International Classification of Sleep Disorders

Third Edition

American Academy of Sleep Medicine

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ICSD-3

American Academy of Sleep Medicine

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In memory of Peter Hauri, PhD
mentor, colleague and friend

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Michael Sateia, MD, is Professor of Psychiatry at the Geisel School of Medicine at Dartmouth. He has served in a variety of leadership capacities in Sleep Medicine. He is Past-President of the American Academy of Sleep Medicine. Dr. Sateia was Associate Editor for the *Journal of Clinical Sleep Medicine* and chaired the Scientific Program Committee of the Associated Professional Sleep Societies. He was a member of the Research Advisory Board of the National Center on Sleep Disorders Research and held a five year Academic Award from the National Heart, Lung, and Blood Institute. He served on the Accreditation Council on Graduate Medical Education Advisory Committee for Sleep Medicine and the American Board of Internal Medicine Policy and Test Committee for Sleep Medicine. His editing responsibilities have included the International Classification of Sleep Disorders, 2nd Edition; the comprehensive textbook, Sleep Medicine; and Insomnia: Diagnosis and Treatment. In 2009 he received the Nathaniel Kleitman Award from the American Academy of Sleep Medicine. He currently serves as task force chair and editor for the International Classification of Sleep Disorders, 3rd Edition, and chair of the task force on the pharmacological management of insomnia. He has authored numerous scientific articles in sleep medicine, focused primarily on insomnia and professional education in sleep.

Editor's Notes

Many people contributed to the development of this manual. The members of the Task Force on ICSD-3, who also chaired individual work groups, devoted countless hours and tireless dedication to the work, as did the members of their respective work groups. Numerous reviewers also provided thoughtful recommendations which served to improve the text. These individuals are acknowledged individually on the following pages.

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Introduction

Classification of disorders plays several key roles in medicine. The most familiar of these is that is serves as a guide to clinicians in the identification of specific disease states. In doing so, classification systems provide clinicians with important information regarding numerous related factors including pathogenesis, prognosis, course, and heritability. Moreover, therapeutic interventions are largely guided by the nosological decisions made by clinicians. In turn, information accrued regarding therapeutic response of these disease states is utilized to further refine the nosology. Classification systems also serve to define the domain of a given discipline, a factor of particular importance for fields such as sleep medicine which cut across many related specialties. Finally, by identifying areas of uncertainty and overlap among related pathologies, these systems play a critical role in guiding future research agendas which will enhance our knowledge and understanding of the clinical features, pathophysiology and treatment response specific to each disorder.

Since its infancy 35 years ago, the field of sleep medicine has paid particular attention to the issue of classification, beginning with the 1979 American Sleep Disorders Association's Diagnostic Classification of Sleep and Arousal Disorders. Since that time, as our knowledge and understanding of sleep disorders has grown, several different structural approaches have been utilized in revisions of the classification system, culminating in the International Classification of Sleep Disorders, 2nd Edition. The organization of that edition, although not without its limitations, has proven effective and user-friendly and has been maintained in the current revision.

Ideally, classification systems are based largely on pathophysiology. However, such an approach is dependent on adequate knowledge concerning the various pathophysiologies of disease or disorder within a given discipline. As is the case with many diagnostic systems, our current knowledge and understanding of the pathophysiology of many sleep disorders is inadequate. As a result, International Classification of Sleep Disorders, 3rd Edition, not unlike its predecessors, employs a hybrid approach which utilizes pathophysiology, where known, but also relies heavily on phenomenology and organ system approaches. Despite these shortcomings, this approach is one that has proven familiar and workable for sleep medicine clinicians.

Recognizing the need for currency and relevance in a rapidly evolving field, the American Academy of Sleep Medicine Board of Directors approved a revision of International Classification of Sleep Disorders, 2nd Edition in 2011. Following appointment of a chair/editor, a task force, consisting of individual work group chairs for each

major division of the manual, was selected, along with two pediatric consultants. A focus group of experts was convened in June 2011 to obtain input on major structural and content issues. Based on this feedback, individual work groups then set about to define the list of disorders to be included within their sections as well as proposed criteria for each diagnosis. This process included comprehensive literature searches for every potential diagnosis as well as for their major features. The draft diagnostic criteria which emanated from this work were then reviewed and modified by the task force (consisting of the work group chairs and pediatric advisors), as well as by the board of the AASM. The edited criteria were then distributed to external peer reviewers with expertise in the respective areas, as well as to international societies and membership sections of the AASM for comment. These reviews were carefully considered and revisions made based on this input. Subsequent to this, text revisions were begun and the same review process and modifications were undertaken once text drafts were completed. Further modifications were made based on recommendations from the AASM board before finalization of the edition. At all points in this process, efforts were made to rely as heavily as possible on available and current scientific evidence. However, due to the paucity of available evidence in many areas, decisions regarding the nosology were often made by consensus of the work groups, task force, and reviewers.

Using ICSD-3

As noted above, the general structure of the current edition closely parallels that of the second edition. The major clinical divisions remain unchanged. As with International Classification of Sleep Disorders, 2nd Edition, pediatric diagnoses are fully integrated into the major clinical diagnoses, with the exception of *obstructive sleep apnea, pediatric*. Where pediatric presentations call for variation in the diagnostic criteria, those variations are noted within the criteria section. In an effort to better identify those clinical features of a disorder which are developmentally-specific, a text heading for *Developmental Issues* has been added for each diagnosis. Specific ICD codes (9-CM and 10-CM) are listed at the beginning of each diagnosis. Because of the complexities and differences between International Classification of Sleep Disorders diagnoses and the ICD system, assignment of codes is challenging. These issues are discussed further under *Coding* below.

Although classification systems are, by their nature, intended to define disorders in the most specific terms possible, clinicians must recognize that there is inevitably some degree of variability in presentation which may result in clinically significant conditions which do not meet all specific criteria for a given diagnosis. Therefore, some degree of judgment is necessary in the application of these criteria. Bearing this exception in mind, all listed criteria should generally be met for establishment of a given diagnosis, unless otherwise specified. Clinicians should note that most diagnoses

within the International Classification of Sleep Disorders include a criterion, or criteria, that connote clinical significance (i.e., disturbing symptoms, significant consequences, distress or impairment in one or more functional realms). These criteria are particularly important because, without them, many phenomena related to sleep-wake do not rise to a level that requires clinical attention and treatment. Users should also pay particular attention to the *Notes* section (where included), as these notes provide essential definitions and details concerning application of the criteria.

Clinicians will note a number of significant content changes from the former edition. The most apparent of these is the collapse of all previous chronic insomnia diagnoses into a single *chronic insomnia disorder* diagnosis. The rationale for this is described in the introductory section of *Insomnia* disorders. A separate diagnosis is retained for *short-term insomnia*. Within the *Central Disorders of Hypersomnolence* section, the nomenclature for narcolepsy has been changed to *narcolepsy type 1* and *type 2*. This modification is discussed in the introduction to that section. Users will also find several new diagnoses within the *Sleep Related Breathing Disorders*. Within the *Central Sleep Apnea Syndromes*, a diagnosis of *treatment-emergent central sleep apnea* now appears. This term is preferred to the widely used term *complex sleep apnea* because it describes a more specific and well-defined disorder in which the central apnea arises in the context of positive airway pressure treatment for obstructive sleep apnea and is not attributable to another cause. Central sleep apnea associated with other identifiable etiologies such as Cheyne-Stokes breathing or substance-induced central sleep apnea are not classified as treatment-emergent. Assigning a diagnosis of a *sleep related hypoventilation disorder* requires demonstration of elevated $PaCO_2$ (by direct measure of arterial blood gas or, more commonly, by proxy measures such as end-tidal or transcutaneous CO_2 determination). The new diagnosis of *sleep related hypoxemia disorder* should be employed when there is sustained drop in SaO_2 but $PaCO_2$ has not been measured. Within the parasomnia section, a single set of general criteria and a unified text now describe disorders of arousal from non-rapid eye movement sleep, although additional, specific criteria and separate coding are maintained for the diagnoses within this section (i.e., confusional arousal, sleepwalking and sleep terror). Other, somewhat less consequential additions, deletions and reassignment of diagnoses also appear in this edition. International Classification of Sleep Disorders, 2nd Edition contained a separate chapter for *Isolated Symptoms and Normal Variants*. A small number of these were felt to qualify as formal diagnoses at this time and have been moved to relevant sections. Other symptoms and variants appear at the conclusion of the chapter to which they are most applicable (e.g., *snoring* to the *Sleep Related Breathing Disorders*, *long sleeper* to *Central Disorders of Hypersomnolence*, and movement related variants to the *Sleep Related Movement Disorder* section).

A wealth of information regarding each diagnosis is contained within the separate text headings within each diagnostic section. The outline below details some of the specific content to be found within each text heading. These terms are not indexed in the hard copy version of this manual because they appear throughout the document. Users should refer to the relevant text heading within a specific diagnosis for information related to these terms:

Alternate Names

Diagnostic Criteria

Essential Features

Associated Features

Clinical and Pathophysiological Subtypes

Demographics

includes:

- Prevalence
- Gender bias
- Racial / ethnic bias
- Cultural issues

Predisposing and Precipitating Factors

includes:

- Risk factors

Familial Pattern

includes:

- Genetics
- Familial clusters

Onset, Course and Complications

includes:

- Medical
- Neurological
- Psychiatric / social

Developmental Issues

includes:

- Pediatric
- Geriatric

Pathology and Pathophysiology

Objective Findings

includes:

- Sleep logs
- Actigraphy
- Questionnaires
- Polysomnography
- Multiple sleep latency test
- Neurological
  - Electroencephalogram
  - Cerebrospinal fluid
  - Neuroimaging
  - Electromyogram
  - Autonomic
- Endocrine
- Genetic testing
- Physical findings
- Respiratory
  - Arterial blood gas
  - Pulmonary function
  - Ventilatory response
- Cardiac
  - Electrocardiogram
  - Echocardiogram
  - Cardiac catheterization
- Serum chemistry

Relationship to Other Classification Systems

Historically, there have been three major classifications systems for sleep disorders. Although the International Classification of Sleep Disorders system has, for many years, been the primary nosology for sleep medicine specialists, both the Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association and the International Classification of Diseases (ICD) nosology of the World Health Organization have also classified sleep disorders. Unfortunately, these competing systems have differed significantly in structure and content over the years. Development of DSM-5 was ongoing during the development of this manual and an effort was undertaken to achieve the greatest degree of concordance possible between these two systems, recognizing that the International Classification of Sleep Disorders will inevitably contain a greater level of detail than DSM due to differences in their target users. This goal was largely achieved although some differences will still exist. The major change to the *Insomnia* section (i.e. establishment of a single *chronic insomnia disorder* diagnosis) within this new system is paralleled in DSM-5. *Central Disorders of Hypersomnolence* diagnoses are organized somewhat differently in the DSM classification than in this manual and narcolepsy criteria differ slightly. *Circadian Rhythm Sleep-Wake Disorder* diagnoses are identical within the two systems with the exception that DSM does not include a *jet lag disorder*. *Sleep Related Breathing Disorders* are significantly more detailed within International Classification of Sleep Disorders than DSM-5, although the organizational structures in this section are quite similar. *Sleep Related Movement Disorders* and *Parasomnias* are likewise similar but with fewer overall diagnoses within DSM-5.

With the publication of International Classification of Sleep Disorders, 2nd Edition, a major effort to expand and reorganize sleep related diagnoses within ICD-9-CM was undertaken. This effort resulted in the inclusion of many additional sleep related diagnoses in ICD-9-CM (primarily within the Diseases of the Nervous System section). The archaic distinction between "organic" and "non-organic" disorders has historically been a guiding principle of ICD, resulting in dissemination of sleep diagnoses to both the neurological and mental disorder categories. Clinicians familiar with the ICD-9-CM categories which have been employed since the most recent changes will find general concordance between the assigned diagnostic codes found herein and the most current version of ICD-9-CM. These ICD-9-CM codes for sleep disorders are essentially carried over to ICD-10-CM. However, certain content revisions in International Classification of Sleep Disorders, 3rd Edition (e.g., chronic insomnia) necessitates a significant departure from the coding approach utilized in ICD-9-CM and International Classification of Sleep Disorders, 2nd Edition. This is discussed further below.

Coding

Diagnostic codes for the relevant ICD-9-CM and ICD-10-CM diagnoses can be found at the beginning of each diagnosis section of the book. In the United States, the former codes (ICD-9-CM) should be employed until the implementation date for ICD-10-CM which, at the time of this writing, is to be no sooner than October 1, 2015. Following that date, only the ICD-10-CM codes should be used. As already stated, clinicians should recognize that there is not precise concordance between the assigned codes for International Classification of Sleep Disorders, 3rd Edition diagnoses and the diagnoses listed within ICD. Changes to the International Classification of Sleep Disorders classification system are not reflected in the ICD system for many years. Moreover, the ICD classification of sleep disorders has historically been significantly less detailed than ICSD (particularly for international users not employing the Clinical Modification (CM) version used in the United States). Hence, clinicians will find many areas in which assigned codes found in this manual do not correspond as closely as one would like to ICD codes. Most notably, with the collapse of chronic insomnia diagnoses into a single disorder in International Classification of Sleep Disorders, 3rd Edition, the assigned codes for this diagnosis within International Classification of Sleep Disorders, 3rd Edition are 307.42 (ICD-9-CM) – "Nonorganic persistent disorder of initiating or maintaining sleep" and F51.01 (ICD-10-CM) – "Primary insomnia." A variety of other insomnia diagnoses will continue to appear in the ICD system but, with the classification and coding changes recommended herein, these become essentially defunct for sleep medicine clinicians. In summary, the assigned codes in this edition represent "best approximations" to the corresponding ICD codes, but some degree of discrepancy between the systems will exist in a number of areas.

Insomnia

Isolated Symptoms and Normal Variants

This section includes sleep disorders chiefly characterized by the complaint of insomnia. For the purpose of this manual, insomnia is defined as a persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment. These three components of insomnia—persistent sleep difficulty, adequate sleep opportunity, and associated daytime dysfunction—are collectively implied by text references to the term insomnia. Among adults with insomnia, sleep complaints most typically include difficulties initiating or maintaining sleep. Concerns about lengthy periods of nocturnal wakefulness, insufficient amounts of nocturnal sleep, or poor sleep quality often accompany these complaints. Individuals who report these sleep related symptoms in the absence of daytime impairment are not regarded as having an insomnia disorder that warrants clinical attention other than education and reassurance. Insomnia among children is often reported by their caretakers and characterized by bedtime resistance, frequent nighttime awakenings and/or an inability to sleep independently. Regardless of the exact nature of the nocturnal sleep concerns, daytime impairments are reported, presumably caused by the nighttime sleep difficulties or by some common but unidentified mechanism during sleep and wakefulness. Daytime symptoms typically include fatigue, decreased mood or irritability, general malaise, and cognitive impairment. Among adults, chronic insomnia may impair social or vocational functioning and reduce quality of life, whereas in children it may lead to poor school performance, impaired attention, and behavioral disturbance. In some patients, physical symptoms such as muscle tension, palpitations, or headache may also be attributed to the insomnia. Others with more severe forms of insomnia may be at increased risk for motor vehicle and work-site accidents as well as psychiatric and cardiovascular disorders. Insomnia often accompanies comorbid medical illnesses, mental disorders, and other sleep disorders. It may also arise in association with the use, abuse, or exposure to certain substances. When insomnia occurs comorbid to these conditions and is persistent and prominent, a separate insomnia diagnosis is warranted.

The insomnia nosology presented in this text represents a marked departure from the previous International Classification of Sleep Disorders, 2nd Edition insomnia classification system in terms of its conceptual framework and relative simplicity. The previous insomnia nosology of the International Classification of Sleep Disorders promoted the concept that insomnia can exist as a primary sleep disorder or arise as a secondary form of sleep disturbance related to an underlying *primary* psychiatric, medical, or substance abuse disorder. However, many symptoms and associated features of so-called primary and secondary insomnias are overlapping, thus making differentiation among such subtypes difficult, if not impossible. There is increasing recognition that even when insomnia arises "secondary" to another condition, it often develops an independent course over time and may remain as a clinically significant condition, even if the so-called primary condition is adequately treated. Evidence suggests that insomnia, if left untreated, may adversely affect the outcome of these comorbid conditions. Moreover, it appears that treatment of the insomnia may improve outcome of both the sleep disturbance and the comorbid conditions. Given these observations, insomnia seems best viewed as a comorbid disorder that warrants separate treatment attention.

In addition to the primary vs. secondary insomnia distinction, prior editions of the International Classification of Sleep Disorders delineated multiple putative "primary insomnia" diagnostic subtypes. Specifically, both the original 1990 version of the International Classification of Sleep Disorders and the International Classification of Sleep Disorders, 2nd Edition described primary insomnia subtypes such as psychophysiological insomnia, idiopathic insomnia, inadequate sleep hygiene, and paradoxical insomnia, as discrete diagnostic entities. Experience suggests that, in practice, it is rare to encounter patients who meet the diagnostic criteria for exclusively one of these subtypes. In fact, many of the diagnostic criteria delineated for these subtypes represent generic characteristics (e.g., engaging in sleep-disruptive habits; underestimation of sleep time, evidence of conditioned arousal) of insomnia, per se, and do not facilitate discrimination among these subtypes or between these subtypes and those presumed to have "secondary" forms of insomnia.

Both clinical experience and a growing body of empirical findings have shown that the diagnostic distinctions advocated by previous versions of the International Classification of Sleep Disorders are difficult to reliably ascertain and are of questionable validity. In view of such considerations, the current manual abandons the previously employed complex and highly specific insomnia classification scheme described by the original International Classification of Sleep Disorders and the 2nd Edition in favor of a more global and defensible nosology.

The manual includes three diagnostic categories for insomnia: chronic insomnia disorder, short-term insomnia disorder, and other insomnia disorder. These diagnoses apply to patients with and without comorbidities regardless of whether those comorbidities are viewed as potentially sleep disruptive. Chronic insomnia disorder is characterized by chronic sleep onset and/or sleep maintenance complaints with associated daytime impairment, and is reserved for individuals whose sleep difficulties exceed minimal frequency and duration thresholds shown to be associated with clinically significant morbidity outcomes. Short-term insomnia disorder is characterized by sleep/wake difficulties that fail to meet the minimal frequency and duration criteria of chronic insomnia disorder. Nonetheless, short-term insomnia disorder is associated with clinically significant sleep dissatisfaction or waking impairment. Other insomnia disorders should be assigned to those rare cases that fail to meet criteria for short-term insomnia disorder, yet are thought to have sufficient symptoms of insomnia to warrant clinical attention.

Chronic Insomnia Disorder

ICD-9-CM code: 307.42 ICD-10-CM code: F51.01

Alternate Names

Chronic insomnia, primary insomnia, secondary insomnia, comorbid insomnia, disorder of initiating and maintaining sleep, behavioral insomnia of childhood, sleep-onset association disorder, limit-setting sleep disorder.

Diagnostic Criteria

Criteria A-F must be met

A. The patient reports, or the patient's parent or caregiver observes, one or more of the following:[1]
    1. Difficulty initiating sleep.
    2. Difficulty maintaining sleep.
    3. Waking up earlier than desired.
    4. Resistance to going to bed on appropriate schedule.
    5. Difficulty sleeping without parent or caregiver intervention.
B. The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty:
    1. Fatigue/malaise.
    2. Attention, concentration, or memory impairment.
    3. Impaired social, family, occupational, or academic performance.

4. Mood disturbance/irritability.
5. Daytime sleepiness.
6. Behavioral problems (e.g., hyperactivity, impulsivity, aggression).
7. Reduced motivation/energy/initiative.
8. Proneness for errors/accidents.
9. Concerns about or dissatisfaction with sleep.

C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e., enough time is allotted for sleep) or inadequate circumstances (i.e., the environment is safe, dark, quiet, and comfortable) for sleep.

D. The sleep disturbance and associated daytime symptoms occur at least three times per week.

E. The sleep disturbance and associated daytime symptoms have been present for at least three months.[2]

F. The sleep/wake difficulty is not better explained by another sleep disorder.

Notes

1. Reports of difficulties initiating sleep, difficulties maintaining sleep, or waking up too early can be seen in all age groups. Resistance going to bed on an appropriate schedule and difficulty sleeping without parent or caregiver intervention is seen most commonly in children and older adults who require the supervision of a caretaker due to a significant level of functional impairment (e.g., those with dementia).
2. Some patients with chronic insomnia may show recurrent episodes of sleep/wake difficulties lasting several weeks at a time over several years, yet not meet the three-month duration criterion for any single such episode. Nonetheless, these patients should be assigned a diagnosis of chronic insomnia disorder, given the persistence of their intermittent sleep difficulties over time.
3. Some patients who use hypnotic medications regularly may sleep well and not meet the criteria for an insomnia disorder when they take such medications. However, in the absence of such medications these same patients may meet the above criteria. This diagnosis would apply to those patients particularly if they present clinically and voice concerns about their inability to sleep without their sleep medications.
4. Many comorbid conditions such as chronic pain disorders or gastroesophageal reflux disease (GERD) may cause the sleep/wake complaints delineated here. When such conditions are the sole cause of the sleep difficulty, a separate insomnia diagnosis may not apply. However, in many

patients such conditions are chronic and are not the sole cause of sleep difficulty. Key determining factors in the decision to invoke a separate insomnia diagnosis include: "How much of the time does the sleep difficulty arise as a result of factors directly attributable to the comorbid condition (e.g., pain or GERD)?" or "Are there times that the sleep/wake complaints occur in the absence of these factors?" "Have perpetuating cognitive or behavioral factors (e.g., negative expectations, conditioned arousal, sleep-disruptive habits) arisen, suggesting an autonomous aspect to the ongoing insomnia?" If there is evidence that the patient's sleep/wake complaints are not solely caused by the medical condition, and those sleep/wake complaints seem to merit separate treatment attention, then a diagnosis of chronic insomnia disorder should be made.

Essential Features

The essential feature of chronic insomnia disorder is a frequent and persistent difficulty initiating or maintaining sleep that results in general sleep dissatisfaction. The sleep complaint is accompanied by distress about poor sleep and/or impairment in family, social, vocational, academic, or other important areas of functioning. Furthermore, the sleep disturbance and associated waking symptoms occur despite having adequate time and circumstances each night to obtain necessary sleep. Chronic insomnia disorder can occur in isolation or comorbidly with a mental disorder, medical condition, or substance use.

The sleep complaints that comprise chronic insomnia disorder may include difficulties initiating sleep or difficulties maintaining sleep. The latter complaint may include waking up during the night with difficulty returning to sleep or having a final awakening occurring too early, well before the desired rising time. Chronic insomnia disorder may be characterized solely by sleep onset or sleep maintenance complaints or, more commonly, by both types of complaints occurring together. Individuals' sleep complaints may also change over time such that those with solely sleep onset complaints may subsequently develop sleep maintenance complaints and vice versa. Also, those who present initially with mixed sleep onset and sleep maintenance difficulties may later evidence one or the other of these difficulties but not both. Complaints about poor-quality, unrefreshing, or nonrestorative sleep often accompany sleep onset and sleep maintenance complaints, but do not suffice to define insomnia disorder when occurring as the sole sleep complaint.

The degree of sleep disturbance required to assign a chronic insomnia disorder diagnosis is somewhat arbitrary in that it relies primarily on individuals' subjective sleep

complaints. Moreover, the degree of sleep disturbance required to connote clinical significance varies across age groups. Nonetheless, sleep onset latencies and periods of wakefulness after sleep onset > 20 minutes generally connote clinically significant sleep disturbances in children and young adults. In middle and older aged adults, onset latencies and periods of wakefulness during sleep > 30 minutes typically connote clinical significance. Complaints of early morning awakening are less well defined, but typically entail the termination of sleep at least 30 minutes before the desired rising time and a concomitant reduced total sleep time compared with the usual premorbid sleep pattern. The exact time at which early morning awakenings occur may vary considerably as a function of usual bedtimes. For example, a final awakening at 4:00 a.m. is likely to connote clinical significance when the usual bedtime is 11:00 p.m. but not when the usual bedtime occurs at 9:00 p.m.

Symptoms during wakefulness accompany the sleep difficulties and result in the impairment of normal functioning. Common waking symptoms include fatigue; reduced motivation; reduced concentration, attention, and memory functioning; and irritability or reduced mood. Complaints of subjective daytime sleepiness are also common, although, in contrast to patients with hypersomnolence conditions, many with this complaint are not able to nap in the daytime and few show unintentional sleep episodes. Reports of reduced performance at work or school or impaired social functioning also are common. Some affected individuals attribute errors or accidents at work to their sleep difficulties. Somatic symptoms such as headaches or gastrointestinal dysfunction are occasionally attributed to the ongoing sleep difficulties as well.

The fatigue of insomnia sufferers is manifest mainly as a lack of energy and desire to reduce or limit activity levels. This symptom should be differentiated from reports of subjective sleepiness as well as from unintended sleep episodes. Insomnia sufferers commonly report subjective sleepiness characterized by a sense of reduced alertness and enhanced need or desire to sleep. However, they seldom fall asleep spontaneously without intending to do so. Despite a desire to nap, many individuals with insomnia are unable to do so. Frequent, unintentional daytime sleep episodes are more characteristic of other types of sleep disorders such as sleep disordered breathing, narcolepsy, idiopathic hypersomnia, and the like.

