other central nervous system depressant medications. Seizure activity may be a rare cause of sleep-related laryngospasm in children and adults.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

Laryngospasm is a common cause of death in multiple system atrophy. Animal models suggest that seizure-induced laryngospasm may be contributing to death in sudden unexpected death in epilepsy (SUDEP).

Developmental Issues

Not applicable or known.

Pathology and Pathophysiology

The pathology and pathophysiology are uncertain when not associated with neurodegenerative disorders of known pathology (e.g., multiple system atrophy). Sleep-related laryngospasm can be related to tracheal muscle dysfunction, postnasal drip, or reflux of gastroesophageal contents causing irritation of soft tissue

in the upper airway. Laryngeal tumors can cause laryngeal dysfunction or upper airway obstruction, resulting in sleep-related laryngospasm. Multiple system atrophy is associated with vocal cord dysfunction resulting in inspiratory vibrations through a narrowed vocal cord, causing stridor. Dynamic glottic collapse due to adductor laryngeal dystonia can also present with laryngospasm.

Objective Findings

Sleep-related laryngospasm may be identified with video PSG accompanied by audio recording. It is seen in all stages of sleep but is most severe in REM sleep. Laryngospasm can appear similar to snoring on the polysomnographic snoring channel, but the audio recording will confirm the high-pitched inspiratory sound as laryngospasm. OSA has also been detected in some cases. Patients or family members may mistake laryngospasm for snoring or sleep apnea. PSG evaluation may be necessary to distinguish these disorders. In children and adults, sleep-deprived EEG may demonstrate seizures that result in laryngospasm.

Endoscopy of the upper airway is necessary to examine vocal cord function and exclude upper airway pathology. If awake endoscopy is normal, one can consider drug-induced sleep endoscopy (DISE) to rule out vocal cord dysfunction or confirm sleep-related laryngospasm. In patients with MSA and sleep-related laryngospasm, electromyography (EMG) performed during drug-induced endoscopy can reveal paradoxical activation or persistent tonic activity of laryngeal adductor muscles during inspiration. Gastroesophageal studies may reveal evidence of reflux. Low field magnetic resonance fluoroscopy can also be employed to confirm the diagnosis as it allows sufficient time to evaluate the upper airway during sleep.

Differential Diagnosis

Obstructive sleep apnea may cause awakenings with choking or gasping for air, chronic cough, excessive daytime sleepiness, restlessness, or insomnia. If OSA is a diagnostic consideration, an attended polysomnogram is warranted.

Sleep-related gastroesophageal reflux may result in coughing or choking episodes during the night without true laryngospasm. However, these episodes usually are described in the setting of chest pain or "heartburn." Possible causes of sleep-related laryngospasm associated with GERD include an overreaction of laryngeal chemoreflex or occult acid reflux into the upper airway, causing irritation or swelling.

Sleep terrors may be associated with sensations of impaired breathing or choking, rapid heartbeat, and agitation. However, sleep terrors are most common in children, and most patients do not focus on upper airway choking.

Panic disorder can involve abrupt awakening with respiratory distress, signs of sympathetic activity, and fear of dying. However, most patients also have daytime episodes of panic.

Nocturnal asthma can result in sleep-related coughing, wheezing, or shortness of breath.

REM sleep behavior disorder (RBD) is generally recognizable by polysomnographic features of RBD and a history of dream enactment.

Head and neck tumors involving the laryngeal area can cause nighttime stridor and can be easily diagnosed on imaging or endoscopy. **Laryngomalacia** can present with nocturnal stridor and increased work of breathing at nighttime. The condition can be diagnosed with sleep-induced endoscopy.

Anti-IgLON5 disease can present as OSAS, nocturnal stridor, and NREM and REM parasomnias.

Breath-holding spells due to nocturnal frontal lobe seizures can be confused with nocturnal laryngospasm and can be diagnosed on video polysomnogram with extended EEG.