In young children, difficulty falling asleep, staying asleep, or both are often the result of inappropriate sleep associations or inadequate limit setting. Inappropriate sleep associations result from a child's dependency on specific stimulation, objects, or settings for initiating sleep or returning to sleep following an awakening; in the absence of these conditions, sleep onset is significantly delayed. This manifestation usually presents as

frequent nighttime awakenings and/or nighttime fears or anxiety about sleeping alone. The process of falling asleep is associated with a specific form of stimulation (e.g., rocking, watching television), object (e.g., bottle, excessive feedings), or setting (e.g., lighted room, parents remaining in the room, or child taken to parents' bed). When such conditions are absent, children with this disorder experience difficulty falling asleep at bedtime and following normal nighttime arousals. If the conditions associated with falling asleep are reestablished, the child usually resumes sleep relatively quickly. Because sleep-onset associations are highly prevalent in young children, the phenomenon is defined as a disorder only if (1) the associations are highly problematic or demanding (e.g., extended rocking, car rides); (2) sleep onset is significantly delayed or sleep is otherwise disrupted in the absence of the associated conditions; and (3) caregiver intervention is frequently required to aid the onset or resumption of sleep. Limit-setting issues are characterized by bedtime stalling or bedtime refusal that is met with and reinforced by inadequate limit setting by a caregiver. Sleep problems occur when caregivers institute no or few limits or when limits are instituted inconsistently or in an unpredictable manner. Limit-setting sleep problems may also result in prolonged nocturnal awakenings, depending on caregiver response during the night.

It also should be noted that some children's needs for specific conditions for sleeping or their resistance to go to bed may reflect underlying anxiety or fears. Fear of sleeping alone, being in the dark, or having nightmares may lead some children to demand certain sleep promoting conditions (presence of parent in bedroom) or to repeatedly delay their bedtimes.

Although transient and episodic forms of insomnia occur, the clinically significant daytime consequences of insomnia and the longer term, more serious morbidity outcomes most typically develop when the sleep difficulties occur at least three times per week and persist for at least three months. For this reason, these frequency and duration criteria must be met for the assignment of a chronic insomnia disorder diagnosis. However, it is recognized that more acute and episodic forms of insomnia may cause significant distress and functional impairment and require clinical attention. Cases that meet all criteria except the frequency or duration criteria for chronic insomnia disorder should be assigned a diagnosis of short-term insomnia disorder.

Associated Features

Individuals with chronic insomnia disorder typically note feelings of reduced well-being and general malaise during the day. In addition, excessive focus on and worry about ongoing sleep difficulties and their associated daytime consequences are common. Thoughts about ongoing sleep difficulties may occur through the day and may be amplified as bedtime

approaches. Frank performance anxiety about sleep is common. Although many with insomnia may appear anxious and worry-prone, their anxiety and worry are often focused mainly on their sleep difficulties. When anxiety and worry are more pervasive and not solely focused on sleep problems, a comorbid anxiety disorder may be present. Many with chronic insomnia disorder show a pattern of conditioned arousal in response to environmental cues in their bedrooms or conscious efforts to initiate sleep. Such individuals may fall asleep easily in settings outside of their bedrooms when not trying to sleep, but show a pattern of cognitive and physiological arousal when lying down in their beds with the intention to fall asleep. Some patients with this pattern may report sleeping better when away from home than when at home. Unlike noncomplaining normal sleepers, individuals with chronic insomnia disorder often express conscious intentions and excessive effort to sleep, only to find sleep difficult to initiate under such circumstances.

In children, the sleep disturbance may be accompanied by daytime behavioral problems and limit-setting difficulties during the day. In addition, the nighttime sleep disturbance often results in poor parental sleep and associated daytime impairment. Marital conflicts regarding how to respond to or intervene with the ongoing sleep problem may arise. Parents also may develop negative feelings toward the child who disrupts their sleep and demands their attention during the night.

Clinical and Pathophysiological Subtypes

Various clinical and pathophysiological subtypes of insomnia have been described in previous nosologies. Both the American Psychiatric Association's Diagnostic and Statistical Manual, 4th Edition, Text Revision (DSM-IV-TR) and the International Classification of Sleep Disorders, 2nd Edition describe independently occurring or *primary* forms of insomnia. Within DSM-IV-TR, the global term, *primary insomnia*, is applied to all forms of insomnia that are not better explained by a coincident psychiatric, medical or substance use/abuse disorder. Within the International Classification of Sleep Disorders, 2nd Edition system, multiple primary insomnia subtypes are delineated. The specific primary insomnia subtypes listed in the previous International Classification of Sleep Disorders, 2nd Edition include the following:

Psychophysiological insomnia is characterized primarily by heightened arousal and learned sleep-preventing associations that result in a complaint of insomnia. Patients presumed to have this type of insomnia often have sleep difficulty when trying to sleep in their usual sleep setting at home but may fall asleep easily in a novel sleep setting or when not trying to sleep. They also demonstrate excessive focus on and worry about sleep and suffer from elevated levels of cognitive and somatic arousal, particularly at bedtime.

Idiopathic insomnia is characterized by a longstanding complaint of sleep difficulties with insidious onset occurring during infancy or early childhood. It is presumed to arise in infancy or early childhood without discernible cause and to persist over time without sustained periods of remission. Given its early onset, stability over time, and lifelong course, this disorder is thought to arise from either genetically determined or congenital aberrations in the sleep-inducing or arousal systems in the brain, or both. No consistent genetic markers or neural pathology have been identified among those presumed to suffer from this condition.

Paradoxical insomnia, which has previously been called sleep state misperception, is described as a complaint of severe sleep disturbance without corroborative objective evidence of the degree of sleep disturbance claimed. Those presumed to have this form of sleep difficulty have a marked propensity to underestimate the amount of sleep they actually are obtaining. In essence, they are thought to perceive much of the time they actually sleep as wakefulness. Although many such patients routinely obtain normative amounts of sleep, as documented by standard polysomnographic measures, they complain of the common sleep/wake symptoms of other insomnia disorders. Some studies using neuroimaging or sleep electroencephalograph (EEG) spectral analysis techniques have suggested that an altered sleep/wake arousal system in such individuals may explain the apparent mismatch between their conventional objective sleep measures and subjective sleep reports.

Inadequate sleep hygiene is presumed to result from or be sustained by daily living activities that are inconsistent with the maintenance of good-quality sleep and normal daytime alertness. Patients with this form of insomnia have ongoing sleep/wake difficulties as a function of practices such as daytime napping, maintaining a highly variable sleep/wake schedule, routinely using sleep-disruptive products (caffeine, tobacco, alcohol) too close to bedtime, engaging in mentally or physically activating or emotionally upsetting activities too close to bedtime, routinely using the bed and bedroom for activities other than sleep, or failing to maintain a comfortable environment for sleep.

Behavioral insomnia of childhood is presumed to result from improper sleep training or limit setting by parents or caretakers. Within this broader diagnosis, several subtypes have been described. *Sleep-onset association type* is characterized by the child's dependency on specific stimulation, objects, or settings for initiating sleep or returning to sleep following an awakening; in the absence of these conditions, sleep onset is significantly delayed. *Limit-setting type* is characterized by bedtime stalling or bedtime refusal that is the result of inadequate limit setting by a caregiver. A *mixed type*

characterized by features of sleep-onset association difficulties and bedtime resistance represents a third subtype within this diagnostic category.

The DSM-IV-TR and International Classification of Sleep Disorders, 2nd Edition also describe several so-called *secondary insomnias*, arising from co-occurring primary or causative conditions. Among these are the following:

Insomnia due to (another) mental disorder is thought to be caused by or secondary to a co-occurring psychiatric condition. Insomnia is a common complaint, particularly among patients with mood disorders and anxiety disorders. Likewise, sleep disturbance is commonly seen in those with psychotic spectrum disorders and various Axis II (personality) disorders. Among those individuals presumed to have insomnia due to a mental disorder, insomnia has historically been regarded as a secondary symptom, caused by the mental disorder itself.

Insomnia due to (a) medical condition is thought to be caused by or secondary to a co-occurring medical condition. Like the mental disorders, many medical conditions may have an ongoing insomnia complaint associated with them. In particular, those conditions that cause some form of ongoing pain or discomfort, mobility limitation, or breathing disturbance commonly have insomnia complaints accompanying them. Among those individuals presumed to have insomnia due to a medical disorder, insomnia has historically been regarded as a secondary symptom, caused by the medical disorder itself.

Insomnia due to drug or substance is thought to be caused by or secondary to use of or withdrawal from a drug or substance. Many forms of prescription and nonprescription medications, street drugs, and other commonly used substances may produce sleep disturbances either during periods of use or upon withdrawal. Given these effects, insomnia complaints may arise either during periods when these substances are used or following their discontinuance. Among those individuals presumed to have insomnia due to drug or substance, insomnia has historically been regarded as a secondary symptom, caused by the drug or substance itself.

Despite the heuristic appeal of these various subtypes, it is often difficult to discriminate among them in clinical practice. Many of the defining features of the so-called primary insomnia subtypes such as conditioned arousal, poor sleep hygiene practices, and underestimation of sleep time are ubiquitous among insomnia sufferers, per se, and are not specific to one subgroup. This is true whether the so-called primary insomnia subtypes are considered in isolation or if all of the primary

and secondary subtypes mentioned are considered. There is substantial symptom overlap both within the group of primary insomnias as well as among the primary and secondary insomnias. Furthermore, many individuals with insomnia have multiple medical and psychiatric comorbidities, making it difficult to assign causation to any single factor. As a result, discrimination among these subtypes has proven difficult given their current definitions and available methods for their ascertainment. Furthermore, it is not clear that insomnia is always the result of co-occurring medical, mental, or substance use disorders. Often insomnia may precede the onset of such conditions, and even when precipitated by such conditions, the insomnia may evolve and develop partial or total independence over time. In such circumstances, the term secondary insomnia seems inappropriate. Currently there is limited understanding of mechanistic pathways in chronic insomnia, so it is not possible to draw firm conclusions about the association or direction of causality between insomnia and such co-occurring conditions. Furthermore, other than the differing treatments required for distinctive comorbidities, efficacious treatments for insomnia generally are similar across the range of insomnia subtypes. Finally, research has provided very limited support for the reliability and validity of the various specific subtypes discussed.

International Classification of Sleep Disorders, 2nd Edition additionally delineates the separate pediatric diagnosis, *behavioral insomnia of childhood*, characterized by sleep difficulties resulting from inappropriate sleep associations or inadequate limit setting by parents or caretakers. Although perhaps more common in young children, inappropriate sleep associations can occur in older age groups. For example, adults with insomnia may report intolerance for quiet and dark settings and may not be able to fall asleep unless the television is on. Similarly, it is not clear that limit-setting issues are involved in the sleep difficulties of only young children. Such difficulties also can manifest during adolescence as a function of volitionally delaying bedtimes. Similarly, they may occur in older, cognitively impaired adults when their caretakers allow liberal daytime napping that in turn results in disruptive awakenings and night wandering. It is also clear that many of the features of sleep/wake dysfunction assigned to this childhood insomnia subtype overlap substantially with the global insomnia disorder. Given these considerations, a separate childhood insomnia diagnosis is of questionable merit.

In addition to these various subtypes, a distinctive subtype of *insomnia with objectively short sleep duration* has been recently described. This group is characterized by insomnia complaints, along with an objectively documented average sleep time less than six hours per night and elevated morbidity risk. Because evidence in support of this

insomnia is currently limited, it is premature to delineate a separate insomnia category for this presentation at this juncture.

Given all of these considerations, a more global and defensible approach has been chosen for the diagnosis of those with chronic insomnia complaints. Specifically, the single diagnosis of chronic insomnia disorder is provided for all patients who have persistent and frequent insomnia complaints whether they occur in the presence or absence of a potentially sleep-disruptive comorbid psychiatric illness, medical disorder, or pattern of substance use.

Demographics

The full clinical syndrome of chronic insomnia disorder occurs in about 10% of the population, but the prevalence of transient insomnia symptoms is much higher (30% to 35% of the population). Chronic insomnia disorder is more common in women, those with medical/psychiatric/substance disorders, and in people in lower socioeconomic strata. It may occur at any age but is more commonly diagnosed in older adults, most likely due to age-related deterioration in sleep continuity and increase in medical comorbidities and medication use that increase insomnia risk.

Insomnia associated with requirements of parental/caregiver presence at bedtime and/or during the night, along with insomnia due to limit-setting difficulties, are estimated to occur in 10% to 30% of children, depending on the exact definitions used. Certain subgroups of children, such as those suffering from chronic illnesses or neurodevelopmental disorders, have a somewhat higher prevalence of insomnia symptoms. Because children are not expected to sleep through the night with regularity until they are three to six months of age, six months is a reasonable age to first consider a diagnosis of chronic insomnia disorder, unless the sleeplessness is very marked at an earlier age. Furthermore, sleep-onset associations and limit-setting problems are strongly associated with caregivers' behaviors, bedtime interactions, and culture. Thus, the interpretation of the nighttime awakenings and demands for parental contact should be considered in the context of the family and culture. Identification of sleep problems in children and adolescents are often based on specific cultural definitions. Studies on adolescents indicate prevalence rates of 3% to 12%, depending on the diagnostic criteria utilized, with higher frequency in girls than boys after puberty.

Predisposing and Precipitating Factors

Individuals who have difficulty sleeping during stressful times or who report being habitual light sleepers appear to have elevated propensity to develop chronic insomnia.

Prior transient episodes of poor sleep elevate the risk for subsequent development of a chronic insomnia disorder. Job-related stress and factors such as death of a loved one, divorce, a marked change in work schedule, job loss, and other major life changes are often precipitating circumstances for chronic insomnia disorder. Personality factors that produce anxious overconcern about health, general well-being, or daytime functioning may serve as predisposing characteristics because individuals with chronic insomnia disorder often display excessive preoccupation with daytime consequences of insomnia, and they devote particular effort to what they presume are sleep-promoting practices. A psychological style characterized by the repression and internalization of disturbing affect is characteristic of those with chronic insomnia disorder and also may represent a predisposing trait. Parents who have unrealistic sleep expectations for their children may predispose them to insomnia by putting them in bed too early or assigning them too much time in bed each night.

Comorbid psychiatric conditions, particularly mood and anxiety disorders, are associated with increased risk for chronic insomnia disorder. Likewise, comorbid restless legs syndrome or medical disorders such as GERD or those conditions that result in chronic pain, breathing difficulties, or immobility also are associated with increased risk for chronic insomnia disorder. A pattern of alcohol dependence/abuse as well as the excessive use of caffeine or other stimulants may raise risk for chronic insomnia disorder. Insomnia in children is often associated with difficult temperament, as well as other comorbid medical and psychiatric conditions. Unstable home situations, safety concerns and domestic abuse are likewise significant risk factors in both children and adults. Caregiver and relationship factors are also important to consider. Furthermore, parents of children with a current or past history of medical problems may have difficulty setting limits, whether because of guilt, a sense that the child is "vulnerable," or concerns about doing psychological harm. Environmental factors such as the child sharing a room with a parent or with other siblings, the presence of extended family or others in the home, and cramped living accommodations may contribute to negative sleep-onset associations or poor limit setting.

Familial Patterns

The familial pattern of insomnia is not well documented. Nonetheless, the prevalence of insomnia is higher among monozygotic twins relative to dizygotic twins; it is also higher in first-degree relatives than in the general population. The association is stronger with mothers and daughters. The extent to which familial aggregation represents shared genetic predisposition, shared environment, learned behavior (e.g., by observations of parental behavior), or a by-product of psychopathology remains undetermined.

Onset, Course, and Complications

Onset may be insidious or acute. In the former case, individuals often report symptoms of insomnia in early life or young adulthood. Onset of insomnia is often associated with major life events (e.g., separation, death of a loved one), minor daily stressors, or changes in sleep schedule.

The course of insomnia can be situational, recurrent, or persistent. The specific type of sleep complaint may also change over time. Individuals who complain of difficulty falling asleep at one time may later complain of difficulty maintaining sleep, and vice versa. Although short-term insomnia often remits when the precipitating event subsides or the individual adapts to it, sleep difficulties may also persist over time even after the initial triggering factor has disappeared. When left untreated, insomnia may persist and gradually lead to a vicious cycle of poor sleep, daytime impairments, apprehension of insomnia, and further sleep disturbances. Among predisposed individuals, insomnia can also follow an intermittent course, with recurrent episodes of sleep difficulties associated with stressful life events. Even in persistent insomnia, there is extensive night-to-night variability, with an occasional good night's sleep intertwined with several poor night's sleep. Approximately 70% of individuals with insomnia at a given time continue reporting insomnia a year later, and 50% still have insomnia three years later. Complications of persistent insomnia include increased risks for depression, hypertension, work disability, and prolonged use of prescription or over-the-counter sleep aids.

Among children, chronic insomnia disorder may have its onset at any time during late infancy through the childhood years. The course of chronic insomnia disorder in young children varies and depends on the reasons for the sleeplessness. When limit-setting factors and negative sleep associations resolve, sleep often improves. With age, independence and privacy become more important, and sleep difficulties may decrease. Complications may result from the consequent sleep loss and include irritability and decreased attention and school performance. Increased family tensions and caregiver sleep loss may also result. Some who develop insomnia during childhood may continue to suffer from chronic insomnia disorder into adulthood.

Developmental Issues

Developmental issues during childhood, such as separation anxiety and age/developmental milestones, may predispose a child to developing sleep problems. For example, limit-setting issues are often more common after the child is old enough to climb out of the crib or is moved into a bed, has increased verbal skills, and desires greater independence. Because children are not expected to sleep through the night with regularity until

they are three to six months of age, six months is a reasonable age to first consider a diagnosis of insomnia disorder, unless the sleeplessness is very marked at an earlier age. However, when sleep difficulties are persistent and pronounced in infants, underlying medical causes should be considered (e.g., sleep disordered breathing, GERD, pain).

The specific symptoms of chronic insomnia disorder, as well as precipitating and perpetuating factors, may vary across the adult age range. These changes may in part reflect developmental changes across adulthood, such as the phase delay of endogenous circadian rhythms in adolescence and young adulthood, and the phase advance and increased number of awakenings often seen even among healthy older adults. Epidemiological studies confirm that sleep onset difficulties and nonrestorative sleep are most common among young adults with chronic insomnia disorder, whereas sleep maintenance insomnia and early morning awakening are more common in middle-aged and older adults. Objective daytime sleepiness is uncommon in younger adults with insomnia, but more common in older adults. However, older adults may have less sleep dissatisfaction than their younger counterparts, despite objectively worse sleep continuity. Precipitating factors for chronic insomnia disorder may also change across the adult age range, with medical and medication factors assuming a larger role in older adults. Likewise, perpetuating factors may vary with the life circumstances of adults of different ages. One common example is the option of older adults to spend large amounts of time in bed after retirement, which may exacerbate the effects of age on sleep continuity. Finally, medical disorders and symptoms (e.g., pain, dyspnea, and impaired mobility) and medications often play a larger role in the insomnia of older adults in comparison with younger adults. Hypnotic medications are disproportionately prescribed to older adults, often with limited benefit and the potential for rebound and withdrawal insomnia.

Pathology and Pathophysiology

Studies of the pathophysiology of chronic insomnia disorder have focused on one or more dimensions of physiological hyperarousal during sleep and wakefulness. These studies contrast groups of insomnia sufferers, typically those without significant comorbidities, with healthy controls using a variety of physiological measures. Many of these studies are characterized by small sample sizes and lack of replication. Collectively these studies suggest increased physiological arousal among individuals with insomnia, characterized by measures such as increased heart rate, altered heart rate variability, increased whole-body metabolic rate, elevated cortisol, adrenocorticotropic hormone, and CRF levels (particularly near sleep onset), increased body temperature and increased high-frequency electroencephalographic (EEG) activity during nonrapid eye movement (NREM) sleep. These studies imply

heightened activity of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis across sleep and wakefulness that is thought to perpetuate sleep/wake dysfunction. Some evidence also suggests that physiological dysregulation may be more evident in certain subgroups of individuals with insomnia (e.g., those with extreme subjective-objective sleep discrepancies or those with insomnia and short objective sleep duration). There is also some evidence that these findings may not generalize to insomnia comorbid with mental disorders, which may have different pathophysiological findings.

No discrete structural brain pathology can be identified in most individuals with insomnia. Patients with insomnia comorbid with neurological disorders such as stroke, brain trauma, and multiple sclerosis may have identifiable brain lesions, but insomnia is rarely their sole neurological symptom. Recent studies have provided conflicting evidence regarding the finding of reduced hippocampal or anterior cingulate volume, with most studies reporting negative findings.

Objective Findings

Although polysomnography is not indicated in the routine evaluation of insomnia, it may be useful to rule out other sleep disorders (e.g., sleep-disordered breathing) among some patients who appear to meet criteria for chronic insomnia disorder. In the absence of other sleep disorders, results of polysomnographic sleep monitoring of patients with chronic insomnia disorder may show increased sleep latency and/or increased wake time after sleep onset coupled with reduced sleep efficiency in comparison with age-appropriate norms. Sleep onset latency or wake time after sleep onset often exceeds 30 minutes, although one-hour to two-hour periods of wakefulness in bed are not uncommon. A subset of patients shows reduced sleep duration of less than six hours per night. Some patients show altered sleep architecture with an increase in stage N1 sleep and a decrease in slow wave sleep. Patients with a pronounced conditioned sleep difficulty in the home environment may show a reverse first-night effect in the sleep laboratory (i.e., better sleep on the first vs. the second recording night). However, some patients show normal sleep times and an absence of sleep onset or sleep maintenance difficulties on standard polysomnographic (PSG) measures. Some insomnia patients have alterations in power density measures of the sleep EEG when compared with individuals without sleep complaints. Specifically, these patients often show relatively greater power in the high frequency (beta and gamma ranges) bandwidths. Some reports have shown that elevated high-frequency power is characteristic of insomnia patients with marked subjective-objective discrepancies in sleep measures, compared to insomnia patients with more obvious objective sleep disturbances or individuals without sleep complaints.

Serial monitoring with PSG or actigraphy typically shows marked night-to-night variability in all sleep measures as well as in recorded bed and rising times. This variability is typically greater than that of comparison groups of good sleepers.

Many patients with insomnia underestimate the actual sleep time shown by polysomnography, and some may provide sleep estimates that fall far short of actual PSG-recorded sleep time. This latter group has previously been categorized as having subjective insomnia, sleep state misperception, or paradoxical insomnia. In general, patients with insomnia tend to underestimate sleep duration and overestimate sleep latency and awakenings, whereas good sleepers tend to overestimate sleep duration and underestimate sleep latency and awakenings relative to PSG. This subjective-objective mismatch may be related to physiological hyperarousal, and may be one of the core features of insomnia.

Results of the Multiple Sleep Latency Test (MSLT) usually show normal daytime alertness. In several studies, patients with insomnia have longer mean MSLT values than control subjects, suggesting hyperalertness or hyperarousal. A minority of insomnia patients, particularly older adults with insomnia, have reduced mean MSLT values indicating increased sleepiness. Such a finding should prompt consideration of other concurrent sleep disorders such as obstructive sleep apnea.

Young children typically show essentially normal sleep during PSG monitoring when the caregiver is present and appropriate limits are set in the laboratory.

Although PSG and MSLT testing usually are not helpful in the establishment of an insomnia disorder diagnosis, there are circumstances that may warrant such testing with selected patients. PSG should be considered when there are reported symptoms or bed partner observations of sleep disordered breathing or periodic limb movements during sleep. Patients who present insomnia symptoms accompanied by excessive daytime sleepiness may warrant PSG and MSLT testing, particularly if narcolepsy is suspected. Patients who show acceptable adherence to trials of well-established insomnia therapies but fail to show adequate treatment response may benefit by PSG to rule out a comorbid sleep disorder.

Finally, a small number of functional imaging studies have been conducted during sleep and wakefulness in insomnia and control groups. These studies suggest regionally specific increases of relative glucose metabolism in insomnia compared to controls. Specifically, these studies show smaller wake to NREM decreases of relative glucose metabolism in sleep/wake-regulating regions including thalamus, upper brainstem,

anterior cingulate, and limbic cortex in insomnia patients. Self-reported and objective sleep disruptions are related to increased relative metabolism in these regions. These findings are similar to regional activation patterns during sleep in an animal model of stress-induced insomnia. Other studies using nuclear magnetic resonance spectroscopy have identified reduced gamma-aminobutyric acid (GABA) signaling in sleep-regulating regions in insomnia that correlate with objective measure of sleep continuity. Studies examining task-related changes in blood flow using blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI) paradigms have shown reduced activation relative to baseline levels in individuals with insomnia when compared to normal sleeping controls. Task-related activation changes in the direction of "normalization" following cognitive behavioral treatment.

Differential Diagnosis

A chronic insomnia disorder that presents as difficulty initiating sleep should be differentiated from *delayed sleep-wake phase disorder*. In the latter condition, sleep initiation is consistently later than desired because the individual's endogenous circadian rhythm is delayed relative to the desired sleep schedule. Sleep-onset difficulties persist, and sleep time is reduced whenever the individual chooses bedtimes and rising times that are too early and out of phase with the endogenous circadian rhythm. However, patients with delayed sleep-wake phase disorder are able to fall asleep with less difficulty, and sleep a normal amount of time, when sleeping in phase with their delayed endogenous rhythm by selecting late bed and rising times. By comparison, those with a chronic insomnia disorder often feel sleepy at the desired bedtime but are unable to sleep regardless of the timing of their bed and rise times. Furthermore, sleep problems tend to be more variable on a night-to-night basis in insomnia disorder. Given the prevalence of delayed sleep-wake phase disorder in teenagers and young adults, it is particularly important to consider the possibility of this alternate or comorbid diagnosis when evaluating individuals from these age groups presenting with sleep onset insomnia complaints.

A chronic insomnia disorder that presents as a difficulty maintaining sleep with premature morning rise times also should be differentiated from *advanced sleep-wake phase disorder*. The latter tends to be more common in older adults than it is in younger adults and children. Among those with an advanced sleep phase pattern, sleep initiation is consistently earlier than desired because the individual's endogenous circadian rhythm is advanced relative to the desired sleep schedule. However, total sleep time is adequate when the individual chooses early bed and rise times that coincide with the advanced endogenous circadian rhythm. In contrast, those with chronic insomnia disorder may display sleep maintenance difficulties and early morning rise time regardless of the sleep schedule they select.