Seizures arising from the frontal operculum can cause epileptic laryngospasms without EEG correlates. SPECT may be helpful in the diagnosis of such seizures.

Further, any cause of daytime stridor can present with nocturnal stridor (e.g., paradoxical vocal fold movement disorder).

Unresolved Issues and Further Directions

Published reports generally have been limited to case series. Clarification of the relationship between laryngospasm, sleep-related breathing disorders, and gastroesophageal reflux is needed.

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Sleep-related Gastroesophageal Reflux

Alternative Names

Gastroesophageal reflux, nocturnal gastroesophageal reflux, supine gastroesophageal reflux, nocturnal heartburn, reflux esophagitis, esophagitis, heartburn.

Essential Features

Sleep-related gastroesophageal reflux (GER) occurs when gastric contents breach the lower esophageal sphincter (LES) into the esophagus and, potentially, into more proximal sites during sleep time. Symptoms may become evident when lying down to sleep and occur during arousals or awakenings. GER can be silent but, if present, the most common symptoms are heartburn and regurgitation. In addition, substernal burning, chest discomfort, a sour or bitter taste in the mouth, water brash, coughing, or choking may result. These symptoms may occur even in the absence of the typical reflux symptoms. Patients who complain of nighttime heartburn three times per week or more have significantly more nighttime reflux than those who complain only of daytime heartburn and individuals without heartburn.

Associated Features

Associated features of this disorder include dysphagia, odynophagia, laryngopharyngitis with sore throat and hoarseness, laryngospasm with stridor, epigastric burning, chronic cough, wheezing, or chest pain that may mimic angina. Other associated features of sleep-related GER include sleep onset and sleep maintenance insomnia, early morning awakenings, short sleep duration, poor sleep quality with sleep fragmentation, and increased arousals. Unexplained daytime sleepiness, daytime fatigue, poor daytime functioning, and reduced work productivity may also result. GER can impact quality of life, including mood, wellbeing, and work and social life. In addition, GER can result in new non-gastrointestinal symptoms such as cough, worsening, or exacerbation of preexisting medical conditions such as asthma and other complications. GER commonly coexists in patients with chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, and bronchiolitis obliterans syndrome in lung transplant recipients. Sleep-related GER is associated with sleep-related laryngospasm and is also commonly noted in patients with OSA. Bruxism is also associated with symptomatic reflux disease.

Clinical and Pathological Subtypes

Not applicable or known.

Demographics

GER symptoms, defined as heartburn or regurgitation occurring at least once a week, affect 18-28% of adults in North America. Sixty-five percent of patients with GER report both daytime and nighttime symptoms, whereas 13% experience only nocturnal symptoms. Among patients with weekly heartburn, 79% report GER symptoms during sleep time, 47-57% report waking up during sleep due to heartburn, and 40% report that GER during sleep time resulted in impaired daytime function the next day. Among the 15,315 Sleep Heart Health Study subjects, 25% reported heartburn during sleep. In a review of five large population studies, the mean prevalence of heartburn during sleep time was 54%.

There is no known predisposition by sex. However, men are more likely than women to develop Barrett's esophagus.

Predisposing and Precipitating Factors

Predisposing factors for sleep-related GER include poor esophageal motility, delayed gastric emptying, reduced LES tone, eating within two hours of bedtime, an elevated body mass index, erosive esophagitis, and hiatal hernia. Predictors of heartburn during sleep include consumption of alcohol or carbonated beverages or the use of benzodiazepines before sleep time. Other predictors of heartburn during sleep include the presence of OSA, abdominal obesity, hypertension, asthma, snoring, and daytime sleepiness. In patients with OSA, sleep-related reflux symptoms are present in up to 62%. Treatment with CPAP significantly reduces the incidence of reflux events in patients with OSA. However, patients with OSA treated with CPAP who experience aerophagia have a higher prevalence of GER than those who do not. Systemic sclerosis, diabetes, and sleeve gastrectomy are also associated with increased risk for sleep-related GER.