There can be some overlap between chronic insomnia disorder and both *delayed and advanced sleep-wake phase disorders*. Patients with a delayed sleep pattern may become chronically frustrated or anxious about their inability to initiate sleep at their desired times, and this frustration or anxiety may continue to disrupt sleep and delay sleep onset well beyond the sleep onset time promoted by the endogenous rhythm. Early morning awakenings may similarly have arousing sleep disruptive effects in the setting of an advanced sleep phase. In such circumstances both a circadian rhythm sleep-wake disorder diagnosis and a chronic insomnia disorder diagnosis may apply and should be assigned.

Chronic insomnia disorder should also be discriminated from situational sleep difficulties arising from *sleep-disruptive environmental circumstances*. A variety of environmental factors including excessive noise or light and extreme temperatures will disrupt the sleep of most individuals. Also, sleeping in an area where there is imminent threat or danger to one's safety can also be disruptive to sleep. Bed partners who snore loudly, move excessively during sleep, or have parasomnias may also disrupt one's sleep. When an individual reports environmental circumstances that would be regarded as disruptive to the sleep of most individuals, a chronic insomnia disorder should not be assigned. Chronic insomnia disorder applies only when the individual reports sleep difficulty in the context of sleep-conducive environment circumstances or when the insomnia symptoms show some independence from the environmental factors. When environmental circumstances are a primary cause of sleep disturbance and associated consequences, a diagnosis of *other sleep disorder* may be considered.

Chronic insomnia disorder should also be differentiated from patterns of *chronic volitional sleep restriction (insufficient sleep syndrome)*. Some individuals show excessive daytime sleepiness, fatigue, and reduced sleep at night as a result of electing overly demanding daytime schedules or by volitionally delaying sleep in order to engage in desired recreational or social activities. However, when allowing themselves sufficient time to sleep, they are able to initiate and maintain sleep easily and for a normal duration. Those with chronic insomnia disorder tend to have excessive wake time and reduced sleep time despite routinely allotting sufficient time to sleep. Moreover, chronic insomnia disorder is not typically associated with excessive daytime sleepiness and unintentional daytime sleep episodes, which are often observed in those with patterns of volitional sleep restriction.

Insomnia symptoms may occur comorbid with another sleep disorder, such as *sleep apnea* or *restless legs syndrome*. A chronic insomnia disorder diagnosis would apply

only when: (1) the insomnia symptoms show some independence in their onset or variation over time from the other symptoms of the co-occurring sleep disorder; or (2) when insomnia symptoms persist despite adequate treatment reflected by marked symptom improvement in the coincident sleep disorder. A chronic insomnia disorder diagnosis would not apply when effective treatment of the coincident sleep disorder resolves the insomnia symptoms.

Among children, sleep difficulties may be present when the child has to sleep alone in a separate room, but absent when the child is allowed to sleep with parents or when a parent is present in the child's bedroom. An absence of sleep difficulties under the latter circumstances does not indicate the insomnia is resolved. Only when the child is able to sleep consistently independently is there no longer an insomnia problem. In some children, the persistence of sleep difficulties in the absence of parents may reflect underlying conditions such as separation anxiety or an anxiety disorder.

In young children, sleep difficulties can be the result of medical issues, including gastroesophageal reflux, as well as developmental milestones, such as motoric, language, and cognitive development. Children, adolescents, and adults may develop a chronic insomnia disorder *comorbid with a medical or psychiatric disorder*. Insomnia symptoms may arise as a result of either another sleep disorder, a medical condition, or a psychiatric disorder that has sleep-disruptive effects. A chronic insomnia disorder diagnosis would apply when: (1) the insomnia symptoms show some independence in their onset or variation over time from the other symptoms of the co-occurring sleep, medical ,or psychiatric disorder; or (2) when insomnia symptoms persist despite adequate treatment reflected by marked symptom improvement in the coincident sleep, medical, or psychiatric disorder. Because insomnia symptoms often develop some independence over time, a chronic insomnia disorder diagnosis usually will be warranted when those symptoms are persistent in association with a chronic medical or psychiatric disorder. A chronic insomnia disorder diagnosis would not apply when effective treatment of the coincident sleep, medical, or psychiatric disorder resolves the insomnia symptoms.

Unresolved Issues and Further Directions

Much remains to be learned about the underlying pathophysiological pathways leading to insomnia and whether insomnia should be classified as a unitary disorder or subdivided into several subtypes. Clearly, these issues are closely linked. Further studies that clarify the pathophysiological pathways leading to insomnia ultimately will reveal whether those meeting current criteria for chronic insomnia disorder suffer from a single disease or multiple separate diseases with similar outward presentations.

A related unresolved issue is whether the current global classification promotes a generic approach to insomnia therapy that ultimately fails to benefit some insomnia subgroups. Perhaps this global classification scheme will overlook distinctive insomnia subtypes with specific treatment needs that vary from the generic treatments typically provided.

Previous editions of the International Classification of Sleep Disorders allowed for the assignment of an insomnia diagnosis to patients who present exclusively with complaints of nonrestorative sleep; that is, patients who complain only of sleep that is poor in quality or unrefreshing, in the absence of sleep-onset or sleep maintenance complaints, could qualify for an insomnia diagnosis in previous versions of this nosology. The current version of this nosology excludes such patients from the insomnia diagnostic categories. This decision was based on several considerations. Most insomnia patients present with complaints of sleep initiation or maintenance difficulties. Although a small subset of patients present with isolated complaints of nonrestorative sleep, this complaint more commonly arises in association with other symptoms of insomnia, or in conjunction with sleep disordered breathing, other sleep disorders or certain chronic medical conditions (e.g., fibromyalgia or chronic fatigue syndrome). Although various epidemiological studies have identified subgroups who are presumed to have an insomnia disorder and present solely with a complaint that their sleep is nonrestorative or unrefreshing, such studies typically lack polysomnography that would be needed to rule out other occult sleep disorders as a cause. Finally, nonrestorative sleep remains a poorly defined construct that may reflect not only a type of sleep disturbance, but also the daytime consequences of poor sleep such as fatigue and anergia. This construct would benefit from further definitional efforts and research to explore its clinical significance in the context of insomnia. Given these considerations, the isolated complaint of nonrestorative sleep was not retained as part of the diagnostic definition of the insomnia disorders delineated in this manual.

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Short-Term Insomnia Disorder

ICD-9-CM code: 307.41 ICD-10-CM code: F51.02

Alternate Names

Acute insomnia, adjustment insomnia.

Diagnostic Criteria

Criteria A-E must be met

A. The patient reports, or the patient's parent or caregiver observes, one or more of the following:[1]
   1. Difficulty initiating sleep.
   2. Difficulty maintaining sleep.
   3. Waking up earlier than desired.
   4. Resistance to going to bed on appropriate schedule.
   5. Difficulty sleeping without parent or caregiver intervention.

B. The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty:
   1. Fatigue/malaise.
   2. Attention, concentration, or memory impairment.
   3. Impaired social, family, vocational, or academic performance.
   4. Mood disturbance/irritability.
   5. Daytime sleepiness.
   6. Behavioral problems (e.g., hyperactivity, impulsivity, aggression).
   7. Reduced motivation/energy/initiative.
   8. Proneness for errors/accidents.
   9. Concerns about or dissatisfaction with sleep.

C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e., enough time is allotted for sleep) or inadequate circumstances (i.e., the environment is safe, dark, quiet, and comfortable) for sleep.
D. The sleep disturbance and associated daytime symptoms have been present for less than three months.
E. The sleep/wake difficulty is not better explained by another sleep disorder.

Notes

1. Reports of difficulties initiating sleep, difficulties maintaining sleep, or waking up too early can be seen in all age groups. Resistance going to bed on an appropriate schedule and difficulty sleeping without parent or caregiver intervention is seen most commonly in children and older adults who require the supervision of a caretaker due to a significant level of functional impairment (e.g., those with dementia).
2. Patients with short-term insomnia disorder may complain of sleep/wake difficulties fewer than three times per week on average, yet have clinically significant concerns about their symptoms and warrant clinical attention.
3. Many conditions such as grief, acute pain, or other acute stressors are quite often associated with poor sleep. When such conditions are the sole cause of the sleep difficulty, a separate insomnia diagnosis may not apply. The primary factor in determining application of a short-term or adjustment insomnia diagnosis is the extent to which the sleep disturbance becomes a significant focus for the individual and/or warrants independent clinical attention.

Essential Features

The essential feature of short-term insomnia disorder is a short-term difficulty initiating or maintaining sleep that results in general sleep dissatisfaction. The sleep complaint is accompanied by daytime distress about poor sleep or impairment in family, social, occupational, academic, or other important areas of functioning. Furthermore, the sleep disturbance and associated daytime symptoms occur despite having adequate time and circumstances each night to obtain necessary sleep. Short-term insomnia disorder can occur in isolation or comorbid with a mental disorder, medical condition, or substance use. In many cases of short-term insomnia lasting less than three months, there is an identifiable cause that serves as the precipitant. In other cases, insomnia occurs episodically, often coincident to daytime stressors that account for the insomnia.

As is the case for chronic insomnia disorder, sleep complaints that compose short-term insomnia disorder may include difficulties initiating sleep or difficulties maintaining sleep. The latter complaint may include waking up during the night with difficulty returning to sleep or having a final awakening occurring too early, well before the desired rising time. Short-term insomnia disorder may be characterized solely by sleep onset or sleep maintenance complaints or, more commonly, by both types of complaints occurring together. Individuals' sleep complaints may vary such that sleep onset difficulties are apparent on some nights, whereas sleep maintenance difficulties are present on other nights. Complaints about poor-quality, unrefreshing, or nonrestorative sleep may accompany sleep onset and sleep maintenance complaints, but do not meet the definition of this condition when they occur in isolation.

Associated Features

Sleep disturbance is the primary feature of short-term insomnia disorder, but it is commonly accompanied by waking symptoms similar to those seen in chronic insomnia disorder. Specific symptoms such as fatigue, impaired attention and concentration, poor memory, irritability, and distress about poor sleep are common. When the insomnia arises in reaction to a stressful life event, such as the loss of a loved one, major illness, or divorce, the associated features may include anxiety, worry, ruminative thoughts, sadness, or depression in relation to the specific stressor. If the individual uses alcohol, illicit drugs, or medications for self-treatment, additional symptoms related to these substances may be seen.

Clinical and Pathophysiological Subtypes

None.

Demographics

Short-term insomnia disorder can occur at any age. However, a short-term form of insomnia may be difficult to establish in infants because it is often difficult to link stressors to sleep disturbances in this age group. The exact prevalence of short-term insomnia disorder is unknown. The one-year prevalence of short-term insomnia disorder among adults appears to be in the range of 15% to 20%. Like chronic insomnia disorder, short-term insomnia disorder is more prevalent in women than in men, and in older age groups.

Predisposing and Precipitating Factors

Affected individuals may note a lifelong tendency toward light sleep or difficulty sleeping during times of stress. A previous history of anxiety or depressive

symptoms and disorders also may predispose an individual to develop a short-term insomnia disorder. In children, having a parent with insomnia or living in a household lacking parental reinforcement of a consistent sleep/wake schedule may be predisposing factors.

An acute, identifiable event or stressor usually precipitates this form of insomnia. Common precipitating events include changes or disputes in interpersonal relationships, occupational stress, personal losses, bereavement, diagnosis or onset of a new medical condition, visiting or moving to a new location, or physical changes to the usual sleep environment or schedule. Changes or stresses with a positive emotional tone also may serve as precipitating events. In children or dependent adults, such insomnia can arise when the caretaker makes abrupt changes in the child's or adult's sleep routines or schedule. As is the case for chronic insomnia disorder, environmental factors such as the child sharing a room with a parent or with other siblings, the presence of extended family or others in the home, and cramped living accommodations may contribute to negative sleep-onset associations or poor limit setting in children.

Familial Patterns

Familial patterns are less well documented for cases of short-term insomnia disorder than they are for individuals meeting criteria for chronic insomnia disorder. Nonetheless, the familial aggregation found for chronic insomnia disorders is expected to also occur among individuals with more transient forms of insomnia. Data support a greater genetic diathesis to psychophysiologic arousal among certain individuals in response to stressors. This may, in turn, suggest a constitutional predisposition to short-term or adjustment insomnia in such individuals.

Onset, Course, and Complications

Many individuals who develop short-term insomnia disorder experience remission of their insomnia symptoms over time. This occurs as distress over the precipitating event diminishes over time or in response to withdrawal of the stressor. However, a portion of those who initially experience short-term insomnia may develop a more chronic form of insomnia and subsequently meet criteria for chronic insomnia disorder. These individuals will then have the course and complications described for chronic insomnia disorder.

Developmental Issues

As is the case for chronic insomnia disorder, short-term insomnia disorder would not be considered until after a child reaches at least six months of age.

The propensity to experience sleep disturbance in response to stress may dispose young and older individuals toward acute forms of insomnia. As is the case for chronic insomnia disorder, sleep onset difficulties are most common among young adults with short-term insomnia, whereas sleep maintenance complaints and early morning awakening are more common in middle-aged and older adults. Objective daytime sleepiness is uncommon in younger adults with short-term insomnia disorder, but is more common in older adults. Balancing job and family stressors may contribute to intermittent short-term insomnia problems in younger and middle-aged adults. In contrast, older, retired adults may have short-term insomnia disorder related to exacerbations in comorbid chronic medical conditions or due to loss of loved ones that commonly occurs with advancing age.

Pathology and Pathophysiology

Research on the pathology and pathophysiology of short-term variants of insomnia disorder is generally lacking because the majority of studies addressing this issue have focused on samples with chronic insomnia disorders.

Differential Diagnosis

Short-term insomnia disorder shares many features with chronic insomnia disorder. The primary difference between the two conditions is that short-term insomnia disorder does not meet the duration and frequency criteria required for the chronic insomnia disorder diagnosis. Short-term insomnia disorder also should be distinguished from *circadian rhythm sleep-wake disorders* resulting from rotating *shift work* or *jet lag*. In the latter case, the sleep disturbance arises from a sleep-wake schedule alteration that results in a mismatch between the endogenous circadian rhythm and the sleep-wake schedule chosen—for example, having to sleep in the daytime rather than during the nighttime. In the case of short-term insomnia disorder, no such mismatch exists; yet, the individual demonstrates sleep onset or maintenance difficulties nonetheless.

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Other Insomnia Disorder

ICD-9-CM code: 307.49 ICD-10-CM code: F51.09

This diagnosis is reserved for individuals who complain of difficulty initiating and maintaining sleep and yet do not meet the full criteria for either chronic insomnia disorder or short-term insomnia disorder. In some cases, this diagnosis may be assigned on a provisional basis when more information is needed to establish a diagnosis of chronic insomnia disorder or short-term insomnia disorder. It is expected that this diagnosis will be used sparingly, given its nonspecific nature.

Isolated Symptoms and Normal Variants

Excessive Time in Bed

Some individuals may present with isolated insomnia symptoms such as prolonged sleep latencies or long periods of wakefulness during the night, yet not complain of insomnia nor show daytime impairments. In children, this pattern may emerge when parents or caregivers have unrealistic expectations for the child's sleep needs and routinely allot too much time for the child to be in bed each night. In adults, this pattern is perhaps most common in noncomplaining groups who routinely allot significantly more time in bed than needed for sleep. For example, some individuals who are retired from work or not currently employed may routinely spend excessive time in bed each night and are not bothered by the expanded periods of wakefulness they routinely experience. At present, epidemiological and laboratory studies are unable to ascertain whether adverse health outcomes are more strongly associated with perceived sleep difficulties/dissatisfaction or with particular objective indices of sleep duration, sleep latency, and sleep continuity.

Short Sleeper

Some individuals routinely obtain less than six hours of sleep per night on average yet have no sleep/wake complaints. Such individuals are considered to be normal short sleepers if they have no complaints of sleep difficulties and show no obvious daytime dysfunction. Among these individuals, the observed relatively low average sleep time does not result from chronic volitional sleep restriction, as in the case of insufficient sleep syndrome, but rather indicates a constitutional disposition for reduced sleep requirement. The clinical significance of chronic short sleep duration, and the identification of possible subtypes, remain open questions. Various studies have linked short sleep duration with metabolic, cardiovascular, and other forms of medical morbidity. However, these studies are typically unable to distinguish between individuals who have short sleep in the context of insomnia or another sleep disorder, those who are voluntarily restricting their sleep, and those who may have naturally short sleep. Short sleep resulting from different causes may have different pathophysiological significance. At present, those who demonstrate less than six hours of sleep per night should not be assigned an insomnia diagnosis unless they also meet the criteria for one of the insomnia disorder subtypes described herein.

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Sleep Related Breathing Disorders

The sleep related breathing disorders are characterized by abnormalities of respiration during sleep. In some of these disorders, respiration is also abnormal during wakefulness. The disorders are grouped into obstructive sleep apnea (OSA) disorders, central sleep apnea disorders, sleep related hypoventilation disorders, and sleep related hypoxemia disorder. However, many patients will meet diagnostic criteria for more than one of these groups. In particular, many patients have a combination of obstructive and central sleep apnea. Although a diagnosis is often based on which disorder

predominates, this may vary from night to night as well as over time in individual patients. There is also overlap in pathophysiology, as some central apneas are associated with a closed upper airway and many obstructive apneas begin during a time of falling ventilatory drive.

In the sections that follow, individual respiratory events (e.g., apneas, hypopneas, and hypoventilation) are not defined; rather, reference is made to the most recent version of the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events for these definitions. The AASM Manual for the Scoring of Sleep and Associated Events includes different scoring rules for adult and pediatric individuals, definitions of obstructive and central apneas and hypopneas, and rules for scoring Cheyne-Stokes breathing and hypoventilation.

The OSA disorders are separated into adult and pediatric categories, as the presentation, diagnostic criteria, course, and complications differ significantly. These disorders are characterized by upper airway narrowing or closure during sleep while respiratory effort continues (at least during some portion of the event). The use of out-of-center sleep testing (OCST) with limited channels (electroencephalogram [EEG] is not usually recorded) is now included in the diagnostic criteria for adult OSA.

The central sleep apnea syndromes are characterized by reduction or cessation of airflow due to absent or reduced respiratory effort. Central apnea or hypopnea may occur in a cyclical or intermittent fashion. Patients with central sleep apnea of various etiologies may also exhibit OSA.

In primary central sleep apnea, the cause of the disorder is unknown (idiopathic). The arterial partial pressure of carbon dioxide ($PaCO_2$) during wake in these patients is normal or low. Patients do not meet diagnostic criteria for other central sleep apnea disorders. In central sleep apnea with Cheyne-Stokes breathing, there is a cyclical pattern of crescendo-decrescendo respiration separated by central apneas or central hypopneas. Most patients with this disorder have congestive heart failure (reduced or preserved ejection fraction), although, less commonly, others exhibit this breathing pattern following stroke or in association with other neurological disorders. In high-altitude periodic breathing, the disorder is associated with acute ascent to high altitude. Symptoms must be present to establish the diagnosis of high-altitude periodic breathing, as this breathing pattern is an expected finding after ascent to altitude. Central sleep apnea due to medical or neurological condition (not Cheyne-Stokes) is usually due to a structural lesion in the central nervous system. These disorders should be excluded before a diagnosis of primary central sleep apnea is made. In central sleep apnea due to drug

or substance, the patient demonstrates central apneas secondary to the effects of potent opioids or other respiratory depressants on respiratory control centers.

Treatment-emergent central sleep apnea is a new addition to the International Classification of Sleep Disorders. In this disorder, the patient exhibits predominantly obstructive events during diagnostic sleep testing (e.g., obstructive or mixed apneas and obstructive hypopneas), but central apneas or central hypopneas emerge or persist on positive airway pressure treatment without a backup rate and are the predominant residual breathing abnormality (i.e., obstructive events have resolved). A diagnosis of treatment-emergent central sleep apnea is made when the central sleep apnea component is not better explained by another diagnosis (i.e., another central sleep apnea disorder).

Sleep related hypoventilation disorders are characterized by an abnormal increase in the arterial PCO_2 ($PaCO_2$) during sleep. Adult and pediatric hypoventilation disorders are defined by different criteria. For adults, an increase in the arterial PCO_2 (or surrogate) to greater than 55 mm Hg for at least 10 minutes or an increase $\geq$ 10 mm Hg above the awake value to a value of 50 mm Hg or greater for at least 10 minutes is required. In pediatric patients, the $PaCO_2$ (or surrogate) must be greater than 50 mm Hg for greater than 25% of total sleep time.

In this edition of the International Classification of Sleep Disorders, there are a number of changes in the classification of sleep related hypoventilation disorders. The obesity hypoventilation syndrome is listed as a separate disorder given that it is both prevalent and has distinct clinical characteristics. In contrast to other sleep related hypoventilation disorders, a diagnosis of obesity hypoventilation syndrome requires documentation of awake (daytime) hypoventilation ($PaCO_2$ > 45 mm Hg). For the other disorders in this category, awake hypoventilation may or may not be present.

In the previous version of the International Classification of Sleep Disorders, a group of disorders were listed under the category of sleep related hypoventilation/hypoxemia disorders. In the International Classification of Sleep Disorders, 3rd Edition, disorders manifesting hypoventilation are separated from disorders in which only a finding of hypoxemia (arterial oxygen desaturation) during sleep is documented. Demonstrating sleep related hypoventilation rather than simply hypoxemia has important diagnostic and treatment consequences. Sleep related hypoxemia disorders are characterized by sustained periods of significantly reduced oxyhemoglobin saturation during sleep. This diagnostic category is used when sleep related hypoventilation is either not present or the status is unknown. Sleep related hypoxemia can occur due to hypoventilation, ventilation-perfusion mismatch, low partial pressure of oxygen, shunt, or a combination of

these factors. Many diverse etiologies can be associated with sleep related hypoxemia. There are no longer separate diagnostic categories for the various types of medical and neurological pathology that may contribute to hypoventilation or hypoxemia. In the International Classification of Sleep Disorders, 2nd Edition, these included lower airway obstruction, pulmonary parenchymal and vascular pathology, and neuromuscular and chest wall disorders. In the International Classification of Sleep Disorders, 3rd Edition, the specific pulmonary or neurological disorder should be diagnosed separately, in association with a diagnosis of sleep related hypoventilation due medical or neurological condition or sleep related hypoxemia.

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Obstructive Sleep Apnea Disorders

Obstructive Sleep Apnea, Adult

ICD-9-CM code: 327.23 ICD-10-CM code: G47.33

Alternate Names

OSA syndrome, sleep apnea, sleep apnea syndrome, obstructive apnea, sleep disordered breathing, obstructive sleep apnea hypopnea syndrome.

The term upper airway resistance syndrome (UARS) is subsumed under this diagnosis because the pathophysiology does not significantly differ from that of obstructive sleep apnea. Use of the term Pickwickian syndrome is discouraged because not only has it been applied to those with OSA, but also indiscriminately used to describe persons who are only obese and those with obesity hypoventilation syndrome.

Diagnostic Criteria

(A and B) or C satisfy the criteria

A. The presence of one or more of the following:
   1. The patient complains of sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms.
   2. The patient wakes with breath holding, gasping, or choking.
   3. The bed partner or other observer reports habitual snoring, breathing interruptions, or both during the patient's sleep.
   4. The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus.

B. Polysomnography (PSG) or OCST[1] demonstrates:
   1. Five or more predominantly obstructive respiratory events[2] (obstructive and mixed apneas, hypopneas, or respiratory effort related arousals [RERAs])[3] per hour of sleep during a PSG or per hour of monitoring (OCST).[1]

   OR

C. PSG or OCST[1] demonstrates:
   1. Fifteen or more predominantly obstructive respiratory events (apneas, hypopneas, or RERAs)[3] per hour of sleep during a PSG or per hour of monitoring (OCST).[1]

Notes

1. OCST commonly underestimates the number of obstructive respiratory events per hour as compared to PSG because actual sleep time, as determined primarily by EEG, is often not recorded. The term respiratory event index (REI) may be used to denote event frequency based on monitoring time rather than total sleep time.
2. Respiratory events defined according the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events.
3. RERAs and hypopnea events based on arousals from sleep cannot be scored using OCST because arousals by EEG criteria cannot be identified.

Essential Features

OSA is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstruction occurring during sleep. These events often result in reductions in blood oxygen saturation and are usually terminated by brief arousals from sleep. By definition, apneic and hypopneic events last a minimum of 10 seconds. Most events are 10 to 30 seconds in duration but occasionally persist for one minute or longer. Events can occur in any stage of sleep but more frequently occur in stages N1, N2, and R sleep than in stage N3 sleep. Events are usually longer and associated with more severe decreases in oxygen saturation when they occur in stage R sleep and when the individual is sleeping supine. Oxygen saturation usually returns to baseline values following resumption of normal breathing but may remain low if the apneic or hypopneic events are very frequent and prolonged, or if there is underlying pulmonary pathology. Snoring between apneas is typically reported by bed partners, as are witnessed episodes of gasping or choking and body movements that disrupt sleep. Most patients awaken in the morning feeling tired and unrefreshed regardless of the duration of their time in bed. Apneas, hypopneas, and snoring may be exacerbated following the ingestion of alcohol, use of sedating medications prior to sleep, or following an increase in body weight.

Excessive sleepiness is a major presenting complaint in many but not all cases. The sleepiness is most evident during relaxing or inactive situations. With extreme sleepiness, sleep may occur while actively conversing, eating, walking, or driving. In women, excessive sleepiness is a less prominent complaint. Additionally, reports of insomnia, poor sleep quality, and fatigue are common, particularly among women. Quality of life generally is adversely affected by unrefreshing sleep, sleepiness, and fatigue. Bed partners may also report sleep disruption and associated consequences. The frequency of apneas and hypopneas during sleep correlates poorly with daytime symptom severity

and impact on quality of life. In some cases, affected individuals will not endorse any symptoms or confirm any bed partner observations.