The relationship between GER and sleep disturbance is bidirectional. Sleep-related GER is associated with short sleep duration, difficulty falling asleep, arousals, poor sleep quality, and early morning awakenings. In a trial examining consecutive individuals with asthma, 50% had awakenings from sleep because of heartburn. Conversely, sleep deprivation induces a state of esophageal hyperalgesia to acid, thus worsening heartburn symptoms.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

GER occurs in all age groups, including infants and children. Sleep disruption occurs more frequently in infants and children with GER than in those without GER. The incidence of GER increases with age. GER may be more severe and has more complications in older adults.

GER is a chronic disease and is rarely cured, but it may be controlled with lifestyle and medical or surgical therapies. In patients with sleep-related GER, medical GER therapy improved sleep disturbances and daytime functioning in placebo-controlled trials. Long-term outcome data are currently lacking. If GER is left untreated, the disease generally progresses and can be associated with many complications. Esophageal complications include esophagitis, esophageal erosions, esophageal stricture, ulcerations with stricture, and Barrett's esophagus, a precursor to esophageal adenocarcinoma. Reflux can also result in dysphagia, weight loss, and upper gastrointestinal bleeding. Sleep-related GER is more commonly associated with erosive esophagitis, stricture, Barrett's esophagitis, and esophageal adenocarcinoma than diurnal reflux. Extra-esophageal complications include the pulmonary complications previously discussed in the Associated Features section.

Pathology and Pathophysiology

Two primary pathophysiologic mechanisms cause individual reflux episodes: transient lower esophageal sphincter (LES) relaxation and a reduction of LES pressure below intragastric pressure. Transient LES relaxations (LES relaxations occurring without esophageal contractions) account for 53% to 74% of GER episodes in patients with GER disease. It is the most common cause of GER. Transient LES relaxations decrease the LES to gastric pressure gradient, facilitating the retrograde flow of gastric contents. An LES pressure of 10 mm Hg or less is the second mechanism by which intra-abdominal pressure overcomes the LES pressure and results in the retrograde flow of gastric contents into the esophagus.

Pathophysiology of sleep-related GER is similar to diurnal GER (i.e., transient LES relaxations and a low LES pressure). However, sleep impacts esophageal physiology by impairing esophageal acid clearance mechanisms when GER events occur. With sleep onset, the upper esophageal sphincter (UES) pressure decreases and is lowest during N3 sleep, thus predisposing to aspiration. The UES contractile reflex remains intact during sleep, including REM sleep. Lower esophageal sphincter (LES) pressure remains unchanged during sleep and maintains tonic contraction during different sleep stages. Sleep increases the vagal threshold for triggering transient LES relaxations. Therefore, they usually do not occur during stable sleep and are typically confined to arousals. When GER events occur during sleep, esophageal refluxate clearance is prolonged, and arousal is required. Sleep facilitates proximal refluxate migration toward the UES. Saliva secretion, with its acid-neutralizing bicarbonate, ceases during sleep. Swallowing, required for esophageal peristalsis and refluxate clearance, is markedly decreased during sleep and is typically dependent on an arousal. Sleep also delays gastric emptying by disrupting gastromyoelectric function, predisposing to sleep-related GER. Events causing arousals, including periodic limb movements and apneas, may trigger transient LES relaxations and thus GER events. Because refluxate clearance requires an arousal, medications decreasing the arousal response (including benzodiazepines and zolpidem) may prolong refluxate clearance and increase the risk of aspiration during sleep. In addition, poor sleep quality

and sleep deprivation have been associated with hyperalgesia of the esophageal mucosa in response to acid contact and increased mucosal acid contact time.

Several mechanisms for the causal relationship between reflux and respiratory events have been proposed in patients with OSA. The association of reflux events with respiratory arousals may vary with OSA severity. At least one study found that nearly all reflux events were associated with respiratory-related arousals in those with severe obstructive apnea. In contrast, only 26% of reflux events were related to respiratory events in individuals with mild or moderate apnea. Another study examining the relationship between obesity and airway obstruction as a cause of reflux suggested that obesity, rather than airway obstruction, is the primary cause of reflux in OSA.