Associated Features

Systemic hypertension is a common finding in patients with OSA. There is substantial clinical and epidemiologic evidence implicating OSA as a significant risk factor for development of systemic hypertension independent of other conditions such as obesity and smoking. Additionally, OSA is frequently observed in patients with coronary artery disease, atrial fibrillation, and stroke, and it may be an independent risk factor for these conditions. OSA is also associated with type 2 diabetes, and there are accumulating data to suggest that it is a risk factor for the development of type 2 diabetes. Patients with severe disease may be at risk for developing pulmonary hypertension and cor pulmonale, although this is usually seen only in patients with daytime hypercapnia due to comorbid conditions such as morbid obesity or chronic obstructive pulmonary disease (COPD). When OSA coexists with dilated cardiomyopathy or ischemic heart disease, there may be worsening of the underlying heart disease and predisposition to congestive heart failure. Gastroesophageal reflux symptoms, nocturia, mood disturbance, and erectile dysfunction are sometimes reported in patients with OSA. The disorder can also be associated with the following motor parasomnias: OSA-induced arousals from non-rapid eye movement (NREM) sleep mimicking a primary disorder of arousal (confusional arousal, sleepwalking, or sleep terrors); OSA-induced arousals from REM sleep mimicking REM sleep behavior disorder; disorders of arousal from NREM associated with slow wave sleep rebound during initiation of nasal continuous positive airway pressure (CPAP) therapy of OSA; OSA-induced arousals linked with sleep related eating disorder; and OSA-induced nocturnal seizures or cerebral anoxic attacks with prominent motor activity.

Severity of OSA as determined by the frequency of apneas and hypopneas and/or degree of oxygen desaturation correlates poorly with symptomatic sleepiness. Different measures of sleepiness, including self-reported severity of sleepiness, commonly used indices such as the Epworth Sleepiness Scale, and objective measures such as the Multiple Sleep Latency Test (MSLT), are not strongly correlated and, thus, assessment of sleepiness can be difficult and relatively unreliable. In addition, patients may adapt to any level of sleepiness over time and fail to view it as a reportable problem. Bed partner-observed breathing pauses and disruptive snoring may not always be accompanied by patient complaints of sleepiness. Finally, it is important to note that sleepiness is a condition with a number of possible etiologies and a range of manifestations (see Differential Diagnosis).

Clinical and Pathophysiological Subtypes

Apneas and hypopneas are believed to have similar pathophysiology and consequences. Therefore, from a clinical perspective, there is little importance in distinguishing patients who have predominantly apnea from those who have predominantly hypopnea. Occasionally, patients may demonstrate only REM-related apneas or hypopneas, but there is no consensus to suggest that this is a distinct clinical or pathophysiological subtype.

Some patients have relatively few arterial oxygen desaturations but a significant number of respiratory events characterized by narrowing of the upper airway resulting in brief arousals from sleep. Depending on the definition of hypopnea employed, these events typically meet criteria for either hypopneas associated with arousal but no desaturation, or for RERAs. When initially described, this latter group was said to have UARS. Current data suggest that this condition represents simply a variant of OSA in which obstructive events result in arousal but minimal arterial oxygen desaturation. Patients with this condition commonly snore and report daytime sleepiness or fatigue. However, there are some reports of patients with frequent respiratory arousals in the absence of snoring. They tend to be less obese than individuals who have respiratory event-associated arterial oxygen saturation. The prevalence of this group of patients is unknown. When advanced technology is used to detect changes in airflow (as described in the AASM Manual for the Scoring of Sleep and Associated Events), most of these patients will be diagnosed as having OSA, as defined by the criteria listed above.

COPD and OSA frequently coexist, but there is no common pathophysiologic relationship. Nevertheless, individuals with both disorders have greater nocturnal oxygen desaturation and daytime hypercapnia for the same degree of bronchial airflow obstruction, and greater risk of developing pulmonary hypertension and right heart failure. The prevalence rate for having both conditions has been estimated to be 1%.

Demographics

OSA can occur in any age group. Estimates of prevalence are very dependent on how sleep related respiratory events are defined, as well as their frequency and other criteria used to define disease. Nevertheless, general population-based studies from a number of countries indicate that OSA associated with daytime sleepiness occurs in 3% to 7% of adult men and 2% to 5% of adult women. However, because many individuals with OSA do not endorse daytime sleepiness, the prevalence of the disease is likely much higher. A major study yielded prevalence rates as high as 24% in men and 9% in women using only an apnea-hypopnea index (AHI) criterion of $\geq$ 5/hour, although addition of a daytime sleepiness criterion reduced these estimates to 4% in males and 2% in females.

The prevalence of OSA increases with age, although it appears to plateau in the elderly. The ratio of OSA in men compared to women is approximately two to one. This disparity may decline in middle to older age as a result of a greater risk for OSA in women after menopause.

OSA occurs in all racial and ethnic groups. In younger and elderly groups, but not in middle-aged groups, OSA has been reported to be more prevalent in blacks than whites. The prevalence of OSA in Asian patients is comparable to that of whites, despite having a generally lower body mass index (BMI). Differences in craniofacial features that predispose Asians to developing OSA are the likely explanation. Data comparing OSA prevalence rates among Hispanics and Native Americans to other racial/ethnic groups are sparse, although it is clear that OSA occurs commonly in these groups.

Predisposing and Precipitating Factors

The major predisposing factor for OSA is excess body weight. It has been estimated that ~60% of moderate to severe OSA is attributable to obesity. The risk of OSA increases as the degree of additional weight increases, with an extremely high prevalence of OSA in people with morbid obesity. OSA patients with normal or below-normal body weight are more likely to have upper airway obstruction due to a localized structural abnormality such as a maxillomandibular malformation or adenotonsillar enlargement. Increasing neck circumference predicts higher AHIs; it is not, however, independent of BMI. Instability in ventilatory control appears to increase risk of OSA. Those patients with an exaggerated ventilatory response to a respiratory disturbance have a greater propensity for obstructive events. Menopause is a risk factor for this disorder in women, even after adjustment for age and BMI. However, use of hormone replacement therapy may be protective. There are conflicting data concerning smoking as a risk factor for OSA. Various abnormalities of the bony and soft tissue structures of the head and neck may predispose the individual to having OSA. These may be hereditary (e.g., mandibular size, mandibular position, palatal height) or acquired (e.g., enlarged adenoids and tonsils). Endocrine disorders such as acromegaly and hypothyroidism are risk factors for OSA. Adults and children with Down syndrome also have a high prevalence of OSA. OSA is common in patients with some neurologic disorders that affect peripheral muscles, such as myotonic dystrophy. OSA is likely made worse following alcohol consumption or use of sedating medications before sleep and by nocturnal nasal restriction or congestion due to abnormal morphology, rhinitis, or both.

Familial Patterns

OSA is a heritable condition as demonstrated by familial clustering of OSA patients. First-degree relatives of OSA patients are twice as likely to have OSA in comparison

to those not affected. Clustering of symptoms that are associated with OSA such as snoring, daytime sleepiness, and snorting or gasping also occurs. Heritability explains approximately one third of the variation in the AHI, with a substantial proportion of the heritability explained by obesity. Other inherited traits that might predispose an individual to developing OSA include craniofacial morphology and ventilatory control. Familial environmental factors such as physical activity and eating habits may play a role as well. Nevertheless, genetic studies to date have not identified a unique gene or genes responsible for OSA heritability.

Onset, Course, and Complications

As documented in longitudinal population studies, the severity of untreated OSA measured by the AHI tends to slowly progress over time. OSA becomes more severe in patients whose BMI increases, but may improve with weight reduction. However, the effect of weight gain on increasing OSA severity is greater than the impact of weight loss on decreasing OSA severity. Moreover, the consequences of weight change are more evident in men than women.

Substantial evidence implicates OSA as a risk factor for incident systemic hypertension, coronary artery disease, congestive heart failure, stroke, and premature mortality. Data suggest that these effects are more evident in men and middle-aged individuals. In addition, there is accumulating evidence to suggest that OSA is a risk factor for the development of type 2 diabetes mellitus independent of obesity. Various arrhythmias are commonly observed in association with OSA. Evidence suggests that OSA is particularly related to the onset and recurrence of atrial fibrillation.

OSA may increase the severity of depression. Because of daytime sleepiness, functional impairment occurs commonly as manifested by poor job performance, loss of employment, impaired family relationships, and reduction in overall quality of life. The risk of motor vehicle accidents is significantly increased among those with OSA.

Developmental Issues

OSA can occur in any age group, but in adults, prevalence accelerates between young adulthood and middle age, with a plateau reached after approximately age 65 years. Although OSA occurs in the elderly, it is commonly observed with few symptoms. In addition, some evidence suggests that risk of cardiovascular disease related to OSA may be less important in the elderly. This has raised the possibility that its presence in this age group represents a distinct clinical variant. Pediatric OSA is discussed in a separate section (below).

Pathology and Pathophysiology

The pathophysiology underlying upper airway narrowing during sleep is multifactorial. Patients with OSA commonly have reduced cross-sectional area of the upper airway lumen due to either excessive bulk of soft tissues (tongue, soft palate, and lateral pharyngeal walls) or craniofacial anatomy, or both. During inspiration, negative pressure is generated in the lumen of the upper airway, promoting closure. However, pharyngeal dilating muscles act to maintain patency. The activity of these muscles decreases with sleep onset, but is normally adequate to maintain an open airway. In persons with OSA, the activity of the pharyngeal dilating muscles becomes insufficient to prevent narrowing and/or closure of the upper airway. This state-dependent change is the major contributing factor leading to an obstructed upper airway. There is a further reduction in tone and phasic activity of pharyngeal dilating muscles during REM sleep, particularly in phasic REM, which likely contributes to apneas and hypopneas that are longer and more pronounced. Decreased end-expiratory lung volume and falling ventilatory drive associated with hypocapnia also predispose to upper airway narrowing or closure. In the breaths leading up to obstructive apnea, end-expiratory upper airway caliber progressively decreases. Smaller end-expiratory lung volume may result in smaller upper airway size due to decreased downward traction (tracheal tug). Some patients have unstable ventilatory control (high loop gain) with resulting periods of hypocapnia that may also contribute to upper airway narrowing.

The mechanisms of apnea/hypopnea termination are controversial. Event termination may occur with or without an associated arousal. Some events may resolve with augmentation of upper airway muscle tone from chemical (low PaO_2, high $PaCO_2$) and mechanical (upper airway mechanoreceptors) stimuli, whereas others may depend on a change of sleep state (arousal) at either a cortical or subcortical level. Cortical arousals are associated with changes detectable by EEG, whereas other changes of state may be detectable only by direct or indirect measures of sympathetic tone. Even if arousals are not required for termination of all obstructive events, sleep fragmentation from arousals is nevertheless believed to be a significant cause of excessive daytime sleepiness. Apneas and hypopneas typically last considerably longer in REM and, in some patients, are only present in this sleep stage. The explanation for this finding is unknown.

As an apnea or hypopnea event progresses, the patient gradually becomes more hypoxemic; the degree of oxygen desaturation is dependent not only on the duration of the event, but also on the patient's baseline oxygen saturation and lung volume and the presence of comorbid lung conditions. Slight hypercarbia also occurs during apneas and hypopneas and is worse during REM sleep.

Accumulating evidence indicates that persons with OSA have elevated levels of circulating inflammatory mediators related to repetitive episodes of oxygen desaturation and increased sympathetic nervous system activity. Both of these findings may be important in the pathogenesis of hypertension and cardiovascular disease related to OSA.

Objective Findings

Obstructive apneas are documented by a cessation of airflow with ongoing respiratory efforts during PSG or an OCST. When breathing effort is recorded with respiratory inductance plethysmography, it typically shows paradoxical movement of the rib cage and abdomen. If esophageal manometry is used, increasingly large swings between inspiratory and expiratory efforts are observed. Obstructive hypopneas are a reduction rather than a cessation of airflow with ongoing respiratory effort. Increasing respiratory effort with constant or reduced flow is indicative of increased upper airway resistance. This state is most accurately identified with a quantitative measurement of flow and esophageal manometry, although it can be inferred when there is obvious inspiratory airflow limitation (flattening of the inspiratory flow) on a nasal pressure recording. Although patients with OSA have predominantly obstructive events, they may also have variable amounts of central apneas. In some patients, these resolve with administration of positive airway pressure, whereas in others frequent central apneas either persist or emerge, at least during the initial night of positive airway pressure treatment.

Oxygen saturation typically declines for a variable period of time following the onset of an event (apnea or hypopnea), with the nadir usually occurring after normal breathing resumes. The degree of oxygen desaturation may range from as little as 1% to 2%, up to 30% to 40% or greater. If the baseline oxygen saturation is normal, there may be no discernible drop in oxygen saturation despite evidence of airflow limitation followed by arousal. As a result, some events associated with evidence of increased respiratory effort (and/or flattening of inspiratory flow) and an arousal at event termination may not meet diagnostic criteria for apnea or hypopnea. These events are defined as RERAs. These events are presumed to have the same underlying pathophysiology as obstructive apneas and hypopneas (upper airway obstruction) and are considered to be as much of a risk factor for symptoms of unrefreshing sleep, daytime somnolence, and fatigue as frank apnea or hypopnea.

The EEG may provide evidence of a brief arousal from sleep, and the submental electromyogram may demonstrate a burst of activity indicating upper airway dilating muscle activation immediately preceding the resumption of normal breathing. Microphones may record a sudden resumption of loud snoring. Obstructive apneas and hypopneas may be accompanied by bradyarrhythmias, tachyarrhythmias, or both; however, the

prevalence of this finding in patients varies widely. At the time of arousals, there is often a surge in both sympathetic nervous system activity and systemic blood pressure.

Differential Diagnosis

In contrast to patients with OSA, those with *isolated snoring* will not exhibit obstructive apneas, hypopneas, or RERAs on PSG or OCST and do not have other sleep symptoms attributable to breathing disturbance. However, because arousal-based hypopneas and RERAs cannot be identified with OCST, OSA cannot be excluded if the OCST is negative.

Patients with *central sleep apnea* have predominantly central rather than obstructive apneas, hypopneas, or RERAs as the primary finding on PSG or OCST. If mixed apneas are predominant, a diagnosis of OSA should be made.

Patients with *obesity hypoventilation syndrome* will demonstrate daytime hypercapnia. Snoring may not be a prominent feature, although daytime sleepiness can occur. Patients with *sleep related hypoventilation disorders* may show episodes of oxygen desaturation without evidence of airflow obstruction on PSG or OCST. Confirmation of nocturnal hypercapnia will be diagnostic. However, if obstructive apneas or hypopneas are evident, a diagnosis of OSA should be made instead of, or in addition to, the diagnosis of sleep related hypoventilation.

OSA must be differentiated from other causes of sleepiness such as *narcolepsy*, *idiopathic hypersomnia*, and *insufficient sleep*. These conditions often can be identified on the basis of history, but PSG and/or MSLT may be required to confirm the diagnosis.

OSA should be distinguished from *other causes of nocturnal dyspnea*, such as nocturnal panic attacks, nocturnal gastroesophageal reflux, asthma, paroxysmal nocturnal dyspnea from congestive heart failure, and nocturnal angina pectoris. In many cases, absence of snoring and daytime sleepiness will be highly suggestive of etiologies other than OSA. However, the absence of obstructive apneas, hypopneas, or RERAs on PSG will definitively exclude OSA as the diagnosis.

Unresolved Issues and Further Directions

Although substantial evidence implicates OSA as a risk factor for coronary artery disease and stroke, it has not been clearly demonstrated that treatment mitigates this risk. This is especially a concern for patients with mild OSA who are not hypersomnolent. The pathophysiologic mechanisms linking OSA to increased risk of coronary artery disease, stroke, and hypertension require further investigation. Although there

is a clear association between OSA and type 2 diabetes mellitus, further studies are needed to determine whether OSA is an independent risk factor and what mechanisms are involved.

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Obstructive Sleep Apnea, Pediatric

ICD-9-CM code: 327.23 ICD-10-CM code: G47.33

Alternate Names

Obstructive sleep apnea syndrome, sleep apnea, sleep apnea syndrome, obstructive apnea, sleep disordered breathing, sleep hypopnea syndrome, obstructive hypoventilation, and upper airway obstruction.

The term upper airway resistance syndrome (UARS) is subsumed under this diagnosis because the pathophysiology does not significantly differ from that of OSA. Use of the term Pickwickian syndrome is discouraged, as this term has been used loosely to cover a constellation of conditions including OSA and central hypoventilation.

Diagnostic Criteria

Criteria A and B must be met

A. The presence of one or more of the following:
    1. Snoring.
    2. Labored, paradoxical, or obstructed breathing during the child's sleep.
    3. Sleepiness, hyperactivity, behavioral problems, or learning problems.
B. PSG demonstrates one or both of the following:
    1. One or more obstructive apneas, mixed apneas, or hypopneas, per hour of sleep.[1]

    OR

    2. A pattern of obstructive hypoventilation, defined as at least 25% of total sleep time with hypercapnia ($PaCO_2$ > 50 mm Hg) in association with one or more of the following:
        a. Snoring.
        b. Flattening of the inspiratory nasal pressure waveform.
        c. Paradoxical thoracoabdominal motion.

Notes

1. Respiratory events defined according to the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events.

Essential Features

Pediatric criteria for OSA apply to patients younger than 18 years. However, for the purpose of PSG scoring, the AASM Manual for the Scoring of Sleep and Associated Events states that adult diagnostic criteria may be used for patients aged 13 to 18 years.

Pediatric OSA is characterized by intermittent complete or partial obstruction (obstructive apnea or hypopnea); prolonged partial upper airway obstruction; or both prolonged and intermittent obstructions that disrupt normal ventilation during sleep, normal sleep patterns, or both. Children with OSA may demonstrate several breathing patterns during sleep. Some children have cyclic episodes of obstructive apnea, similar to that of adults with the syndrome. However, some patients, particularly younger children, have a pattern of obstructive hypoventilation, which consists of long periods of persistent partial upper airway obstruction associated with hypercapnia, arterial oxygen desaturation, or both. Some children may manifest a pattern of UARS similar to that seen in adults, including snoring without identifiable airflow obstruction and increasingly negative esophageal pressure swings and cyclic arousals. In children, upper airway obstruction occurs predominantly during REM sleep. Children often do not have cortical arousals in response to the upper airway obstruction, although they may have movement or autonomic arousals. Perhaps as a result of this higher arousal threshold, sleep architecture is usually normal, with normal amounts of slow wave sleep. Even short obstructive apneas may be associated with severe hypoxemia because children have a lower functional residual capacity and a higher metabolic rate than adults.

Most children with OSA present with a history of snoring and difficulty breathing during sleep. Snoring is usually loud and may be punctuated by pauses and gasps, with associated movements or arousal from sleep. However, some patients, particularly infants and those with neuromuscular weakness, may not snore. Patients with obstructive hypoventilation often have continuous snoring without pauses or arousals. Children have a very compliant rib cage. As a result, paradoxical breathing is a prominent sign in these patients (note that paradoxical breathing during REM sleep is a normal phenomenon in young children up to at least age three years). A pectus excavatum may be present. Thoracic retractions may be present. Children may sleep in unusual positions, such as seated or with their neck hyperextended. Diaphoresis may be observed. Morning headaches may also occur. Many parents of children with OSA are so concerned about their child's breathing that they sleep with their child or stimulate their child to terminate the apneas.

Excessive daytime sleepiness may be present, especially in older children and adolescents, but is seen less commonly in children than in adults with OSA. Developmental, behavioral, and learning issues are frequently present. These may include attention problems, hyperactivity, moodiness, irritability, and impaired academic performance.

Associated Features

Hypoxemia and hypercapnia are often present during sleep and may be severe. A prominent sinus arrhythmia is often seen, although other arrhythmias are rare. Secondary enuresis may occur. Breathing during wakefulness is normal, although mouth breathing secondary to adenoidal hypertrophy may be present. Other nonspecific daytime symptoms related to adenotonsillar hypertrophy, such as frequent upper respiratory tract infections or dysphagia, may occur. Although studies have shown that children with OSA generally have larger tonsils and adenoidal tissue than do other children, the size of the tonsils and adenoidal tissue does not predict disease in individual patients.

Clinical and Pathophysiological Subtypes

Clinical presentations include OSA, obstructive hypoventilation, and recurrent arousal associated with increased respiratory effort (RERAs).

Demographics

The prevalence in children has been estimated at 1% to 4%, but the prevalence may currently be higher due to the pediatric obesity epidemic. The prevalence in infants and adolescents is unknown. In prepubertal children, the disease occurs equally among boys and girls; in adolescents, data suggest the prevalence may be higher in males. There appears to be a higher prevalence in black children than white children; the prevalence in other ethnic groups is unknown. The disease can occur at any age, from the neonatal period to adolescence, but in otherwise healthy children it is most common in the preschool age (in association with adenotonsillar hypertrophy) and in adolescents (in association with obesity).

Predisposing and Precipitating Factors

Adenotonsillar hypertrophy and obesity are the most common predisposing/precipitating factors. Children with craniofacial abnormalities, particularly micrognathia or midfacial hypoplasia, are at risk. Those with Down syndrome are particularly at risk for having OSA. Children with neuromuscular diseases often have upper airway muscle weakness, which predisposes to airway collapse. Children with cerebral palsy may be predisposed to OSA because of spasticity, weakness, or incoordination of the upper airway muscles. Infants with gastroesophageal reflux may develop OSA due to upper airway edema or laryngospasm. Other medical conditions such as mucopolysaccharidosis and sickle cell disease may predispose to OSA. Pharyngeal flap operations, typically performed to improve speech quality in patients with cleft palate, can result in OSA. Environmental tobacco smoke exposure has been associated with snoring and OSA.

Familial Patterns

There is evidence for an increased risk of OSA in children with affected family members. Potential mechanisms for familial aggregation include heritability of predisposing skeletal, soft tissue, body habitus, or respiratory control characteristics. However, the relative roles of genetic factors versus environmental factors have not been determined.

Onset, Course, and Complications

The exact course of pediatric OSA has not been well studied. Symptoms typically begin within the first few years of life, although the disease may not be diagnosed until many years later. The natural course of untreated OSA is not known. A few short-term studies suggest that some children with mild disease may improve, or conversely, have worsening of the condition; long-term studies are not available. Complications are frequent and may be severe. In early childhood, OSA can cause growth failure, especially when associated with a comorbid genetic or craniofacial disorder. Cognitive and behavioral complications are common and may include developmental delay, poor school performance, attention deficit hyperactivity disorder, inattention and impairment in concentration, and aggressive behavior. Rarely, cases of severe asphyxial brain damage, seizures, and coma have been reported. Cardiovascular complications include pulmonary hypertension, cor pulmonale, and systemic hypertension.

Developmental Issues

Developmental issues are reviewed within individual sections.

Pathology and Pathophysiology

In children, as in adults, OSA results from a combination of abnormal neuromuscular control and anatomical narrowing of the collapsible (supracartilaginous) portion of the upper airway. During wakefulness, the patient with OSA compensates by augmenting upper airway muscle tone to dilate the upper airway; thus, obstructive apnea does not occur. During sleep, there is a decrease in ventilatory drive and in neuromuscular tone, facilitating upper airway collapse. The resultant recurrent hypoxemia, hypercapnia, and sleep disruption may lead to neurobehavioral, cardiovascular, and growth abnormalities. Childhood OSA has also been associated with metabolic and inflammatory abnormalities.

In most children who are otherwise healthy, upper airway narrowing is primarily due to adenotonsillar hypertrophy. Pediatric OSA also occurs in association with obesity, which is becoming increasingly prevalent. Other causes for upper airway narrowing

include craniofacial anomalies, particularly those involving midface hypoplasia or micrognathia/retrognathia. In addition, children with decreased upper airway muscle tone or abnormal upper airway muscle function, such as children with muscular dystrophy or cerebral palsy, are at increased risk for OSA.

Objective Findings

PSG demonstrates obstructive and mixed apneas, hypopneas, or periods of obstructive hypoventilation. In children, obstructive apneas lasting two respiratory cycles or longer are scored. In contrast to adults with OSA, EEG arousals may or may not be present following apneas, especially in young children, although subcortical/autonomic arousals (as manifested by body movements, tachycardia, or measurements of pulse transit time or arterial tonometry) may occur. Possibly as a result of the higher arousal threshold, sleep architecture is usually preserved. Apneas and hypopneas occur primarily during REM sleep, and breathing may be totally normal during NREM sleep. Obstructive events are frequently associated with desaturation and hypercapnia. Evaluation of the upper airway by endoscopy, radiography, computed tomographic scans, or magnetic resonance imaging studies may show large tonsils and adenoidal tissue and a narrow upper airway, although these tests are not performed routinely. Echocardiography may show evidence of right, left, or biventricular hypertrophy.

Differential Diagnosis

Pediatric OSA must be differentiated from *isolated snoring*. Children with snoring but without observed apnea, labored breathing during sleep, daytime behavioral issues, sleepiness, or other symptoms of OSA may not require further laboratory investigation. However, children who have snoring *and* symptoms of OSA need evaluation to determine whether they have isolated snoring or OSA (*N.B. this distinction cannot reliably be made clinically but should be based on PSG).* Children with primary snoring do not have apneas, gas exchange abnormalities, or frequent arousals on PSG. *Central sleep apnea* can be differentiated from OSA by the lack of chest or abdominal wall movement associated with the central apneas. Mixed apneas may be seen and are included in the diagnosis of OSA. Children with fixed upper airway obstruction due to structural abnormalities tend to obstruct both awake and asleep, and have *stridor* rather than snoring. OSA in children must be distinguished from *nonobstructive alveolar hypoventilation*. Children with lung or chest wall disease may have desaturation and hypercapnia during sleep. It may be difficult to separate nonobstructive hypoventilation and desaturation from OSA, especially because the two conditions may coexist. In general, children with nonobstructive hypoventilation will not snore and will not have paradoxical inward rib cage motion during inspiration, although the latter may be present in children with neuromuscular disease. OSA must be differentiated from

other causes of sleepiness such as *narcolepsy*, idiopathic hypersomnia, and *insufficient sleep*. *Sleep related epilepsy* may mimic obstructive apnea during sleep and may be indistinguishable from OSA without the appropriate EEG monitoring, especially in infants who may have only subtle motor components of seizures.

Unresolved Issues and Further Directions

There is a need for further research in many aspects of pediatric OSA. Although studies of prevalence have been performed in the past, the prevalence has probably increased in recent years due to the increasing prevalence of childhood obesity. Further data regarding the prevalence in infants and adolescents is needed. The natural course of the disease, the optimal techniques for monitoring patients during PSG, the effects of mild OSA, and the threshold necessitating treatment require further study. The role of genetic, ethnic, and anatomic factors in the pathophysiology of childhood OSA also requires further study.

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Central Sleep Apnea Syndromes

Central Sleep Apnea with Cheyne-Stokes Breathing

ICD-9-CM code: 786.04 ICD-10-CM code: R06.3

Alternate Names

Cheyne-Stokes respiration.

Diagnostic Criteria

(A or B) + C + D satisfy the criteria

A. The presence of one or more of the following:
   1. Sleepiness.
   2. Difficulty initiating or maintaining sleep, frequent awakenings, or nonrestorative sleep.
   3. Awakening short of breath.
   4. Snoring.
   5. Witnessed apneas.

B. The presence of atrial fibrillation/flutter, congestive heart failure, or a neurological disorder.

C. PSG (during diagnostic or positive airway pressure titration) shows all of the following:
   1. Five or more central apneas and/or central hypopneas per hour of sleep.[1]
   2. The total number of central apneas and/or central hypopneas is > 50% of the total number of apneas and hypopneas.[2]
   3. The pattern of ventilation meets criteria for Cheyne-Stokes breathing (CSB).[1]

D. The disorder is not better explained by another current sleep disorder, medication use (e.g., opioids), or substance use disorder.

Notes

1. As defined by the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events.
2. If criterion C2 is not met, CSB can be listed as a polysomnographic finding.
3. A diagnosis of central sleep apnea (CSA) with CSB does not exclude a diagnosis of OSA.

Essential Features

CSA-CSB is characterized by recurrent central apneas or central hypopneas alternating with a respiratory phase exhibiting a crescendo-decrescendo pattern of flow (or tidal volume). The longer cycle length (> 40 seconds; typically 45 to 60 seconds) distinguishes CSB from other central sleep apnea types. The vast majority of patients with CSA-CSB have either systolic or diastolic heart failure. In systolic heart failure the cycle length is longer (longer respiratory phase) than in patients with diastolic heart failure, and there is often a delay in the nadir of the associated oxygen desaturation. Patients with CSA-CSB have normal or low daytime arterial PCO_2 ($PaCO_2$). Some patients with heart failure have a mixture of obstructive and central apneas with more central apneas in the later part of the night or when the patient is placed on positive airway pressure (PAP). A diagnosis of CSA-CSB requires that events be predominantly central apneas and hypopneas with an average frequency of at least 5/hour during a diagnostic PSG or either the diagnostic or therapeutic portion of a split-night study. For patients with a mixture of OSA and CSA-CSB, the central apneas may appear only after elimination of obstruction on positive airway pressure. In patient with CSA-CSB, arousal from sleep tends to occur at the zenith of respiratory effort between contiguous central apneas or hypopneas. This can result in sleep fragmentation. However, patients may complain of disturbed nocturnal sleep or nocturnal dyspnea rather than daytime sleepiness.

Associated Features

Presenting features of CSB pattern during sleep may include excessive daytime sleepiness, insomnia, or nocturnal dyspnea. Because many patients with CSA-CSB have known heart failure, their complaints of frequent awakenings or disturbed sleep may be falsely assumed to be entirely secondary to heart failure. Because studies have shown that approximately 60% of patients with heart failure have some form of sleep apnea, a high index of suspicion is indicated. A CSB pattern can also occur during wakefulness and can be observed at bedside or in the clinic. Some studies suggest that the presence of CSA-CSB during wakefulness is associated with a worse prognosis. Although heart failure is the major cause of CSA-CSB, recent studies suggest that it can be noted after stroke. CSA-CSB can rarely present in an idiopathic form or be associated with renal failure.

As in other forms of CSA, apneas and hypopneas are associated with absent or reduced ventilatory effort, respectively, due to diminished central respiratory drive. Of interest, a longer respiratory phase between apneas is associated with a longer circulation time and delay in the saturation nadir. The CSB breathing pattern is characteristically observed during stages N1 and N2 and usually resolves or is attenuated during REM

sleep. In patients with both OSA and CSA-CSB, the relative amount of central and obstructive apnea can vary over time or even within the same night.

Clinical and Pathophysiological Subtypes

Some patients have combined OSA and CSA, and the CSA-CSB may not manifest until the patient is placed on positive airway pressure treatment. These patients are considered to have both OSA and CSA with CSB. Patients with systolic or diastolic heart failure may have CSB, but the cycle length is longer in those with systolic dysfunction. Patients with neurological disorders may have CSB, but the characteristic cycle length is less well described.

Demographics

CSA with CSB generally is seen in subjects older than 60 years. The prevalence of this breathing disorder in the setting of chronic congestive heart failure has been reported to be 25% to 40%, depending on how patients are divided into those with predominant OSA and those with CSA. In patients with heart failure there is a striking male predominance in the occurrence of CSA-CSB. Of interest, the use of β-blockers and angiotensin-converting enzyme inhibitors for treatment of congestive heart failure has not decreased the prevalence of CSA-CSB. Some form of sleep apnea is reported in 50% to 70% of patients following stroke, depending on the AHI cutoff used for diagnosis. Although OSA predominates, central sleep apnea is also common especially in the first few days following stroke. CSA-CSB has been reported to occur in 26% to 50% of patients in the acute period following stroke.

Predisposing and Precipitating Factors

The most important predisposing factors are the presence of congestive heart failure, stroke, and possibly renal failure. Within the heart failure population, risk factors for CSB pattern during sleep include male sex, age older than 60 years, the presence of atrial fibrillation, and daytime hypocapnia (i.e., awake $PaCO_2$ of 38 mm Hg or less). In general, greater pulmonary congestion (higher left ventricular end-diastolic pressure) predicts lower $PaCO_2$. Some studies suggest that CSA-CSB occurs more commonly in the supine position. Although renal failure is often listed as a possible cause of CSA-CSB, there is scant literature documenting this association.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

There are no definitive data concerning the onset. However, because it is seen in the setting of congestive heart failure, stroke, and possibly renal failure, CSA with CSB most likely has its onset following the development of one of these illnesses. In the setting of systolic congestive heart failure, it is associated with a poor prognosis, as indicated by a greater adjusted relative risk for mortality-cardiac transplantation compared to patients without CSB. These data suggest that CSB pattern during sleep participates in the pathophysiology and progression of heart failure. Its clinical significance in the setting of stroke or other neurological disorders remains less certain. In some patients with CSA after stroke, the pattern can transition to one of OSA. The presence of obstructive apnea following stroke has been found to be associated with a worse prognosis.

Developmental Issues

Although there are reports of CSB in children, the condition is extremely rare in this age group. Of interest, one study of patients with congestive heart failure across all age groups found CSB to be absent in children but present in 40% of the adult patients with congestive heart failure. A limitation of the study was that only ten children with congestive heart failure were studied.

Pathology and Pathophysiology

CSA with CSB generally arises because of instability in the respiratory control system. A high ventilatory drive and delay in chemoreceptor response to changes of $PaCO_2$ and PaO_2 (due to increased circulation time) are likely the major factors. This breathing disorder tends to occur in individuals with a chronically low $PaCO_2$ when awake and asleep. Hyperventilation occurs due to an increase in the responsiveness of the peripheral and central chemoreceptors. The increased responsiveness is believed to be due to both increased sympathetic tone and stimulation of vagal irritant receptors in the lungs by pulmonary congestion. The $PaCO_2$ in individuals with CSB pattern and heart failure is closer to their apneic threshold than in those without CSB pattern (primarily due to a smaller sleep related rise in $PaCO_2$ in those with CSB), so that even modest increases in ventilation can drive $PaCO_2$ below the apneic threshold. The most common trigger factor for central apnea is an arousal from sleep, which abruptly augments ventilation and drives $PaCO_2$ below the apneic threshold.

The crescendo-decrescendo pattern of tidal volume results from prolonged lung-to-chemoreceptor circulatory delay, such that changes in $PaCO_2$ in the lung are transmitted only very slowly to the chemoreceptors, resulting in a gradual buildup and falloff of ventilatory stimulation. The length of the cycle is directly proportional to

lung-to-chemoreceptor circulation time and inversely proportional to cardiac output. Accordingly, whereas the length of the ventilatory-apneic cycle in primary CSA is typically shorter than 40 seconds, in CSB pattern it is almost invariably longer than 40 seconds (usually 45-90 seconds). One study of patients with varying degrees of heart failure found a considerably shorter cycle time in patients with normal ejection fraction (e.g., diastolic heart failure). The pathophysiology of CSB pattern in the setting of stroke and renal failure has not been examined in any detail. However, apneas in association with these medical disorders are believed to be due to a reduction in $PaCO_2$ below the apneic threshold. In individuals with renal failure, pulmonary congestion (volume overload) may play a role in stimulating hyperventilation.

Objective Findings

The polysomnographic hallmarks of CSB pattern are recurrent central apneas and central hypopneas alternating with ventilatory periods having a prolonged crescendo-decrescendo pattern of airflow (tidal volume). CSB pattern typically occurs at the transition from wakefulness to NREM sleep and during stages N1 and N2. It tends to dissipate in stages N3 and R. In stage N3 sleep the sleeping $PaCO_2$ is higher (further above the apneic threshold). During REM sleep the hypoxic and hypercapnic ventilatory responses are lower, thereby reducing the tendency for an overshoot in ventilation which may drive $PaCO_2$ below the apneic threshold.

Arousals are frequently seen in association with CSB and are typically noted at or near the zenith in respiratory effort (or airflow), although can occur at or near the onset of the respiratory phase pattern. In contrast, arousals tend to occur at apnea termination in other CSA disorders. As noted above, a longer respiratory phase (and cycle length) is associated with lower cardiac output and longer circulation time.

Central hypopnea, rather than apnea, can occur at the nadir in respiratory effort in patients with CSB and have been included in calculation of the central AHI in a substantial number of investigations. Central hypopneas are characterized by the absence of snoring, flattening in the nasal pressure or PAP device flow signal, and thoracoabdominal paradox.

Central apneas and central hypopneas are usually accompanied by modest oxyhemoglobin desaturation; arterial oxygen saturation seldom falls below 80% to 85%. The combination of oxygen desaturation and arousals from sleep leads to sleep fragmentation with reduced amounts of stage N3 sleep. Additionally, $PaCO_2$ less than 40 mm Hg is typically observed during wakefulness. In patients with both obstructive and central apneas, the proportion of central apneas tends to increase over the night, and this is

associated with a fall in the sleeping $PaCO_2$. The lower sleeping $PaCO_2$ is thought to be due to an increase in pulmonary congestion during the night with stimulation of juxta-capillary (J) receptors in the lung interstitium and a subsequent increase in ventilatory drive. As noted above, some patients have more CSA-CSB in the supine position.

Differential Diagnosis

Primary CSA can usually be distinguished from CSB pattern by the absence of a history of heart failure, stroke, or renal failure and by the absence of a crescendo-decrescendo breathing pattern between central apneas. The cycle length (apnea + ventilatory phase) in primary CSA is typically less than 40 seconds. *High-altitude periodic breathing* only occurs at high altitude and is not associated with heart failure, stroke, or renal failure. Patients with *CSA due to drug or substance* have a history of use of this type of medication, and an ataxic breathing pattern may be present. If patients with CSA associated with opioids manifest periodic breathing, the respiratory phase does not have a crescendo-decrescendo pattern and the cycle length is shorter. Patients with *CSA due to a medical or neurological disease* without *Cheyne-Stokes* will have central apnea that does *not* have Cheyne-Stokes morphology, as the name implies. Sleep related hypoventilation and hypoxemic syndromes can be readily distinguished from CSA-CSB by documentation of an awake $PaCO_2 > 45$ mm Hg and/or sleep related hypoventilation. Patients with CSA-CSB usually have an awake $PaCO_2 < 40$ mm Hg. In patients with sleep related hypoventilation disorders, some central apneas may be present, but these events do not have a Cheyne-Stokes morphology. Additionally, oxygen desaturation in sleep related hypoventilation syndromes is generally more pronounced during REM sleep. *OSA* is distinguished by the presence of respiratory efforts during apneas. A few central apneas or hypopneas at sleep onset or during REM sleep are normal, especially in elderly subjects. These cease once sleep becomes stable.

Unresolved Issues and Further Directions

The pathophysiology and clinical significance of CSB pattern have not yet been elucidated in the setting of stroke and renal failure. Less is also known about the importance of CSB in patients with heart failure with a normal ejection fraction.

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Central Apnea Due to a Medical Disorder without Cheyne-Stokes Breathing

ICD-9-CM code: 327.27 ICD-10-CM code: G47.37

Alternate Names

Not applicable or known.

Diagnostic Criteria

Criteria A-C must be met

A. The presence of one or more of the following[1]:
   1. Sleepiness.
   2. Difficulty initiating or maintaining sleep, frequent awakenings, or nonrestorative sleep.
   3. Awakening short of breath.
   4. Snoring.
   5. Witnessed apneas.

B. PSG shows all of the following:
   1. Five or more central apneas and/or central hypopneas per hour of sleep.[2]

2. The number of central apneas and/or central hypopneas is > 50% of the total number of apneas and hypopneas.
3. Absence of CSB.[2]

C. The disorder occurs as a consequence of a medical or neurological disorder but is not due to medication use or substance use.

Notes

1. In infants and young children, symptoms are supportive but not required.
2. As defined by the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events.
3. Sleep related hypoventilation is not required but may be present. If the patient meets criteria for both sleep related hypoventilation and CSA due to medical or neurological condition not Cheyne-Stokes, both diagnoses can be made.
4. In some patients other abnormalities of breathing such as ataxic breathing may be prominent.
5. A diagnosis of central apnea due to a medical disorder without CSB does not exclude a diagnosis of OSA.

Essential Features

CSA that is attributed to a medical or neurological condition (and does not have the pattern of CSB) is classified here. The majority of these patients have brainstem lesions of developmental, vascular, neoplastic, degenerative, demyelinating, or traumatic origin.

Associated Features

Patients generally present with sleep fragmentation, excessive daytime sleepiness, or insomnia. Other signs and symptoms that are often, but not invariably, present include snoring, witnessed apnea, and awakening with shortness of breath. The presentation varies with the cause of central apnea and may include neurological findings.

Clinical and Pathophysiological Subtypes

None. Some of the common medical and neurological disorders causing central apnea not associated with CSB are listed in *Pathology and Pathophysiology* (below).

Demographics

The prevalence and demographics of this disorder vary with the underlying etiology. Patients with Chiari malformation (CM) can present in infancy or childhood, but the most common age of presentation is 20 to 40 years. Patients with stroke tend to be older.

Predisposing and Precipitating Factors

Because of the heterogeneity of etiologies in this type of CSA, predisposing and precipitating factors are variable. In CM there is herniation of a portion of the brainstem through the foramen magnum. In CM type 1, a portion of the cerebellar tonsils herniate. CSA in these patients is believed to occur due to impaired function of ventilatory control centers in the brainstem.

Familial Patterns

None known.

Onset, Course, and Complications

These factors vary as well with the different etiologies. In CM the presentation is typically age 20 to 40 years of age but can occur in infants and children. With the increased use of magnetic resonance imaging (MRI), cases are often diagnosed before symptoms are severe. The CSA following a cerebrovascular accident (CVA) is abrupt in onset. In patients exhibiting both central and obstructive apnea, the central apneas tend to resolve with time. Some post-CVA patients with central apneas have central apnea with CSB, whereas in others the CSA does not have a pattern consistent with CSB. The central apneas can lead to sleep fragmentation, yielding either hypersomnolence or insomnia or both. There is little evidence that these apneas or their associated hypoxia and hypercapnia lead to pulmonary hypertension, cor pulmonale, or other adverse cardiovascular consequences.

Developmental Issues

Not known.

Pathology and Pathophysiology

CSA is caused by failure of the ventilatory control centers to initiate ventilatory effort. The abnormality is due to dysfunction of central ventilatory control centers. The presence of sleep may unmask ventilatory control abnormalities with the loss of the wakefulness stimulus. Sleep related hypoventilation and/or daytime hypoventilation may coexist with CSA due to medical or neurological disorder, not CSB, in which case both diagnoses can be made.

A number of causes of CSA due to medical or neurological disorders–not Cheyne-Stokes—have been described. Patients with CM exhibit obstructive, central, or a mixture of obstructive and central apneas. Some patient exhibit nocturnal hypoventilation but rarely daytime hypoventilation. CSA and/or OSA can be the initial presentation of the disorder. Symptoms include headache (especially with laughter, coughing,

or exertion), neck pain, and vertigo. An MRI is diagnostic of the condition and should be considered as part of the evaluation of all patients without an obvious cause of central apnea.

Brainstem neoplasm can present with central apnea not of the Cheyne-Stokes type. Patients with a recent cerebrovascular accident show a high incidence of sleep disordered breathing. Although obstructive apnea is more common, central apnea may be noted initially after a cerebrovascular accident. Some patients exhibit a pattern of CSB, whereas in others periodic breathing without the characteristic CSB pattern is present. Patients with multiple system atrophy may also present with CSA that does not have a CSB pattern.

Objective Findings

The polysomnogram of the patient with CSA due to medical or neurological condition—not CSB—demonstrate recurrent (five or more per hour) central apneas and/or central hypopneas. The central apneas and hypopneas meet criteria for these events as defined by the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events. Runs of recurrent central apneas separated by periods of ventilation may occur. The interevent respiratory phase is typically brief with a maximum of five breaths. The central apneas do not have the pattern of CSB.

Differential Diagnosis

Patients with CSA due to medical or neurological disorder—not CSB—should be differentiated from *primary CSA*, in which no known cause is identified. As the name implies, patients with a pattern of *CSB* should be classified as such. Patients with central nervous system neoplasms may have a central hypoventilation syndrome with *sleep related hypoventilation* with or without an increase in daytime $PaCO_2$.

Unresolved Issues and Further Directions

With the possible exception of poststroke central apnea, the disorders classified here are thought to be relatively rare. The presenting symptoms may not be a sleep related complaint. Except for those associated with CM and poststroke CSA, the disorders are not well characterized.

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Central Sleep Apnea Due to High Altitude Periodic Breathing

ICD-9-CM code: 327.22 ICD-10-CM code: G47.32

Alternate Names

None.

Diagnostic Criteria

Criteria A-D must be met

A. Recent ascent to high altitude.[1]

B. The presence of one or more of the following:[2]
   1. Sleepiness.
   2. Difficulty initiating or maintaining sleep, frequent awakenings, or nonrestorative sleep.
   3. Awakening with shortness of breath or morning headache.
   4. Witnessed apnea.

C. The symptoms are clinically attributable to high-altitude periodic breathing or PSG, if performed, demonstrates recurrent central apneas or hypopneas primarily during NREM sleep at a frequency of ≥ 5/hour.

D. The disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use (e.g., narcotics), or substance use disorders.

Notes

1. Typically at least 2,500 meters (8,202 feet), although some individuals may exhibit the disorder at altitudes as low as 1,500 meters.
2. Periodic breathing is a common response to altitude. Associated symptoms are required to make the diagnosis of a disorder. There is no level of the central AHI separating a normal and abnormal response to high altitude.
3. A diagnosis of CSA due to high-altitude period breathing does not exclude a diagnosis of OSA.

Essential Features

High-altitude periodic breathing is characterized by alternating periods of central apnea and hyperpnea associated with recent ascent to high altitude. The pattern of periodic breathing is an expected response to ascent to elevation. Only those individuals who manifest related symptoms, as described below, are diagnosed with this disorder. The cycle length of this respiratory pattern is commonly less than 40 seconds and often as short as 12 to 20 seconds. The percentage of individuals exhibiting periodic breathing during sleep increases at higher altitudes. Approximately 25% exhibit periodic breathing at 2,500 meters (8,202 feet), and virtually 100% demonstrate periodic breathing at 4,000 m (13,123 feet). Periodic breathing has been described at altitudes as low as 1,500 meters (4,900 feet). Chronic exposure to altitude above 2,500 meters has also been associated with periodic breathing in some studies.

Associated Features

At altitude, individuals may complain of frequent awakenings, poor-quality sleep, and a sense of dyspnea. These symptoms will often improve with time at moderate altitude but may persist at extreme altitude. Alterations in sleep associated with ascent to altitude include a reduction in stage N3 sleep and increased arousal frequency. Total sleep time and the amount of REM sleep are either unchanged or decreased. Of note, the degree of both subjective and objective impairment of sleep quality was not correlated with the severity of periodic breathing in a number of studies.

Clinical and Pathophysiological Subtypes

None known.

Demographics

The demographics of high-altitude periodic breathing are not known. High-altitude periodic breathing tends to occur in individuals with a high hypoxic and probably hypercapnic ventilatory response. Because men generally have higher chemoresponsiveness than women, high-altitude periodic breathing may be more common in men than in women. As stated above, periodic breathing will occur in virtually anyone ascending to higher than 4,000 meters and in some individuals at lower altitudes. The latter group probably comprises individuals with increased hypoxic chemoresponsiveness. In one study, individuals both with and without periodic breathing at altitude had alterations in sleep architecture. Those with periodic breathing had a greater arousal index, although their sleep architecture was otherwise not significantly different from individuals who did not develop periodic breathing.

Predisposing and Precipitating Factors

The only known predisposing factor for the development of high-altitude periodic breathing is increased ventilatory chemoresponsiveness, primarily hypoxic ventilatory responsiveness. A high hypoxic ventilatory response will lead to increased hyperventilation on ascent to altitude. This hyperventilation leads to hypocapnic alkalosis that, during sleep, inhibits ventilation. Thus, repetitive cycles of apnea and hyperpnea develop during NREM sleep. The obvious precipitating factor for the development of this periodic breathing is ascent to altitude. The more rapid the ascent, the more likely periodic breathing is to develop.

Familial Patterns

Some data suggest that ventilatory chemoresponsiveness is directly inherited. Because elevated hypoxic responsiveness is a predisposing variable in the development of high-altitude periodic breathing, it would seem likely that there would be a familial pattern in the development of this respiratory abnormality. However, there are no data addressing this issue.

Onset, Course, and Complications

This respiratory pattern will generally be evident during sleep immediately after ascent to altitude. This depends to some extent on the rapidity of the ascent, the elevation, and individual predisposition. However, it will be present most often on the first night at altitude. At moderate altitude, the breathing pattern may become more regular over time, although at extreme altitude it is likely to persist. One recent study found that the amount of periodic breathing continued to increase over three days to two weeks of acclimatization. Studies of adaptation to altitude suggest that sleep quality may improve despite further increases in periodic breathing. It has been hypothesized that hypoxia itself may have an important role in disturbing sleep architecture. Thus, sleep and symptoms may improve during acclimatization to altitude even if the amount of periodic breathing actually increases.

The complications of high-altitude periodic breathing, which are generally limited to disrupted sleep on the initial nights at altitude, include frequent awakenings, often with shortness of breath or a sensation of suffocation that may lead to fatigue or sleepiness on the following day. There is no clear association between periodic breathing and other altitude syndromes (high-altitude pulmonary edema, acute mountain sickness, and high-altitude cerebral edema). In fact, periodic breathing is a marker of high hypoxic responsiveness, which generally yields improved oxygenation at altitude and a reduced frequency of the maladaptive syndromes.

Developmental Issues

Relatively little is known about differences between children and adults concerning periodic breathing at altitude. One study did compare breathing in children and their fathers. The children revealed reduced nocturnal oxygen saturation and associated hyperventilation at high altitude similar to the adults, but their breathing pattern was more stable. The investigators hypothesized that children may have a lower apnea threshold for CO_2 than adults.

Pathology and Pathophysiology

High-altitude periodic breathing is believed to be a product of the hyperventilation induced by the hypobaric hypoxia encountered at altitude. At 2,500 meters the atmospheric pressure is approximately 570 mm Hg and the ideal alveolar PO_2 around 55 mm Hg (depending on the level of $PaCO_2$). Actual arterial PO_2 values will be lower, especially during sleep. The hypoxic ventilatory response shows a steep increase in ventilation when the arterial PO_2 level drops below 55 mm Hg. The increases in ventilation associated with hypoxemia result in hypocapnic alkalosis. Because $PaCO_2$ is the principal stimulus to respiration during NREM sleep, a low $PaCO_2$ can yield a loss or reduction in respiratory drive, resulting in central apnea or hypopnea. The greater the ventilatory response to hypoxia, the greater the fall in $PaCO_2$. Thus, individuals with brisk hypoxic responses more commonly tend to demonstrate this respiratory pattern. Over the course of the apnea, the PaO_2 falls and $PaCO_2$ rises, eventually stimulating a resumption of ventilation. However, after several large breaths, the $PaCO_2$ again falls below the apnea threshold, initiating another pause in breathing. This cycle is then repeated over the course of the night. Of note, the respiratory pattern is often improved during REM sleep with reduced cycling. This is likely due to the decreased hypoxic and hypercapnic responsiveness characteristic of REM sleep. Of interest, in one study the hypoxic ventilatory response continued to increase up to seven days after ascent to altitude. This resulted in a lower $PaCO_2$ and higher PaO_2. The reduction in periodic breathing in some individuals with adaptation to altitude despite a greater ventilatory response to hypoxemia may be due to a lowering of the apneic threshold. Other studies have found that the amount of periodic breathing continues to increase over three days to two weeks of acclimatization despite improvements in oxygen saturation. The increase in both periodic breathing and oxygen saturation is thought to be due to increased controller gain of the respiratory system.

A number of studies have found that the impairment of sleep architecture does not correlate with the degree of periodic breathing. One study found that the amount of periodic breathing was greater on the third night at altitude compared to the first night. However, both the nocturnal oxygen saturation and amount of stage N3 also increased

on the third night compared to the first night. It has been hypothesized that hypoxia rather than periodic breathing might be the major factor disturbing sleep.