Objective Findings

Establishing a diagnosis of sleep-related GER does not require diagnostic testing. The diagnosis can be made if typical heartburn symptoms or regurgitation are present during sleep time. Therefore, PSG or esophageal impedance-pH monitoring is not routinely indicated. Esophageal impedance-pH monitoring is the current gold standard that objectively measures individual GER events and provides information about the physical and chemical properties of the refluxate. Esophageal pH monitoring is recommended in difficult, refractory cases or when symptoms continue despite therapy.

The pathological findings of GER include abnormalities of esophageal manometry such as marked reduction in the LES pressure and poor acid clearance due to reduced swallowing rate associated with sleep. Esophageal manometry may demonstrate an increased frequency of transient LES relaxations, altered or decreased esophageal peristaltic contraction amplitude, and a decrease in resting LES pressure. Endoscopy and esophageal biopsy may reveal additional pathological findings, including mild erythema, erosions, ulcerations or severe erosions with stricture and Barrett's esophagus.

Sleep-related GER is more likely to occur during the first two hours of sleep time. Furthermore, in studies using combined esophageal pH monitoring with actigraphy, acid reflux events occurred primarily during the recumbent-awake period versus the recumbent-asleep period. Reflux events are more likely to occur in the right-side down and supine positions than the left-side down position. A sleep log documenting arousals from sleep with heartburn is usually sufficient to confirm sleep-related GER.

PSG without esophageal pH or impedance monitoring reveals arousals that are often associated with swallows and a notable increase in chin EMG tone. Esophageal pH monitoring detects acid reflux events and can be integrated with PSG. Esophageal pH monitoring should be performed over a 24-hour period to improve the test's sensitivity and specificity, which are approximately 90%. The distal pH probe is placed 5 cm above the LES. A proximal pH probe is often placed near the UES. An acid reflux event is defined as a pH drop to less than 4.0, and this variable is reported as Acid Exposure time (AET) (% of total recording time with pH < 4). In addition, the percent with pH < 4 is noted for upright and recumbent time. Note that recumbent time (in this testing) is defined as the total time in bed. AET < 4% is considered normal, > 6% is considered abnormal, and values between 4 and 6% are indeterminate and require further evaluation.

Symptom correlation is also helpful using the event marker on the device or diaries. Normal esophageal pH times during the "recumbent" or sleep period are: 1) distal pH < 4 - less than 3.5% of the time; and 2) proximal pH < 4 - less than 0.6% of the time.

If esophageal pH monitoring is integrated with polysomnography, esophageal acid events can be correlated with sleep events, including arousals, apneas, laryngospasm, and increased chin EMG tone. A systematic review has shown that reflux episodes occur during an episode of arousal/awakening rather than preceding it. This finding was confirmed in a study in which most nocturnal GER events (82%) occurred during wake epochs, with arousals/awakenings occurring before almost all GER events.

Esophageal pH monitoring can also be performed simultaneously with actigraphy to correlate acid reflux events with sleep and wake periods. In addition, catheter-free wireless pH systems deployed into the esophagus, usually by endoscopy, can provide monitoring for up to 96 hours.

Other objective diagnostic measures include esophageal manometry, which evaluates esophageal motility, and endoscopy with or without biopsy to evaluate for esophagitis and other esophageal complications. A histologic evaluation is required to establish a diagnosis of Barrett's esophagus.

Differential Diagnosis

Peptic ulcer disease and angina are the key diagnoses to consider in the differential. The chest pain associated with GER is sometimes indistinguishable from that of angina. Duodenal ulcer disease is commonly associated with burning epigastric pain, and this can sometimes be similar to the pain experienced by patients with GER.

OSA, sleep-related abnormal swallowing, and sleep-related laryngospasm must also be considered. PSG with respiratory and pH monitoring can differentiate these disorders.

Unresolved Issues and Further Directions

Not applicable or known.

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Sleep-related Myocardial Ischemia

Alternate Names

Unstable angina, coronary insufficiency-acute, nocturnal angina, angina decubitus, variant angina, Prinzmetal angina, vasospastic angina, angina pectoris, acute coronary syndrome, atherosclerotic heart disease, asymptomatic cardiac ischemia, silent ischemia.

Essential Features

Sleep-related myocardial ischemia is characterized by nocturnal reduction of blood flow to the myocardium during sleep. The symptoms of sleep-related myocardial ischemia are very similar to those of cardiac ischemia during the daytime. Classically, there is a feeling of chest pressure or pain that awakens the patient from sleep and may be described as a "viselike" discomfort. The discomfort may radiate to the chin, the jaw, or the arm, especially the left arm.

Associated Features

Acute episodes of sleep-related myocardial ischemia sometimes elicit atrial or ventricular arrhythmias. Other associated presentations include acute onset of shortness of breath (due, for example, to left ventricular diastolic dysfunction or ischemic mitral regurgitation) that awakens the patient from sleep. Other related features depend on the particular triggers of the cardiac ischemia. Ischemic events related to OSA may present during sleep when nocturnal desaturation is most severe and when there is the greatest mismatch between coronary blood flow and myocardial oxygen demand. Cardiac ischemia related to myocardial demand, hemodynamic changes, or vasospasm occurring during REM sleep may present in the early hours of the morning, around the time of waking. Ischemia associated with nocturnal hypotension may occur during NREM sleep, when blood pressure is lowest.

Clinical and Pathophysiologic Subtypes

None known.

Demographics

The prevalence, sex ratios, and age ranges have not been comprehensively evaluated. However, some insights into demographics can be extrapolated, depending on the cause of nocturnal angina. For sleep-related myocardial ischemia triggered by OSA, the preponderance of OSA in men suggests that middle-aged men with severe OSA are more likely to experience nocturnal angina, particularly if they have more severe coronary artery disease. Variant angina (also called vasospastic or Prinzmetal angina) more commonly affects younger populations, particularly women and those of Asian descent. Cardiac ischemia secondary to nocturnal hypotension is more commonly manifested in older individuals, particularly those on multiple antihypertensive medications with severe vasculopathy. Individuals with autonomic dysfunction (related to age or diabetes) impairing blood pressure homeostatic mechanisms are also more susceptible to hypotensive ischemia.

Predisposing and Precipitating Factors

Predisposing factors include established coronary artery disease or valvular disease such as aortic stenosis or regurgitation. Because coronary filling occurs during diastole, conditions associated with reduced diastolic blood pressure, such as severe aortic regurgitation, may elicit nocturnal angina, particularly in preexisting coronary artery disease. Usual risk factors for coronary artery disease that predispose an individual to the development of sleep-related myocardial ischemia include hypertension, diabetes mellitus, cigarette smoking, and hyperlipidemia.

Retrospective and prospective studies suggest that OSA may trigger myocardial infarction and sudden death at night. More severe oxyhemoglobin desaturations, often encountered in REM, are more likely to trigger cardiac ischemia. Coexisting pulmonary disease or truncal-abdominal obesity may further

contribute to the likelihood of ischemia/infarction. In patients with vasospastic angina, nonselective β -adrenergic receptor-blocking agents may theoretically increase the likelihood of vasospasm. In patients with nocturnal angina secondary to hypotension, an excess of antihypertensive medications, as well as long-acting nitroglycerin administered before sleep, may contribute. Finally, abuse of drugs such as amphetamine, cocaine, and other stimulants, should be considered in evaluating myocardial ischemia.

Familial Patterns

Familial patterns reflect those of the underlying disease process.