Objective Findings

The PSG of individuals with high-altitude periodic breathing demonstrates recurrent central apneas with a cycle time of less than 40 seconds, and typically around 20 seconds. There is some degree of associated arterial oxygen desaturation. The apneas are short, generally 8 to 10 seconds in duration. In one study, the apnea duration was around 8 seconds (7 to 9 seconds) in children and approximately 12 seconds (10-14 seconds) in adults.

The cycle length is commonly less than 40 seconds. This breathing pattern occurs only during NREM sleep with more rhythmic respiration during REM sleep. Because this breathing pattern is a physiologic adaptation to altitude, there is no specific number of apneas per hour of sleep that is considered normal or abnormal. The apneas and associated hyperpnea can lead to recurrent arousals from sleep, which often increase stages N1 and N2 sleep while reducing stage N3 sleep. REM sleep (stage R) duration is generally preserved, as is total sleep time. As noted above, some studies have found a reduction in total sleep time and stage R as well as stage N3. Of interest, the arousal index was only around 25% of the AHI in some investigations.

Differential Diagnosis

High-altitude periodic breathing should be distinguished from other SRBDs. The major distinguishing factor is, of course, recent ascent to high altitude. An individual with *OSA* will likely continue to have this nocturnal respiratory problem at altitude. Altitude might even exacerbate the OSA. Patients with *chronic mountain sickness* demonstrate relative hypoventilation at altitude (i.e., breathe less than is encountered in normal individuals at similar altitude) such that they are more hypoxic than normal individuals who have a greater ventilatory response to the same ambient hypoxia. During sleep, these individuals often demonstrate further arterial oxygen desaturation. Some of the individuals will demonstrate apneas or periodic breathing. A diagnosis of chronic mountain sickness does not imply that periodic breathing is present. However, periodic breathing may be more common in these patients than previously appreciated.

Unresolved Issues and Further Directions

Recent studies suggest that hypoxemia rather than the amount of periodic breathing may be the major factor impairing sleep quality. Further studies relating changes in sleep and periodic breathing at altitude are needed.

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Central Sleep Apnea Due to a Medication or Substance

ICD-9-CM code: 327.29 ICD-10-CM code: G47.39

Alternate Names

Narcotic or opioid induced central sleep apnea.

Diagnostic Criteria

Criteria A-E must be met

A. The patient is taking an opioid or other respiratory depressant.
B. The presence of one or more of the following:
    1. Sleepiness.
    2. Difficulty initiating or maintaining sleep, frequent awakenings, or nonrestorative sleep.
    3. Awakening short of breath.
    4. Snoring.
    5. Witnessed apneas.
C. PSG (diagnostic or on positive airway pressure) shows all of the following:
    1. Five or more central apneas and/or central hypopneas[1] per hour of sleep (PSG).
    2. The number of central apneas and/or central hypopneas is > 50% of the total number of apneas and hypopneas.
    3. Absence of CSB.[1]
D. The disorder occurs as a consequence of an opioid or other respiratory depressant.
E. The disorder is not better explained by another current sleep disorder.

Notes

1. As defined by the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events.
2. Ataxic breathing (irregular variations in respiratory cycle time and tidal volume) may be noted.
3. Nocturnal and/or daytime hypoventilation may be present but are not required. If sleep related hypoventilation is present, a diagnosis of sleep related hypoventilation due to medication or substance use can be made as well as a diagnosis of central sleep apnea due to a medication or substance.
4. A diagnosis of CSA due to a medicationor substance does not exclude a diagnosis of OSA.

Essential Features

Users of potent long-acting opioids may have central apneas during sleep. The most common offending drug is methadone. However, the condition has also been described in patients taking long-acting forms of morphine or oxycodone as well as individuals being treated with fentanyl patches or continuous narcotic infusions. Suboxone (a combination of buprenorphine and naloxone) is often used for treatment of patients with narcotic dependence and pain and can also cause drug-induced central apnea. The description of this population is complicated by the fact that many of the affected individuals may be using multiple drugs (prescribed or illicit) that affect sleep and breathing.

Associated Features

Breathing abnormalities associated with these drugs are not restricted to central apneas and may also include hypoventilation and OSA with prolonged respiratory events. In fact, many patients present with a combination of both OSA and CSA. Patients who have nocturnal hypoventilation may have normal or increased daytime $PaCO_2$. In most patients with daytime hypoventilation, the $PaCO_2$ is only mildly increased (46-50 mm Hg). Patients with drug-induced central apnea who are being treated for chronic pain often report significant daytime sleepiness. Due to the sedating effects of opioid medications, the sleepiness may not substantially improve even if the central apnea is treated successfully. However, one study of patients on chronic methadone maintenance found the average Epworth Sleepiness Scale score to be within normal range. In these patients, who manifested only mild to moderate OSA (average AHI about 18/hour), the degree of sleepiness correlated with a depression index. A case series of patients treated with opioids for chronic pain found AHI values above 30/hour (up to 100/hour) and moderate to severe sleepiness. In this group, 50% to 80% of respiratory events were central apneas. Sleepiness that is disproportionately high in comparison to the severity of the AHI (and in some cases, at least partially unresponsive to treatment) is likely due to the direct sedative effects of the narcotic medication itself.

Clinical and Pathophysiological Subtypes

None known.

Demographics

There are no known sex, racial, or ethnic differences. The prevalence of this disorder is not known, although limited data suggest that it occurs commonly in those being treated with opioids for chronic pain.

Predisposing and Precipitating Factors

Use of a potent long-acting narcotic is the major causative factor. If patients are successfully withdrawn from the offending medication, the central apnea may resolve.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

This disorder is typically seen after opioids have been used for at least two months. An increased risk of death has been reported with the use of potent narcotics. There has been a large increase in deaths associated with methadone due to the increasing use of this medication for chronic pain. Many of these deaths occur during sleep.

Developmental Issues

Information regarding the presentation of this disorder in children is limited. CSA due to opioid medications has been described in children being treated for pain due to cancer.

Pathology and Pathophysiology

The presumed pathophysiology for the development of these varied breathing abnormalities during sleep is the respiratory depression that occurs through action of the drugs on the μ-receptors on the ventral surface of the medulla. Studies have demonstrated depression of the awake hypercapnic ventilatory drive; however, it often improves after five to eight months of continued drug use. In one study the hypoxic ventilatory drive never fully normalized. Another study of patients on chronic methadone maintenance found that the hypoxic ventilatory drive is increased compared to that of control subjects. In this study the hypercapnic ventilatory response was reduced in comparison with that of controls who were not taking opioids. The difference was not due to a lower tidal volume but rather reduced respiratory rate. Differences in technique or patient population may explain the divergent findings. The cause of the ataxic breathing in patients on opiates is not known. However, one study of patients on chronic opioids found that the incidence of ataxic breathing increased with the total narcotic dose.

Objective Findings

The drug-induced central apneas may occur as a form of periodic breathing with runs of central apneas separated by a short ventilatory phase (2 to 4 breaths) or intermittent and sporadic central apneas. The underlying breathing pattern may show a slow respiratory rate or an ataxic breathing pattern. The term ataxic breathing is sometimes used as a synonym of Biot breathing, although definitions of the latter term vary widely.

Ataxic breathing is characterized by an irregular breathing rhythm as well as irregular depth of breathing (tidal volume). Obstructive breathing events are also common in patients taking potent opioids and a diagnosis of both OSA and CSA is often appropriate. Prolonged obstructive apneas with severe arterial desaturation may be noted. The drug-induced central apneas occur mainly during NREM sleep and, in patients without coexistent obstructive apnea, the AHI may be much lower during REM than during NREM sleep. Patients also tend to have a low arousal index and increased stage N3 sleep. Unlike other forms of central apnea, drug-induced central apneas may occur during stage N3 sleep.

Differential Diagnosis

This condition is best distinguished from other types of central sleep apnea by the patient's ongoing use of long-acting opioids. Other SRBDs may be present and may complicate PSG findings.

Unresolved Issues and Further Directions

Further study is needed to determine risk factors and pathogenesis for development of these sleep disordered breathing patterns in users of long-acting opioids. It has been hypothesized that these sleep disordered breathing patterns may play a role in the unexplained increased mortality in this population. This also requires further study.

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Primary Central Sleep Apnea

ICD-9-CM code: 327.21 ICD-10-CM code: G47.31

Alternate Names

Idiopathic central sleep apnea.

Diagnostic Criteria

Criteria A-D must be met

A. The presence of at least one of the following[1]:
   1. Sleepiness.
   2. Difficulty initiating or maintaining sleep, frequent awakenings, or nonrestorative sleep.
   3. Awakening short of breath.
   4. Snoring.
   5. Witnessed apneas.

B. PSG demonstrates all of the following:
   1. Five or more central apneas and/or central hypopneas[2] per hour of sleep (PSG).
   2. The number of central apneas and/or central hypopneas is > 50% of the total number of apneas and hypopneas.
   3. Absence of CSB.[2]

C. There is no evidence of daytime or nocturnal hypoventilation.

D. The disorder is not better explained by another current sleep disorder, medical or neurologic disorder, medication use, or substance use disorder.

Notes

1. In children, daytime symptoms may not be evident.
2. As defined by the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events.

Essential Features

Primary CSA is of unknown etiology (idiopathic) and is characterized by recurrent central apneas, defined as a cessation of airflow during sleep associated with an absence of respiratory effort. Airflow and respiratory effort cease simultaneously in a repetitive

fashion over the course of the night. This recurrent cessation and resumption of ventilation can lead to sleep fragmentation, yielding excessive daytime sleepiness, frequent nocturnal awakenings, or both. Thus, patients may present with symptoms of hypersomnolence or insomnia. Patients with primary CSA tend to have low normal arterial $PaCO_2$ during wakefulness (less than 40 mm Hg). Patients with a known medical or neurological disorder that is believed to cause central apneas are classified elsewhere.

Associated Features

Patients generally present with excessive daytime sleepiness, sleep fragmentation, or insomnia. Other signs and symptoms that are often, but not invariably, present include snoring, witnessed apnea, and awakening with shortness of breath.

Clinical and Pathophysiological Subtypes

The disorder is rare, precluding identification of any definite subtypes.

Demographics

Not known. Most studies suggest this disorder is rare, most common in middle-aged to elderly individuals, and more frequent in men than women, although not all studies support this sex bias.

Predisposing and Precipitating Factors

CSA in these patients occurs because the arterial PCO_2 ($PaCO_2$) drops below the hypocapnic apnea threshold (HAT). During wakefulness, drops in $PaCO_2$ do not result in apnea. However, during sleep, when the $PaCO_2$ drops below the HAT, respiratory effort ceases. For most patients, the HAT is within a few mm Hg of the awake $PaCO_2$. Any factors that narrow the gap between the sleeping $PaCO_2$ and the HAT predispose to central apnea. A high ventilatory response to CO_2 seems to be a major predisposing factor in the development of primary CSA. This can lead to the instability in ventilatory control that characterizes the disorder. Frequent arousal from sleep can also predispose to the development of central apneas, as ventilatory control is somewhat unstable at sleep-wake transitions. Increased ventilation associated with arousal can result in a $PaCO_2$ below the HAT after the return to sleep. Because ventilatory drive is lower during REM than NREM sleep, hypocapnic central apnea is much less common during that sleep stage. Two other variables have been discussed as possible predisposing factors, although their true role in the development of this syndrome is uncertain. First, frequent arousal or awakening due to low arousal threshold or sleep maintenance insomnia have been reported to lead to an increase in central apneas. Because ventilatory control can be somewhat unstable in the normal wake-sleep transition with occasional central apneas being observed in otherwise normal individuals, any disorder

that interrupts sleep may worsen CSA. Some studies have suggested a worsening of primary CSA in the supine position, but this has been more clearly documented in patients with CSB.

Familial Patterns

Some data suggest that ventilatory chemoresponsiveness is directly inherited. Because elevated CO_2 responsiveness is a predisposing variable in the development of idiopathic CSA, it would seem likely that there would be a familial pattern in the development of this respiratory abnormality. However, there are no data addressing this issue.

Onset, Course, and Complications

Not known. The apneas can lead to sleep fragmentation, yielding either hypersomnolence or insomnia. There is little evidence that these apneas or their associated hypoxia and hypercapnia lead to pulmonary hypertension, cor pulmonale, or other adverse cardiovascular consequences.

Developmental Issues

Criteria for apnea of infancy and apnea of prematurity are detailed elsewhere and it should be noted that central apnea is defined somewhat differently in infants and children than in adults. Central apneas that are brief (< 20 seconds in duration) and not associated with desaturation or arousal are commonly observed in both premature and term infants.

In adults, population studies report an increase in the occurrence of central apnea with increasing age, especially in men.

Pathology and Pathophysiology

Primary CSA is caused by instability of the respiratory control system in the transition from wakefulness to sleep and less commonly during stable NREM sleep. Central apnea in patients with primary CSA most often occurs during stages N1 and N2 sleep and is rare during stages N3 and R sleep. Central apneas tend to occur in individuals with a high or increased ventilatory responsiveness to CO_2. Arterial PCO_2 levels below the hypocapnic apnea threshold lead to a cessation in ventilatory effort and, therefore, a central apnea. Individuals with high CO_2 ventilatory responsiveness tend to have lower $PaCO_2$ levels (both daytime and sleep) and a lower gradient between the sleeping $PaCO_2$ and the apneic threshold. Hence, a smaller increase in ventilation is required to reach this apnea threshold and inhibit ventilation. Individuals with high chemoresponsiveness also hyperventilate more in response to small changes in arterial $PaCO_2$. This again often drives the $PaCO_2$ below the apnea threshold, yielding a cessation

of ventilation. However, not all factors that cause greater ventilatory drive have the same effect. Studies suggest that although hypoxemia increases chemoresponsiveness to $PaCO_2$, the gap between the $PaCO_2$ and the apneic threshold is smaller (predisposing to central apnea). Metabolic acidosis and nonhypoxic chemoreceptor stimulants tend to decrease HAT more than they decrease the sleeping $PaCO_2$, resulting in a larger gap between the HAT and the sleeping $PaCO_2$ and lower likelihood of central apnea. Metabolic alkalosis tends to increase HAT as well as decrease ventilatory responsiveness, yielding a smaller gap between the HAT and sleeping $PaCO_2$.

Objective Findings

The PSG of the patient with primary CSA demonstrates more than five central apneas and/or central hypopneas per hour of sleep. The central apneas and central hypopneas meet criteria for these respiratory events in adults or children as defined by the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events. Published studies of patients with primary CSA have required that > 50% to 85% of respiratory events be central apneas. Periodic breathing characterized by episodes of recurrent central apneas separated by periods of ventilation may occur. The interevent respiratory phase is typically brief with a maximum of five breaths. The ventilatory phase between central apneas does not have the crescendo-decrescendo pattern of CSB breathing. Central apneas commonly lead to mild arterial oxygen desaturation, although more severe desaturation can occur. Central apneas may also lead to arousal from sleep, causing fragmentation and yielding increased stages N1 and N2 sleep at the expense of stage N3 sleep. As noted above, central apneas in these patients are less common during REM sleep. In summary, respiration, arterial oxygenation, and sleep architecture are affected by this disorder. Additionally, an arterial $PaCO_2$ less than 40 mm Hg is typically observed during wakefulness. These patients do not exhibit sleep related hypoventilation.

Differential Diagnosis

Normal individuals may have a few central apneas in the wake-sleep transition. However, once stable sleep is achieved, these apneas should cease. Normal individuals should not have more than five central apneas per hour of sleep.

Primary CSA must be distinguished from other sleep related breathing disorders. Some patients with predominantly *OSA* will have central apneas during diagnostic or positive airway pressure titration studies. These apneas tend to resolve immediately or over time on positive airway pressure treatment. The pattern of central apneas in primary CSA differs from that of *CSA with CSB*. Primary CSA lacks the crescendo-decrescendo pattern of respiration between contiguous central apneas noted in patients with CSA

with CSB. The cycle length is longer in CSB (greater than 40 seconds and typically 45 to 90 seconds). The longer cycle length in CSB versus primary CSA is due to a longer respiratory phase between central apneas. In primary CSA, the apnea is often terminated abruptly by a large breath, and there are usually no more that 4 to 5 breaths between apneas. Furthermore, most patients with Cheyne-Stokes respiration will have a history of congestive heart failure or a neurological disorder. Patients with *central apnea due to substance use*, particularly potent long-acting narcotics, may exhibit periodic breathing with central apneas, but the pattern of ventilation between apneas does not have a crescendo-decrescendo pattern and the cycle length is shorter than 40 seconds. In addition, the underlying pattern of breathing is often ataxic (irregular variations in cycle length and tidal volume) and a low respiratory rate may be noted. Unlike primary CSA, central apneas can occur during stage N3 in patients taking opioids. Patients with *CSA due to medical or neurological conditions* not of the Cheyne-Stokes pattern often have a history of a known neurological disorder (recent cerebrovascular accident) but in others a high index of suspicion for an underlying disorder is indicated. For example, patients with Chiari malformation may present in adulthood with unexplained central apneas and relatively few other symptoms. Thus, primary CSA is a diagnosis based on careful exclusion of other causes of CSA.

In *sleep related hypoventilation and hypoxemic syndromes*, patients have normal or increased daytime arterial PCO_2 ($PaCO_2$) with the onset or worsening of hypoventilation during sleep. Daytime hypoventilation is defined as a $PaCO_2 > 45$ mm Hg. Patient with primary CSA usually have an awake $PaCO_2 < 40$ mm Hg. The causes of sleep related hypoventilation include abnormalities in ventilatory control, neuromuscular disease, parenchymal lung disease, or restrictive chest wall disorders. PSG in these patients may reveal a few central apneas, but the predominant pattern is one of reduced tidal volume (shallow pattern of breathing), often without a compensatory increase in respiratory rate. There is usually significant oxygen desaturation secondary to hypoventilation and/or ventilation perfusion mismatch. Patients with parenchymal lung disease, neuromuscular disease, or chest wall disorders typically have abnormal pulmonary function tests and the most severe arterial oxygen desaturation typically occurs during REM sleep.

Unresolved Issues and Further Directions

Although primary CSA is believed to be a relatively rare disorder, additional prevalence data are needed. The pathophysiology of this disorder remains unclear. Specifically, the relative roles of instability in sleep state (low arousal threshold, delayed transition from wake to stable sleep) and respiratory control instability (elevated hypercapnic ventilatory response) require further elucidation.

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Primary Central Sleep Apnea of Infancy

ICD-9-CM code: 770.81 ICD-10-CM code: P28.3

Alternate Names

Infant sleep apnea, apnea of infancy, primary sleep apnea of the newborn.

Inappropriate terms for primary central sleep apnea of the newborn include near-miss sudden infant death syndrome (SIDS), near-SIDS, aborted SIDS, and aborted crib death; these terms imply a causal relationship between apnea and SIDS that is not supported by extensive research. Likewise, the term “apparent life-threatening event (ALTE)” should not be used. Although some infants with primary sleep apnea present with an ALTE, there are many other causes of ALTE, and some children with sleep apnea do not have ALTE.

Diagnostic Criteria

Criteria A-D must be met

A. Apnea or cyanosis is noted by an observer or an episode of sleep related central apnea or desaturation is detected by monitoring.
B. The infant has a conceptional age of at least 37 weeks.

C. PSG or alternative monitoring such as hospital or home apnea monitoring shows either:
   1. Recurrent, prolonged (> 20 seconds duration) central apneas.[1]
   2. Periodic breathing[2] for ≥ 5% of total sleep time.

D. The disorder is not better explained by another sleep disorder, medical or neurological disorder, or medication.

Notes

1. Normative data concerning the number of prolonged central apneas per hour are not well established.
2. As defined by the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events.
3. Short (< 20 seconds) central apneas associated with significant desaturation are more likely to be a sign of decreased pulmonary reserve than of central nervous system pathology.
4. Definitive determination of the central nature of apneas requires simultaneous monitoring of airflow and respiratory effort. Obstructive and mixed apneas may also be present, but central apneas are predominant.

Essential Features

Primary CSA of infancy is characterized by prolonged, predominantly central apneas in children of at least 37 weeks conceptional age. These events are typically associated with physiological compromise (hypoxemia, bradycardia), or the need for intervention such as stimulation or resuscitation. Obstructive and/or mixed apneas or hypopneas may also be seen, although central events are the predominant finding. It is a disorder of respiratory control that can be either a developmental problem associated with immaturity of the brainstem respiratory centers or secondary to other medical conditions that produce apnea by mechanisms such as direct depression of central respiratory control. Apnea in the neonate or infant may be exacerbated or precipitated by a variety of medical conditions, such as anemia, infection, hypoxemia, metabolic disturbances, gastroesophageal reflux, substances, or anesthesia, which must be recognized and treated to stabilize the apnea. If another medical condition appears to be the cause rather than an exacerbating factor for the CSA, then the condition should be classified as CSA due to a medical or neurological condition, or CSA due to a medication or substance.

Despite the heterogeneity of infant risk groups and underlying pathophysiology, most studies report a progressive decrease in frequency of apneas and risk of symptomatic apnea secondary to other medical conditions after the early weeks of life.

Associated Features

Infants may present with an ALTE (defined by a National Institutes of Health Development Conference as "an episode that is frightening to the observer, and that is characterized by some combination of apnea [central or occasionally obstructive], color change, marked change in muscle tone, choking or gagging. In some cases, the observer fears that the infant has died"). Many infants with primary CSA of infancy will not have an ALTE, and many ALTEs are not associated with apnea. Primary CSA of infancy is state dependent, and the frequency of respiratory events increases during active (REM) sleep. Paradoxical chest wall movements are common during active sleep in infants and may cause a fall in arterial oxygen saturation because of ventilation or perfusion defects associated with a decrease in functional residual capacity. Underlying comorbidities (for example, chronic lung disease or abnormal neurological status) can predispose the infant to having a more severe or prolonged course for apnea. Note that a small upper airway will exaggerate the obstructive elements of this disorder.

Clinical and Pathophysiological Subtypes

Not applicable.

Demographics

Less than 0.5% of full-term newborns experience symptomatic apnea. Studies have shown that during the first six months of life, 2% of healthy full-term infants will experience at least one apnea event lasting 30 seconds or longer or an apnea that lasts at least 20 seconds and is associated with a heart rate less than 60 beats per minute. Apnea of infancy occurs equally in males and females, and in infants of all races and ethnic groups.

Predisposing and Precipitating Factors

Many factors may precipitate apneic episodes, including gastroesophageal reflux, intracranial pathology, substances, anesthesia, metabolic disorders, impaired oxygenation, and infection (including sepsis, meningitis, respiratory syncytial virus infections, and pertussis). Infection with respiratory syncytial virus, in particular, can increase the frequency and the duration of apneas.

Familial Patterns

None known.

Onset, Course, and Complications

Onset is usually in the first weeks or months of life. Some infants may be diagnosed by nursing observations or routine monitoring soon after birth. Older infants may present

with an ALTE or may have failure to thrive. The prognosis is generally good, with resolution of apnea over the first few years of life and no residual sequelae. The presence of persistent severe apnea may be an indication of an underlying medical condition and should prompt further evaluation. Patients with persistent severe apnea may develop sequelae related to hypoxic events.

Developmental Issues

This is a condition of infancy that normally improves over time.

Pathology and Pathophysiology

Physiological factors contributing to apnea are related to immaturity of respiratory control. These include developmental alterations in central drive, chemoreceptor or mechanoreceptor responses, and upper airway reflexes. Precipitating factors for worsening apnea include gastroesophageal reflux, intracranial pathology, substances, anesthesia, metabolic disturbances, impaired oxygenation, and infection.

Objective Findings

Apnea is predominantly central, but obstructive and mixed apneas may occur. Apneas are seen most frequently during REM sleep. Other diagnostic tests, such as a full EEG or evaluation for reflux, may be appropriate in individual cases.

Differential Diagnosis

Primary CSA of infancy should be distinguished from the *normal respiratory pauses* that occur during sleep. Normative respiratory data from several large studies show that healthy asymptomatic infants commonly have central respiratory pauses, either as isolated events (particularly during REM sleep) or after sigh breaths or movements.

Primary CSA of infancy should be distinguished from the popular clinical term, *ALTE*, which is not a specific diagnosis but an ill-defined constellation of parent-reported apnea symptoms that range in severity from benign to life threatening.

Recurrent, severe infant sleep apnea is usually due to other comorbid conditions, such as gastroesophageal reflux, metabolic disease, or unrecognized neurological conditions such as seizures, brainstem malformation, or neurodegenerative condition; thus an evaluation for these conditions should be performed. Another diagnostic consideration is a form of child abuse (*Munchausen syndrome by proxy*) manifest as imposed upper airway obstruction or attempted suffocation. Primary CSA of infancy should be disassociated from the postmortem diagnosis of *SIDS*. Although a small percentage of SIDS victims experience apnea symptoms prior to death,

primary apnea in the newborn or infant has not been established as an independent risk factor for SIDS.

Unresolved Issues and Further Directions

Infancy is a developmental period normally characterized by instability of control of breathing; thus, defining what is abnormal is a diagnostic challenge. Further research is needed into the mechanisms of ventilatory control development in the infant and the pathophysiologic factors resulting in infant apnea.

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Primary Central Sleep Apnea of Prematurity

ICD-9-CM code: 770.82 ICD-10-CM code: P28.4

Alternate Names

Apnea of prematurity.

Diagnostic Criteria

Criteria A-D must be met

A. Apnea or cyanosis is noted by an observer, or an episode of sleep related central apnea, desaturation, or bradycardia is detected by hospital monitoring in the postnatal period.
B. The infant has a conceptional age less than 37 weeks at the time of onset of symptoms.
C. PSG or alternative monitoring such as hospital or home apnea monitoring shows either:
    1. Recurrent prolonged (> 20 seconds duration) central apneas.[1]
    2. Periodic breathing[2] for ≥ 5% of total sleep time.

D. The disorder is not better explained by another sleep disorder, medical or neurological disorder, or medication.

Notes

1. Normative data concerning the number of prolonged central apneas per hour are not well established.
2. As defined by the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events.
3. Short (< 20 seconds) central apneas associated with significant desaturation are more likely to be a sign of decreased pulmonary reserve than of central nervous system pathology.
4. Obstructive and mixed apneas may also be present, but central apneas are predominant.

Essential Features

Apnea is very common in preterm infants, and the prevalence varies inversely with gestational age. In the preterm infant, sleep apnea can be anticipated, is primarily related to immaturity, and may require supportive ventilatory and pharmacologic treatment. The condition will improve with maturation unless extenuating conditions, such as hypoxemia due to chronic lung disease or gastroesophageal reflux, are present. Apneas are predominantly central, but mixed or obstructive apneas or hypopneas may be seen. The events are typically associated with physiological compromise (hypoxemia, bradycardia) or the need for intervention such as stimulation or resuscitation.

Associated Features

Apnea in the preterm infant is commonly associated with bradycardia. Primary CSA of prematurity is state dependent, and the frequency of respiratory events increases during active (REM) sleep. Paradoxical chest wall movements are common during active sleep in neonates and may cause a fall in arterial oxygen saturation because of ventilation or perfusion defects associated with a decrease in functional residual capacity. Underlying comorbidities (for example, chronic lung disease or abnormal neurological status) can predispose the infant to having a more severe or prolonged course for apnea. Note that a small upper airway will exaggerate the obstructive elements of this disorder.

Clinical and Pathophysiological Subtypes

None known.

Demographics

The prevalence of apnea of prematurity varies inversely with conceptional age. In studies, approximately 25% percent of infants who weigh less than 2,500 g at birth and 84% of infants under 1,000 g may experience symptomatic apnea during the neonatal period. Ninety-two percent of preterm infants will be symptom free by 37 weeks postconceptional age, and 98% by 40 weeks after conception, with resolution in most infants by 43 weeks postconception. Apnea of prematurity occurs equally in males and females, and in infants of all races and ethnic groups.

Predisposing and Precipitating Factors

Developmental delay in respiratory control associated with premature birth is the major predisposing condition. Diverse factors are known to precipitate development of apneic episodes in predisposed preterm infants. These include thermal instability, gastroesophageal reflux, intracranial pathology, substances, anesthesia, metabolic disorders, impaired oxygenation, and infection. Infection with respiratory syncytial virus can increase the frequency and the duration of apneas in predisposed infants. OSA associated with upper airway abnormalities can present as apnea of prematurity. Persistence of apnea after 43 weeks conceptional age should raise suspicion of additional etiologic factors.

Familial Patterns

None known.

Onset, Course, and Complications

In preterm infants, apnea is rare on day one of life, and its presence usually signals another illness. More typical onset occurs between the second and seventh days. Apnea of prematurity usually ceases by 37 weeks conceptional age but may persist for several weeks beyond term, especially in infants born before 28 weeks postconception; apnea beyond 43 weeks postconception is rare. Adverse outcomes for former preterm infants are more closely related to the prenatal or neonatal course, associated comorbidities, and environmental factors than to the apnea of prematurity per se. For most children, long-term outcomes for uncomplicated apnea of prematurity are excellent. However, the prognosis for infants with persistent recurrent apnea spells requiring frequent resuscitation is more guarded and depends on the cause of the apnea and associated comorbidities.

Developmental Issues

This is a condition related to prematurity that normally improves over time.

Pathology and Pathophysiology

Physiological factors contributing to apnea are related to immaturity of respiratory control. These include developmental alterations in central drive, chemoreceptor or mechanoreceptor responses, and upper airway reflexes. Precipitating factors for worsening apnea in preterm infants include thermal instability, gastroesophageal reflux, intracranial pathology, substances, anesthesia, metabolic disturbances, impaired oxygenation, and infection.

Objective Findings

Most premature neonates are diagnosed with apnea of prematurity based on cardiorespiratory monitoring in the neonatal intensive care unit, rather than by PSG. When PSG is performed, central apneas are often shown to have a mixed component, with mixed apneas accounting for 50% to 75% of apneas in small premature infants; studies suggest that obstructive-type events account for 10% to 20% of events; and pure central events, 10% to 25%. Periodic breathing may be present.

Differential Diagnosis

Apnea of prematurity should be distinguished from *normal, physiologic respiratory pauses* that occur during sleep in infants. Studies have shown that healthy asymptomatic infants commonly have brief (< 20 second) central respiratory pauses, either as isolated events (particularly during REM sleep) or after sigh breaths or movements (in which case the apneas may be longer). These infants are typically asymptomatic, with no changes in color or muscle tone.

The differential diagnosis is long and includes *apnea secondary to severe gastroesophageal reflux*, *central nervous system malformations or hemorrhage*, *seizures*, *sepsis*, and rarely *primary cardiac arrhythmias*. Comorbid conditions should be suspected whenever apneas are severe or continue beyond 43 weeks gestation.

Unresolved Issues and Further Directions

The mechanisms underlying physiologic maturation of ventilatory control are not well understood. Further research is required to determine which infants are at greatest risk for severe apnea.

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Treatment-Emergent Central Sleep Apnea

ICD-9-CM code: 327.29 ICD-10-CM code: G47.39

Alternate names

Complex sleep apnea.

Diagnostic Criteria

Criteria A-C must be met

A. Diagnostic PSG shows five or more predominantly obstructive respiratory events[1] (obstructive or mixed apneas, hypopneas or RERAs) per hour of sleep

B. PSG during use of positive airway pressure without a backup rate shows significant resolution of obstructive events and emergence or persistence of central apnea or central hypopnea with all of the following:
   1. Central apnea—central hypopnea index [CAHI] ≥ 5/hour.
   2. Number of central apneas and central hypopneas is ≥ 50% of total number of apneas and hypopneas.

C. The central sleep apnea is not better explained by another CSA disorder (e.g., CSA with CSB or CSA due to a medication or substance).

Notes

1. Respiratory events defined according the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events.
2. A diagnosis of treatment-emergent central sleep apnea does not exclude a diagnosis of OSA. That is, a diagnosis of OSA can be made based on the diagnostic sleep study.

Essential Features

A diagnosis of treatment-emergent CSA is characterized by predominantly obstructive events (obstructive or mixed apnea or hypopnea) during a diagnostic sleep study with persistence or emergence of CSA during administration of positive airway pressure without a backup rate, despite significant resolution of obstructive respiratory events. If the central apnea is better explained by another CSA disorder, patients are given a diagnosis of OSA and that CSA disorder rather than treatment-emergent CSA (e.g., a patient with heart failure exhibits mainly obstructive events during diagnostic PSG but then exhibits predominantly central apnea with CSB on positive airway pressure).

Associated Features

Patients with treatment-emergent CSA have several characteristics when placed on positive airway pressure without a backup rate. A high number of arousals persist on PAP treatment, and the AHI is often higher during NREM than REM sleep. This is due to the fact that treatment-emergent central apneas almost invariably occur during NREM sleep. Pressures that are effective in controlling obstructive events during REM sleep prove ineffective during NREM sleep due to emergence of central apneas. If patients can attain stage N3, central apneas often decrease until interrupted by an arousal or transition to a lighter stage of sleep that precipitates another run of central apneas or hypopneas. Patients with treatment-emergent CSA can have persistent sleep fragmentation on CPAP treatment and may report little benefit from therapy.

Clinical and Pathophysiological Subtypes

None known.

Demographics

The percentage of patients with persistent or emergent central apnea on the initial polysomnographic positive airway pressure titration varies from 2% to 20% depending on the characteristics of the group studied (community or referral sleep center) and the methodology. If patients who are taking opioids or have underling central apnea with CSB are included, the percentage is at the higher end of the range. The percentage of patients with central sleep apnea that persists on chronic CPAP treatment (approximately 2%) is considerably lower than the percentage identified on the first or second night of CPAP treatment.

Predisposing and Precipitating Factors

A number of factors have been hypothesized to cause treatment-emergent CSA, but definitive data are not available. The patients presumably have characteristics that would predispose them to instability in ventilatory control or sleep maintenance.

These include a low arousal threshold and high ventilatory controller gain. Studies have found that often a small increase in end-tidal PCO_2 can stabilize breathing in patients with treatment-emergent central apneas. Therefore, any events that predispose a patient to hypocapnia can trigger treatment-emergent central apnea. In some, but not all studies, the overall AHI on the diagnostic PSG (or diagnostic portion of a split-night PSG) was higher in the treatment-emergent CSA group compared to the patients without this diagnosis. In other studies, patients with treatment-emergent CSA had more central apneas during the diagnostic PSG and were more likely to be male. However, identified risk factors for treatment-emergent CSA vary considerably from study to study.

Of note, the emergence of central apnea after treatment of obstructive apnea with tracheostomy, maxillomandibular advancement, and oral appliance treatment for OSA has been reported. A case report of the development of central apnea following nasal surgery in a patient with known obstructive apnea has also recently been published.

Familial Patterns

None known.

Onset, Course, and Complications

The recognition of treatment-emergent CSA follows PAP titration. An accurate estimate of the percentage of patients with treatment-emergent central apneas whose central events persist on long-term PAP treatment does not exist, as most published reports are retrospective and had a significant number of patients lost to follow-up. Of interest, one study comparing the results of an initial CPAP titration study with one performed after six months of therapy found patients who did not meet criteria for treatment-emergent CSA on the initial study but met the criteria on the second study. Those patients with treatment-emergent CSA that do not experience resolution of central apneas on chronic PAP treatment are found to have a high number of residual events on PAP machine interrogation in clinic follow-up. Nocturnal oximetry at home on PAP treatment may show persistent arterial oxygen desaturation. Sleep fragmentation and daytime sleepiness may persist if a significant number of central apneas remain. There is the potential for poor adherence and acceptance of PAP treatment as a result of this.

Developmental Issues

Treatment-emergent sleep apnea has not been described in children but this may be due to the relatively small number of children with OSA who are treated with PAP.

Pathology and Pathophysiology

Due to variation in definitions of treatment-emergent CSA, the pathophysiology is not clearly defined. A low arousal threshold and difficulty reaching stage N3 sleep may predispose to sleep instability. Arousals destabilize breathing. A high ventilatory response to $PaCO_2$ and a small difference between the sleeping $PaCO_2$ and the apnea threshold may also predispose patients to treatment-emergent central apneas. Treatment with excessive positive airway pressure may trigger treatment-emergent central apneas in susceptible individuals.

Objective Findings

PSG during a full night diagnostic study (or diagnostic portion of a split-night PSG) shows predominantly obstructive or mixed apneas and hypopneas of five or more per hour of sleep. PSG with PAP (either a full night titration study or PAP treatment portion of a split night study) without a backup rate shows significant resolution of obstructive events and emergence or persistence of central apneas or central hypopneas. The CAHI is five or greater per hour, and more than 50% of the respiratory events are central in nature. A diagnosis of treatment-emergent CSA excludes patients who manifest central sleep apnea on PAP treatment when the CSA is better explained by another CSA disorder or by over-titration.

PSG with administration of PAP often reveals adequate treatment during REM sleep and stage N3 sleep but repetitive episodes of central events during stages N1 and N2. In some patients, progressive increases in pressure with a goal of preventing airflow limitation reach a “break point” at which central apneas appear.

Differential Diagnosis

Many patients with *OSA* have a few central events while on PAP. However, in the majority of cases, the central AHI is not ≥ 5/hour and central events are not ≥ 50% of the total number of apneas and hypopneas. Other patients with OSA, while on PAP, exhibit predominantly central events that are believed to be secondary to a CSA disorder classified elsewhere. In this case, a diagnosis of both OSA and the CSA disorder is appropriate, rather than a diagnosis of treatment-emergent CSA. For example, a patient taking methadone has predominantly obstructive events during the diagnostic portion of a split-night PSG. Once obstructive events are eliminated on PAP, CSA with ataxic breathing is noted. A diagnosis of both OSA and *CSA due to a medication or substance* should be made if criteria for that disorder are met.

Unresolved Issues and Further Directions

The true incidence of treatment-emergent sleep apnea as well as the percentage of patients who have persistent central apnea on chronic PAP treatment remains to be defined. Further prospective studies with clearly defined inclusion and exclusion criteria are needed to better define the exact percentage of patients with treatment-emergent CSA who have persistent CSA after chronic PAP treatment. There may be night-to-night variability in the amount of CSA displayed by a given patient. It is unknown, for example, whether treatment-emergent central apneas that resolve on chronic PAP treatment will re-emerge if the patient discontinues PAP treatment for a period of time and then restarts treatment. A number of factors have been hypothesized to increase the likelihood of treatment-emergent central apneas including overtitration (excessive pressure), undertitration (respiratory effort arousals followed by central apnea), the use of bilevel PAP rather than CPAP, arousals from mask leak, and use of a split night study. Further study is needed to verify that these factors do indeed predispose a patient to develop treatment-emergent central apneas. The evolution of treatment-emergent central apneas on chronic PAP treatment also remains to be determined; that is, to what extent do central events resolve over time and what is the time course of this resolution? In light of the increasing utilization of auto-titrating PAP, further investigation of the incidence of treatment-emergent CSA with this modality is indicated.

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Sleep Related Hypoventilation Disorders

The primary feature of these disorders is insufficient sleep related ventilation, resulting in abnormally elevated arterial partial pressure of carbon dioxide ($PaCO_2$) during sleep. In addition, demonstration of daytime hypoventilation is required for a diagnosis of obesity hypoventilation syndrome (OHS). Awake hypoventilation is defined as an arterial partial pressure of carbon dioxide ($PaCO_2$) greater than 45 mm Hg. In the sleep related hypoventilation disorders other than OHS, daytime hypoventilation may or may not be present. If hypoventilation is present during wakefulness, it worsens during sleep in all of these disorders.

General Criteria Sleep Related Hypoventilation

Criterion A must be met

A. Sleep related hypoventilation, as defined by the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events, is present.[1,2]

Notes

1. Monitoring of arterial PCO_2 during sleep is not practical. Acceptable surrogates include end-tidal PCO_2 or transcutaneous PCO_2.
2. Arterial oxygen desaturation is often present but is not required for the diagnosis.

Obesity Hypoventilation Syndrome

ICD-9-CM code: 278.03 ICD-10-CM code: E66.2

Alternate Names

Hypercapnic sleep apnea, sleep related hypoventilation associated with obesity.

Use of the term Pickwickian syndrome is discouraged because not only has it been applied to those with OSA, but also indiscriminately used to describe persons who are only obese and those with OHS.

Diagnostic Criteria

Criteria A-C must be met

A. Presence of hypoventilation during wakefulness ($PaCO_2$ > 45 mm Hg) as measured by arterial PCO_2, end-tidal PCO_2, or transcutaneous PCO_2.
B. Presence of obesity (BMI > 30 kg/m^2; > 95th percentile for age and sex for children).

C. Hypoventilation is not primarily due to lung parenchymal or airway disease, pulmonary vascular pathology, chest wall disorder (other than mass loading from obesity), medication use, neurologic disorder, muscle weakness, or a known congenital or idiopathic central alveolar hypoventilation syndrome.

Notes

1. PSG shows worsening of hypoventilation during sleep if $PaCO_2$ or noninvasive estimate of the $PaCO_2$ is measured.
2. OSA is often present and, in such cases, a diagnosis of both OSA and OHS should be made.
3. Arterial oxygen desaturation is usually present but is not required for the diagnosis.

Essential Features

OHS is characterized by obesity and daytime hypercapnia (arterial $PaCO_2 > 45$ mm Hg) that cannot be fully attributed to an underlying cardiopulmonary or neurologic disease. Hypercapnia worsens during sleep and is often associated with severe arterial oxygen desaturation. Hypoventilation is often worse during REM than during NREM sleep. The majority of OHS patients have comorbid OSA (80% to 90%). In these patients, daytime hypercapnia may improve or even normalize with adequate PAP treatment and sustained adherence to treatment. Those OHS patients without OSA exhibit sustained or intermittent episodes of shallow breathing during sleep associated with worsening hypoventilation and hypoxemia. Patients with OHS may have few, if any, sleep complaints, or may present with considerable sleep disturbance including reduced sleep efficiency and frequent awakenings. Hypercapnia and hypoxemia may remain unnoticed for quite some time until sudden deterioration with cardiopulmonary arrest or severe decompensation (acute or chronic hypercapnic respiratory failure) develops.

Associated Features

Patients with OHS commonly complain of hypersomnolence. The severity of hypersomnolence may not correlate closely with degree of hypercapnia. Other symptoms include morning headaches, fatigue, mood disturbance and impairments of memory or concentration. Physical examination may reveal features suggestive of cor pulmonale or circulatory congestion, such as plethora, scleral injection, and peripheral edema. Laboratory testing commonly shows polycythemia and elevated serum CO_2 on electrolyte testing ($\approx$ serum bicarbonate), reduced forced vital capacity during pulmonary function testing, right heart strain, right ventricular hypertrophy and right atrial enlargement on electrocardiography and ventricular dysfunction on echocardiography.

Consequences of chronic hypercapnia and hypoxemia include pulmonary artery hypertension, cor pulmonale, and neurocognitive dysfunction.

Clinical and Pathophysiological Subtypes

Not applicable or known.

Demographics

OHS may be underdiagnosed if CO_2 analysis (≈ serum bicarbonate) is not performed in obese patients presenting with complaints suggestive of OHS. The prevalence of OHS in populations of patients with OSA varies across studies but is often in the range of 10% to 15% of obese patients with OSA. Although the prevalence of OHS is higher in men than women the difference is not as prominent as in OSA.

Predisposing and Precipitating Factors

Obesity is believed to be the primary pathophysiologic factor responsible for hypoventilation and hypoxemia. Greater degrees of obesity are often associated with worse sleep related hypoventilation, but individual variations in the severity of hypercapnia at similar weights may be seen. The use of central nervous system depressants, such as alcohol, anxiolytics, and hypnotics, may further worsen respiratory impairment. Patients who are hypercapnic and hypoxemic during wakefulness will invariably become even more so during sleep, in particular REM sleep, but the relationship between wake $SaO_2/PaCO_2$ and sleep related desaturation is not sufficiently strong to have substantial predictive value in individual patients.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

Persons who are eventually diagnosed with OHS either present initially for evaluation of suspected OSA or are identified following one or more episodes of severe hypercapnic respiratory failure. The course can be variable but is generally slowly progressive. Many affected individuals with severe hypercapnia and hypoxemia develop pulmonary hypertension, heart failure, cardiac arrhythmias, and neurocognitive dysfunction. Polycythemia is common in those with chronic hypoxia. Although the risk of increased morbidity and mortality appears to increase with worsening sleep related hypoventilation/hypoxemia, the specific relationship between sleep related hypoventilation/hypoxemia and morbidity and mortality is not well defined. Obesity, itself, can lead to other respiratory complaints, including shortness of breath, dyspnea on exertion and orthopnea, even in the absence of demonstrable elevation of daytime $PaCO_2$.

However, in one study of inpatients with obesity, those with hypoventilation had an 18-month mortality of 23% compared with 9% in the group with equivalent obesity but no hypoventilation. Many patients with OHS respond to CPAP or bilevel PAP with improvement in daytime $PaCO_2$. However, normalization of daytime $PaCO_2$ occurs in only a minority of patients. In one study, 34% of OHS patients using PAP more than 4.5 hours per night had normalization of the $PaCO_2$. In contrast hypercapnia may worsen with oxygen therapy alone for the associated hypoxia.

Developmental Issues

Not known.

Pathology and Pathophysiology

The etiology of hypoventilation is not completely understood. Although comorbid OSA is common, hypercapnia and hypoxemia are not entirely a function of upper airway obstruction. The importance of various factors leading to hypoventilation likely varies among patients. It has been postulated that sustained nocturnal hypercapnia results from the development of short (due to apnea-hypopnea) or longer (secondary to hypoventilation) periods of hypercapnia accompanied by inadequate compensation (i.e., CO_2 unloading) during periods of ventilation between obstructive events. Abnormal ventilatory control (blunted hypercapnic ventilatory response) allows hypercapnia to persist into wakefulness after the cause of acute hypercapnia is no longer present. A chronic hypercapnic state would produce an elevation of bicarbonate. Although this blunts the degree of acidosis due to an elevated $PaCO_2$, it reduces the compensatory CO_2 ventilatory response. Impaired renal bicarbonate excretion rate, as seen in hypoxia, heart failure, or diuretic-related chloride deficiency, may contribute to the persistence of hypercapnia. Obesity itself is also associated with several factors that predispose to CO_2 retention. Obesity itself increases CO_2 production. There is an increased work of breathing due to mass loading from the additional weight on the respiratory pump as well as resistive loading due to intermittent upper airway obstruction during sleep. Numerous factors impair CO_2 elimination including altered lung volumes and mechanics, ventilation-perfusion abnormalities secondary to atelectasis or pulmonary congestion, reduced chemosensitivity and load responsiveness, and suppression of respiratory drive due to obesity-related humoral factors, such as resistance to the elevated leptin levels that occur in patients with the OHS (leptin is a respiratory stimulant). The importance of these factors likely varies from patient to patient.

Objective Findings

Arterial blood gas testing during wakefulness shows hypercapnia and often hypoxemia in untreated patients. Even with effective treatment most OHS patients continue to

exhibit some degree of daytime hypoventilation. The characteristic polysomnographic finding is sleep related hypoventilation and arterial oxygen desaturation during sleep with or without obstructive apneas and hypopneas. Worsening hypoventilation during sleep can be documented by an arterial blood gas measurement of $PaCO_2$ during sleep (rarely performed) or transcutaneous or end-tidal PCO_2 measurements. Periods of decreased tidal volume lasting up to several minutes with sustained arterial oxygen desaturation are usually present. Intermittent arousals may be observed. OSA is present in the majority of OHS patients, during at least a portion of the night. The transient ventilation between obstructive events (even if associated with arousal from the preceding obstructive event) is not sufficient to prevent worsening hypoventilation during sleep. Severe arterial oxygen desaturation is usually associated with the obstructive events. Chronic hypoxia can be associated with polycythemia. Electrocardiography, chest radiography, and echocardiography may demonstrate evidence of pulmonary hypertension.

The serum bicarbonate level is usually elevated due to renal compensation for chronic respiratory acidosis (hypercapnia). In one study, a serum bicarbonate level threshold > 27 mEq/L had a sensitivity of 92% and a specificity of 50% of identifying OHS in obese patients suspected of having OSA. This suggests that the serum bicarbonate level may be useful to screen patients for possible OHS. However, an arterial blood gas is required for diagnosis of OHS, as the serum bicarbonate level may be elevated due to metabolic alkalosis.

Differential Diagnosis

The differential diagnosis includes any disorder that can give rise to hypoventilation during wakefulness and sleep. This includes *pulmonary airway and parenchymal disorders*, *pulmonary vascular pathology*, *neuromuscular and chest wall disorders*, *severe untreated hypothyroidism*, *use of respiratory suppressants*, and *congenital or idiopathic central alveolar hypoventilation syndromes*. *OSA* and *CSA syndromes* can be distinguished from sleep related hypoventilation by the periodic alterations in airflow and accompanying periodic fluctuations in SaO_2. In contrast, oxygen desaturation due to sleep related hypoventilation is generally more sustained, usually several minutes or longer in duration. When more than one disorder is believed to be responsible for the ventilatory insufficiency during sleep, all pertinent diagnoses should be coded.

Unresolved Issues and Further Directions

Future research into the pathogenesis of this disorder, including renal bicarbonate homeostasis, is needed. Because it is clinically impractical to routinely obtain arterial blood samples during sleep in most persons suspected of this disorder, other techniques of measuring CO_2 levels must be investigated. The degree and duration of hypercapnia/

hypoxemia necessary to produce adverse consequences, such as pulmonary hypertension, in individual patients is not well defined. Little information is available regarding the effect of oxygen therapy or noninvasive ventilation on the course of the underlying disease. Studies are needed to determine the optimal time to initiate these interventions and the specific subpopulations of patients who will benefit most from these therapies.

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Congenital Central Alveolar Hypoventilation Syndrome

ICD-9-CM code: 327.25 ICD-10-CM code: G47.35

Alternate Names

Congenital central hypoventilation syndrome.

The term Ondine's curse is no longer recommended due to its negative connotations.

Diagnostic Criteria

Criteria A and B must be met

A. Sleep related hypoventilation is present.
B. Mutation of the *PHOX2B* gene is present.

Notes

1. Sleep related hypoventilation may be associated with either daytime hypoventilation ($PaCO_2$ > 45 mm Hg) or normal daytime $PaCO_2$ levels.

In either case, the $PaCO_2$ is higher during sleep and meets criteria for sleep related hypoventilation.

2. PSG monitoring demonstrates severe hypercapnia and arterial oxygen desaturation. Some central apneas may occur but the predominant pattern is reduced flow/tidal volume.
3. Although the condition is termed *congenital*, some patients with a *PHOX2B* genotype may present phenotypically later in life (and even in adulthood), especially in the presence of a stressor such as general anesthesia or a severe respiratory illness.

Essential Features

Congenital central alveolar hypoventilation syndrome (CCHS) is a syndrome of autonomic dysfunction, primarily the failure of automatic central control of breathing, due to a mutation of the *PHOX2B* gene. CCHS is characterized by the onset of hypoventilation, usually at birth. The hypoventilation is worse during sleep than wakefulness and is unexplained by primary pulmonary, neurological, or metabolic disease. CCHS typically presents in an otherwise normal-appearing infant who is noted to have cyanosis, feeding difficulties, hypotonia or, less commonly, central apnea. Some children are diagnosed following cardiovascular collapse. The infant requires intubation and then cannot be weaned from mechanically assisted ventilation, despite appearing vigorous and having a normal chest radiograph. Some infants may appear to breathe adequately on clinical examination but experience episodes of hypoventilation (not necessarily apnea) characterized by hypoxemia and hypercapnia. Patients with CCHS may occasionally present later in life with cyanosis, an apparent life-threatening event, cor pulmonale, or hypoxic neurological damage. CCHS has been diagnosed in adults who present with respiratory failure following anesthesia or in association with a minor respiratory illness; these patients usually have a mild mutation, and may have evidence of longstanding hypoxemia including cognitive deficits. Most patients with CCHS have sufficiently severe hypoventilation during sleep that they require mechanically assisted ventilation, although this state-dependent difference may not be apparent during early infancy. Some patients (~15%) hypoventilate during wakefulness as well as during sleep and require continuous ventilatory support. However, most patients with CCHS do not require ventilatory support during wakefulness but may have subtle abnormalities in gas exchange when physically inactive or during vigorous exercise.