Onset, Course, and Complications

For angina related to OSA, the first presentation of nocturnal angina may occur only when the severity of sleep apnea and coronary artery disease is sufficient to elicit sleep-related myocardial ischemia. This is likely to be more common in middle-aged to older men, particularly those who are overweight. However, several studies have documented life-threatening OSA-related cardiac ischemia in women. Furthermore, other studies have reported cardiac ischemia in patients with OSA, even in the absence of severe coronary artery stenosis. ST-segment changes occurring as a result of OSA would be expected to resolve with treatment of the OSA. Regardless of the underlying etiology, potential complications of sleep-related myocardial ischemia include acute left ventricular dysfunction, ischemic mitral regurgitation, pulmonary edema, atrial or ventricular arrhythmias, and progression to acute coronary syndromes, including myocardial infarction or sudden death.

Pathology and Pathophysiology

In OSA, the apnea-related hypoxemia and surges in blood pressure and heart rate at the termination of apnea may result in relative myocardial oxygen deficiency. Preexisting severe coronary artery disease will exacerbate this problem. "Variant" angina, with coronary vasospasm, may be more likely to occur during sleep because of the significant and abrupt fluctuations in cardiovascular neural control during REM sleep. Maintenance of diastolic pressures during sleep is critical for adequate myocardial perfusion. Autonomic insufficiency due to old age, diabetes, and medication effects may blunt the ability of the cardiovascular system to maintain adequate blood pressure, thus contributing to hypotensive nocturnal angina.

Objective Findings

Electrocardiographic monitoring during sleep reveals horizontal or downsloping ST-segment depression of greater than or equal to 1 mm, or ST-segment elevation of 1 mm or more. The electrocardiographic evidence of sleep-related coronary artery ischemia is sometimes unaccompanied by chest discomfort or

other symptoms. This finding is termed "silent" ischemia and may be incidentally noted on Holter monitoring or telemetry.

In general, ST-segment abnormalities indicative of myocardial ischemia are 1 mm or more horizontal or down-sloping depression or ST-segment elevation, which may be detected on the single-lead electrocardiogram (ECG) employed in most sleep laboratories. However, because the sensitivity of single-lead ECG in detecting ischemic changes is poor, the patient with symptoms compatible with angina should be further evaluated despite a normal-appearing single ECG channel. This evaluation may include multichannel ECG—and additional cardiac investigations such as CT coronary angiography, stress echocardiography, or myocardial perfusion imaging.

Sleep-related breathing disorders, particularly OSA, may elicit oxygen desaturation and consequent sleep-related myocardial ischemia. Sleep-related myocardial ischemia in patients without sleep-related breathing disorders may be associated with REM sleep. Slow-wave sleep with a fall in blood pressure and heart rate may also provoke ischemia. Cardiac arrhythmias during sleep should prompt an evaluation for nocturnal ischemia or underlying cardiac structural abnormalities.

Differential Diagnosis

Gastroesophageal reflux may also be associated with chest discomfort. The nature of the pain, associated symptoms, and prior history help distinguish GER from cardiac ischemia, although a 12-lead ECG may be necessary in some cases.

Nocturnal panic attacks may be associated with chest wall pain and respiratory distress. Although most patients with nocturnal panic will have a history of daytime panic attacks, a small percentage have only nocturnal events. Nocturnal panic attacks typically occur during the transition from N2 to N3 sleep.

Nocturnal respiratory distress due to poorly controlled heart failure or pulmonary disease may be confused with myocardial ischemic episodes, although typical anginal chest pain is not evident in these cases.

Chest pain due to thoracic mass, pleuritic pain, aortic aneurysm, or other thoracic disease should be considered in the differential diagnosis. In addition, chest wall pain may be secondary to various causes such as trauma, muscle spasm, or immobility.

Unresolved Issues and Further Directions

More comprehensive data are needed to identify the prevalence and demographics of the various causes of sleep-related myocardial ischemia. Further information is also required to explore the relationship between sleep-related myocardial ischemia and the circadian variation in acute coronary syndromes (including myocardial infarction), atrial and ventricular arrhythmia, and sudden cardiac death.

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