Associated Features

Associated autonomic abnormalities include Hirschsprung disease in approximately 16% of patients with CCHS, autonomic dysfunction (e.g., decreased heart rate variability or hypotension), neural tumors (e.g., ganglioneuromas or ganglioneuroblastomas),

swallowing dysfunction during the early years, and ocular abnormalities (e.g., strabismus). Most patients are cognitively normal, although developmental delay may be present, especially in patients in whom the hypoventilation has not been well controlled.

Clinical and Pathophysiological Subtypes

Research suggests that severity of illness is related to the type of mutation present. Most patients have a polyalanine expansion mutation; those with more polyalanine repeats are more likely to have severe disease including waking hypoventilation. Patients with a point mutation or frame shift mutations are at greater risk for neural tumors.

Demographics

The prevalence of CCHS is not known, but the disease is rare. The condition occurs equally among both sexes and all ethnic/racial groups.

Predisposing and Precipitating Factors

This is a congenital genetic syndrome.

Familial Patterns

CCHS usually occurs as a de novo mutation, but siblings with the condition have been reported. As the gene is dominant, patients are at risk of having children with CCHS.

Onset, Course, and Complications

The condition is genetic and is therefore present from birth, but some patients may present later in life. The physiological abnormalities of CCHS persist for life and are not ameliorated over time. However, the clinical consequences of hypoventilation can be prevented by providing adequate ventilatory support. If untreated, death usually results from cor pulmonale or complications of apnea or severe hypoventilation. Patients with poorly controlled CCHS may develop mental retardation, growth failure, seizures, or cor pulmonale. When treated, infants with CCHS may improve over the first six to 12 months. Some patients who initially require ventilatory support 24 hours a day may progress to adequate ventilation during wakefulness. However, patients continue to require ventilatory support during sleep. Conversely, some patients may develop the need for continuous ventilatory support. It is unclear whether these patients had conditions that worsened, were not adequately evaluated and treated initially, or were associated with changing ventilatory demands. Even with treatment, patients with CCHS require close monitoring, particularly during infancy. Minor medical illnesses, such as upper respiratory tract illnesses or diarrhea, may precipitate bouts of respiratory failure. Edema and lethargy are often early signs of impending respiratory failure. The clinical signs of hypoxemia and hypoventilation in these patients may be subtle, as the

children do not show signs of distress or increased work of breathing, such as retractions and nasal flaring. As a result, gas exchange abnormalities may progress for some time without notice until the child appears to deteriorate suddenly with cardiopulmonary arrest or severe decompensation.

Developmental Issues

Not applicable.

Pathology and Pathophysiology

The exact pathophysiology of CCHS is unknown. Radiologic and postmortem studies have not shown gross central nervous system abnormalities. The *PHOX2B* gene plays a role in the development of the autonomic system. Functional MRI and physiologic studies have shown widespread cerebral abnormalities in response to stimuli such as exogenous hypercapnia.

Objective Findings

Hypoxemia and hypercapnia are present on PSG during sleep. Central apneas may be present, but hypoventilation associated with decreased tidal volume and respiratory rate is more common. In contrast to most types of sleep disordered breathing in children, abnormalities may be more severe during NREM than during REM sleep. Patients may not arouse from sleep despite severe gas exchange abnormalities. Paradoxical breathing and snoring do not typically occur.

Patients with CCHS have flat rebreathing hypoxic and hypercapnic responses, although they may respond to transient ventilatory challenges of the peripheral chemoreceptors. Arterial blood gases may be normal during wakefulness but will be abnormal if obtained from an arterial line during sleep. In patients with chronically untreated or poorly controlled CCHS, a compensated respiratory acidosis may be present. In these patients, polycythemia may be present and the serum bicarbonate level may be elevated. Computed tomography and MRI scans of the head are normal. Electrocardiography, echocardiography, or cardiac catheterization may reveal evidence of pulmonary hypertension. Pulmonary function tests may be normal or show evidence of mild obstructive or restrictive lung disease resulting from associated conditions such as tracheitis.

Differential Diagnosis

CCHS must be distinguished from other forms of central hypoventilation, such as *central hypoventilation due to Chiari malformation*, *other causes of central nervous system disturbance* such as *trauma* or *tumors*, *metabolic conditions* such as *Leigh disease*, or *obesity hypoventilation syndrome*. CCHS must also be distinguished from

hypoventilation secondary to muscle weakness due to conditions such as diaphragmatic paralysis or muscular dystrophy. Infants presenting with *apnea or an apparent life-threatening event due to causes such as gastroesophageal reflux* may be thought to have CCHS. However, these infants typically have intermittent episodes of apnea rather than sustained hypoventilation, and the episodes typically resolve once the primary cause has been treated. CCHS patients presenting with cor pulmonale may be misdiagnosed as having *congenital heart disease*.

Unresolved Issues and Further Directions

There are many unresolved issues regarding CCHS, including prevalence data, precise genotype-phenotype correlations, effect of aging on patients with CCHS, long-term outcome of children with CCHS born to parents with CCHS, and the exact nature of the gene-encoded deficit.

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Late-Onset Central Hypoventilation with Hypothalamic Dysfunction

ICD-9-CM code: 327.26 ICD-10-CM code: G47.36

Alternate Names

Late-onset central hypoventilation syndrome; rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD).

Diagnostic Criteria

Criteria A-E must be met

A. Sleep related hypoventilation is present.
B. Symptoms are absent during the first few years of life.
C. The patient has at least two of the following:
    1. Obesity.
    2. Endocrine abnormalities of hypothalamic origin.
    3. Severe emotional or behavioral disturbances.
    4. Tumor of neural origin.
D. Mutation of the *PHOX2B* gene is not present.
E. The disorder is not better explained by another sleep disorder, medical or neurological disorder, medication use, or substance use disorder.

Notes

1. Central apneas may occur but the predominant pattern is reduced flow/tidal volume associated with hypoventilation and arterial oxygen desaturation.

Essential Features

Late-onset central hypoventilation with hypothalamic dysfunction is a disorder of central control of ventilation. Patients are usually healthy until early childhood (often 2-3 years of age) when they develop hyperphagia and severe obesity, followed by central hypoventilation, which often presents as respiratory failure. The respiratory failure may be precipitated by a mild respiratory illness or anesthesia. Patients require ventilatory support during sleep; most patients breathe adequately during wakefulness but some need ventilatory support during both wakefulness and sleep. The hypoventilation persists even if the patients lose weight, differentiating the condition from obesity hypoventilation syndrome. Patients often develop hypothalamic endocrine dysfunction characterized by increased or decreased hormone levels, which may include one or more of the following: diabetes insipidus, inappropriate antidiuretic hormone hypersecretion, precocious puberty, hypogonadism, hyperprolactinemia, hypothyroidism, and decreased growth hormone secretion. Mood and behavior abnormalities, sometimes

severe, have frequently been reported. Developmental delay or autism may be present, but many patients are cognitively normal. Other symptoms of hypothalamic dysfunction, such as temperature dysregulation, have been reported.

Associated Features

Tumors of neural origin such as ganglioneuroma may occur.

Clinical and Pathophysiological Subtypes

None known.

Demographics

There are no prevalence data. The disorder seems to occur equally among males and females.

Predisposing and Precipitating Factors

Unknown. Patients do not have the *PHOX2B* genetic mutation of congenital central hypoventilation syndrome.

Familial Patterns

Familial cases have not been reported.

Onset, Course, and Complications

Patients are typically normal at birth. Obesity often begins in early childhood, perhaps because the child is old enough to walk around and obtain his/her own food. Respiratory failure typically presents several years after the onset of obesity, and requires ventilatory support via face mask or tracheostomy. The respiratory failure does not improve over time. Death has been reported from respiratory failure, cor pulmonale, or hypernatremia secondary to diabetes insipidus; case series have reported a high mortality.

Developmental Issues

Not applicable.

Pathology and Pathophysiology

The cause of the disorder is not known. The brain typically appears normal on imaging or at autopsy, or may show secondary signs of hypoxemia.

Objective Findings

Hypoxemia and hypercapnia are present on PSG during sleep. Central apneas may be present, but hypoventilation associated with decreased tidal volume and respiratory rate is more common. Obstructive apneas may occur but are not the primary abnormality.

Patients have flat hypoxic and hypercapnic responses. Oxygen and carbon dioxide determinations may be normal during wakefulness but will demonstrate hypoxemia and hypercapnia during sleep. In patients with chronically untreated or poorly controlled hypoventilation, a compensated respiratory acidosis may be present, with elevated serum bicarbonate levels. In these patients, polycythemia may be present. Serum tests may show evidence of endocrine abnormalities; hypernatremia is common. Computed tomography and MRI scans of the head are normal. Electrocardiography, echocardiography, or cardiac catheterization may reveal evidence of pulmonary hypertension. Pulmonary function tests may be normal or show evidence of mild obstructive or restrictive lung disease resulting from associated conditions such as tracheitis.

Differential Diagnosis

The disorder can be distinguished from late presentation of *congenital central hypoventilation syndrome* by testing for the *PHOX2B* gene. Genetic testing may also be useful in distinguishing the disorder from *Prader-Willi syndrome*, which is characterized by a known genetic abnormality. Most children with Prader-Willi syndrome have hypotonia at birth and more severe developmental delay. The disorder can be distinguished from *obesity hypoventilation syndrome* by the presence of endocrine abnormalities and other associated hypothalamic abnormalities, and by the persistence of hypoventilation despite weight loss. In addition, the patients typically have a totally flat hypercapnic ventilatory response rather than the blunted response seen in children with obesity hypoventilation syndrome. The disorder should be distinguished from *isolated hypopituitarism or other hypothalamic disease* without hypoventilation, and from *obesity-related OSA*.

Unresolved Issues and Further Directions

The etiology of the disorder is not known. Although the disorder shares some features of congenital central hypoventilation syndrome, including the presence of neural tumors, it does not share the same gene. Little information is available on prevalence or long-term prognosis.

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Idiopathic Central Alveolar Hypoventilation

ICD-9-CM code: 327.24 ICD-10-CM code: G47.34

Alternate Names

Alveolar hypoventilation, central alveolar hypoventilation, idiopathic central alveolar hypoventilation, nonapneic alveolar hypoventilation, primary alveolar hypoventilation.

Diagnostic Criteria

Criteria A and B must be met

A. Sleep related hypoventilation is present.

B. Hypoventilation is not primarily due to lung parenchymal or airway disease, pulmonary vascular pathology, chest wall disorder, medication use, neurologic disorder, muscle weakness, or obesity or congenital hypoventilation syndromes.

Notes

1. The predominant respiratory pattern is one of reduced tidal volume or ataxic breathing with associated arterial oxygen desaturation. Although OSA may be present, it is not believed to be the major cause of hypoventilation. When criteria are met, a diagnosis of both OSA and idiopathic central alveolar hypoventilation may be made.
2. Arterial oxygen desaturation is often present but is not required for the diagnosis.

Essential Features

Idiopathic central alveolar hypoventilation is defined as the presence of decreased alveolar ventilation resulting in sleep related hypercapnia and hypoxemia in individuals with presumed normal mechanical properties of the lung and respiratory pump. Thus, chronic hypoventilation during sleep exists without any readily identifiable impairments of respiration, such as pulmonary airway or parenchymal conditions, neurologic, neuromuscular or chest wall abnormalities, severe obesity, other sleep related breathing disorder, or use of respiratory depressant medications or substances. Diurnal as well as nocturnal hypoventilation is believed to be due primarily to blunted chemoresponsiveness to CO_2 and O_2. However, reported cases are few and not studied in enough detail to conclusively establish a well-defined etiology. Alternatively, these cases may represent a mixed group of patients with varied underlying conditions erroneously deemed idiopathic as a result of incomplete diagnostic work-up. Patient may complain of morning headaches, fatigue, neurocognitive decline and sleep disturbance, or may be entirely asymptomatic. Frequent episodes of shallow breathing may be noted to occur during sleep.

Associated Features

Consequences of chronic hypercapnia and hypoxemia include pulmonary artery hypertension, cor pulmonale, and neurocognitive dysfunction. Patients with other comorbid sleep related breathing disorders are likely to experience greater severity and duration of sleep related hypoventilation than are patients with isolated idiopathic central hypoventilation.

Clinical and Pathophysiological Subtypes

Not applicable or known.

Demographics

Not known. It is likely that some patients with this diagnosis may have an underlying anatomic or functional defect affecting respiratory mechanics and ventilatory drive which remains undiagnosed.

Predisposing and Precipitating Factors

The use of central nervous system depressants, such as alcohol, anxiolytics, and hypnotics, may further worsen hypercapnia/hypoxemia. Patients who are hypercapnic and hypoxemic during wakefulness will generally become even more so during sleep, in particular REM sleep, but the relationship between wake SaO_2/$PaCO_2$ and sleep related desaturation is not sufficiently strong to have substantial predictive value in individual patients.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

The onset of the condition is variable, often presenting in adolescence or early adulthood. The disorder is generally slowly progressive. Many affected individuals with severe hypercapnia and hypoxemia develop respiratory impairment, pulmonary hypertension, heart failure, cardiac arrhythmias, and neurocognitive dysfunction. Polycythemia is common in those with chronic hypoxia. Although the risk of increased morbidity and mortality appears to increase with worsening sleep related hypoventilation/hypoxemia, the specific relationship between sleep related hypoventilation/hypoxemia and morbidity and mortality is not well defined.

Developmental Issues

Not known.

Pathology and Pathophysiology

The etiology of hypoventilation in these patients is not understood. Chronic hypercapnia and hypoxemia in idiopathic central alveolar hypoventilation is believed to be due to defective CO_2 and O_2 homeostasis, with impaired CO_2 unloading, reduced chemoresponsiveness to CO_2 and O_2, and suppression of respiratory drive. Imaging of the central nervous system does not document a structural defect. Hypoventilation worsens during sleep compared to waking levels due to a further reduction in chemosensitivity and decreased activity of the ventilatory muscles. Additionally, daytime hypoxemia, if sufficiently severe, may place the patient near or on the steep portion of the oxyhemoglobin dissociation curve where even relatively small decrements in arterial oxygen tension result in large decrements in oxyhemoglobin saturation. Thus, sleep related hypoventilation in these patients may have a relatively great impact on oxyhemoglobin saturation.

Objective Findings

The characteristic polysomnographic finding is demonstration of sleep related hypoventilation (determination of $PaCO_2$ by arterial blood gas or by a surrogate measure [end-tidal CO_2 or transcutaneous CO_2]). Periods of decreased tidal volume lasting up to several minutes, with sustained arterial oxygen desaturation, are usually present. Intermittent arousals may be observed. Daytime arterial blood gases may be normal or show hypoxia and hypercapnia. Chronic hypoxia can be associated with polycythemia. Electrocardiography, chest radiography, and echocardiography may demonstrate evidence of pulmonary hypertension. Central nervous system imaging is generally unremarkable.

Differential Diagnosis

The differential diagnosis includes any disorder that can cause hypoventilation during sleep. This includes *obesity hypoventilation syndrome*, *pulmonary airway and parenchymal disorders*, *pulmonary vascular pathology*, *neuromuscular and chest wall disorders*, *severe untreated hypothyroidism*, and *use of respiratory suppressants*. *CCHS* is associated with an abnormal *PHOX2B* gene. Unlike patients with *late-onset central hypoventilation with hypothalamic dysfunction*, patients with idiopathic central hypoventilation do not have evidence of hypothalamic dysfunction. It is essential to excluded medical and neurological disorders that are associated with hypoventilation before a diagnosis of idiopathic central hypoventilation can be made. *OSA* and *CSA syndromes* can be distinguished from sleep related hypoventilation by the periodic alterations in airflow and accompanying periodic fluctuations in SaO_2. In contrast, oxygen desaturation due to sleep related hypoventilation is generally more sustained, usually several minutes or longer in duration. When more than one disorder is believed

to be responsible for the ventilatory insufficiency during sleep, all pertinent diagnoses should be coded.

Unresolved Issues and Further Directions

A better understanding of the etiology of idiopathic central alveolar hypoventilation is essential to guide preventive and treatment measures. Because it is clinically impractical to routinely obtain arterial blood samples during sleep in most persons suspected of this disorder, other techniques of measuring CO_2 levels must be investigated. The degree and duration of hypercapnia/hypoxemia necessary to produce adverse consequences, such as pulmonary hypertension, in individual patients is not well defined. Little information is available regarding the effect of oxygen therapy or noninvasive ventilation on the course of the underlying disease. Studies are needed to determine the optimal time to initiate these interventions and the specific subpopulations of patients who will benefit most from these therapies.

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Sleep Related Hypoventilation Due to a Medication or Substance

ICD-9-CM code: 327.26 ICD-10-CM code: G47.36

Alternate Names

Alveolar hypoventilation, nocturnal hypoventilation, nonapneic alveolar hypoventilation, secondary alveolar hypoventilation, sleep related hypoventilation.

Diagnostic Criteria

Criteria A-C must be met

A. Sleep related hypoventilation is present.
B. A medication or substance known to inhibit respiration and/or ventilatory drive is believed to be the primary cause of sleep related hypoventilation.
C. Hypoventilation is not primarily due to lung parenchymal or airway disease, pulmonary vascular pathology, chest wall disorder, neurologic disorder, muscle weakness, obesity hypoventilation syndrome, or a known congenital central alveolar hypoventilation syndrome.

Notes

1. Although OSA or CSA may be present, they are not believed to be the major cause of hypoventilation. The predominant respiratory pattern is one of reduced tidal volume or ataxic breathing and associated arterial oxygen desaturation. When criteria are met, a diagnosis of both OSA and CSA due to medication or substance as well as sleep related hypoventilation due to a medication or substance may be made.
2. Arterial desaturation is often present but is not required for the diagnosis.
3. Hypoventilation may be present during wakefulness but is not required for the diagnosis.

Essential Features

This disorder is characterized primarily by chronic hypoventilation and hypercapnia due to prolonged use of medications or substances known to depress ventilatory drive and/or impair respiratory muscle mechanics. These agents include long-acting narcotics, anesthetics, sedative compounds, and muscle relaxants. The risk of respiratory insufficiency is increased with the concomitant use of alcohol or with polypharmacy. Respiratory depressants can precipitate respiratory failure in patients with limited pulmonary reserves or exacerbate hypoventilation in those with baseline hypercapnia. Hypoxemia is commonly present and can show either a sustained reduction or episodic fluctuations. Sleep related hypoventilation is present. Hypercapnia may also be present during wakefulness in some patients. Patients can either be asymptomatic or present with complaints of dyspnea, chest tightness, or fatigue. Neurocognitive dysfunction may arise following use of narcotics.

Associated Features

Medications and substances that reduce respiratory drive may also alter the mechanics of the upper airway. By decreasing upper airway muscle tone, these agents may precipitate or exacerbate OSA and CSA. It is not currently known whether chronic use of respiratory depressants will eventually give rise to pulmonary artery hypertension or cor pulmonale, but this seems unlikely.

Clinical and Pathophysiological Subtypes

Not applicable or known.

Demographics

The demographics of sleep related hypoventilation due to use of respiratory suppressants are not known. It is clear that baseline hypoventilation prior to initiation of respiratory

depressant medication will worsen following initiation of the medication. Thus, prevalence may be higher in patients with greater perturbations of pulmonary function or neuromuscular weakness. Individuals with chronic hypercapnia during wakefulness will experience even greater decrements of alveolar ventilation during sleep. Studies of patients on methadone maintenance have generally found no or mild daytime hypoventilation. There is scant literature about daytime or nocturnal $PaCO_2$ in patients on potent opioids for pain.

Predisposing and Precipitating Factors

The use of medications or substances that impair respiration mechanics or drive is the primary pathophysiologic factor responsible for hypoventilation and hypoxemia. There are significant inter-individual differences in sensitivity and tolerance to respiratory depressants. Obesity or the presence of medical and neurologic diseases that may produce hypoventilation may further worsen hypercapnia/hypoxemia. Patients who are hypercapnic and hypoxemic during wakefulness will generally become even more so during sleep, in particular REM sleep, but the relationship between wake SaO_2/$PaCO_2$ and sleep related desaturation is not sufficiently strong to have substantial predictive value in individual patients.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

Onset and course of the hypoventilation parallel the use and dosing of medications or substances that can impair respiration, as well as the development of tolerance to these substances. There may be variability in susceptibility to hypoventilation in different individuals. Comorbid pulmonary or neurologic disorders may accentuate the severity of hypoventilation. Patients may present for evaluation of suspected OSA or may be identified following one or more episodes of respiratory failure. It is not known if chronic use of respiratory depressants can lead to the development of pulmonary hypertension, polycythemia, and cardiac arrhythmias. Neurocognitive dysfunction may develop either as a direct result of medication usage or as a consequence of chronic hypoxia and hypercapnia.

Pathology and Pathophysiology

Hypoventilation is a direct result of impaired respiratory drive and CO_2 and O_2 chemosensitivity. Hypoventilation worsens during sleep, especially in REM sleep, compared to waking levels, due to a further reduction in chemosensitivity and decreased activity of the ventilatory muscles. In addition, use of respiratory suppressants may give rise to OSA and CSA that may contribute to hypercapnia and hypoxemia.

Objective Findings

The characteristic PSG finding is demonstration of sleep related hypoventilation by monitoring of $PaCO_2$ or acceptable surrogate during sleep. Sustained oxygen desaturation during sleep that is unexplained by discrete apnea and hypopnea events is common. However, this finding alone is not sufficient to make a diagnosis of sleep related hypoventilation. Medication use can also produce obstructive or central apneas. Intermittent arousals associated with hypoxemia may be observed. An ataxic breathing pattern may be present.

Differential Diagnosis

The differential diagnosis encompasses essentially all disorders that can lead to hypoventilation during sleep. This includes *OHS*, *pulmonary airway and parenchymal disorders*, *pulmonary vascular pathology*, *neuromuscular and chest wall disorders*, *severe untreated hypothyroidism*, and *congenital or idiopathic central alveolar hypoventilation syndromes*. *OSA* and *CSA syndromes* can be distinguished from sleep related hypoventilation by the periodic alterations in airflow and accompanying periodic fluctuations in SaO_2. In contrast, oxygen desaturation due to sleep related hypoventilation is generally more sustained, usually several minutes or longer in duration. When more than one disorder is believed to be responsible for the ventilatory insufficiency during sleep, all pertinent diagnoses should be coded.

Unresolved Issues and Further Directions

Studies of the factors influencing individual susceptibility and tolerance to hypoventilation/hypercapnia due to medications or substances are needed. The long-term consequences of chronic use of respiratory depressants are poorly understood. The value of routinely measuring $PaCO_2$ during sleep in patients taking respiratory depressants is not clear. Additionally, because it is clinically impractical to routinely obtain arterial blood samples during sleep in most persons suspected of this disorder, other techniques of measuring CO_2 levels must be investigated. Little information is available regarding the effect of oxygen therapy or noninvasive ventilation on the course of the underlying disease. Studies are needed to determine the optimal time to initiate these interventions and the specific subpopulations of patients who will benefit most from these therapies.

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Sleep Related Hypoventilation Due to a Medical Disorder

ICD-9-CM code: 327.26 ICD-10-CM code: G47.36

Alternate Names

Alveolar hypoventilation, nonapneic alveolar hypoventilation, secondary alveolar hypoventilation, sleep related hypoventilation.

Diagnostic Criteria

Criteria A-C must be met

A. Sleep related hypoventilation is present.
B. A lung parenchymal or airway disease, pulmonary vascular pathology, chest wall disorder, neurologic disorder, or muscle weakness is believed to be the primary cause of hypoventilation.
C. Hypoventilation is not primarily due to obesity hypoventilation syndrome, medication use, or a known congenital central alveolar hypoventilation syndrome.

Notes

1. Arterial desaturation is often present but is not required for the diagnosis.
2. Although OSA or CSA may be present, they are not believed to be the major cause of hypoventilation. The predominant respiratory pattern is one of reduced tidal volume or ataxic breathing and associated arterial oxygen desaturation. When criteria are met, a diagnosis of both OSA and CSA due to medical or neurological condition as well as sleep related hypoventilation due to a medical disorder may be made.
3. Hypoventilation may be present during wakefulness but is not required for the diagnosis.

Essential Features

Lung airway or parenchymal disease, chest wall disorders, pulmonary hypertension, neurologic and neuromuscular disorders, if sufficiently severe, can result in ventilatory impairment and chronic hypercapnia and hypoxemia. Acute exacerbations of respiratory disorders can accentuate the severity of hypoventilation. Sleep related hypoventilation

is present and is usually most severe during REM sleep. In some patients, hypercapnia may also be present during wakefulness. Patients can either be asymptomatic or present with complaints of dyspnea, chest tightness, or fatigue. Polycythemia is often noted with severe chronic hypoxemia. Specific respiratory disorders are associated with abnormal findings on pulmonary function testing, radiographic imaging, echocardiography, and pulmonary artery catheter measurements. Suspected neurologic or neuromuscular causes of hypoventilation may be investigated using central nervous system imaging or measures of peripheral nerve or muscular function.

Associated Features

Consequences of chronic hypercapnia and hypoxemia arising as a result of medical and neurologic disorders include pulmonary artery hypertension, cor pulmonale, and neurocognitive dysfunction. Some of these disorders are prevalent diseases and commonly overlap. Patients with multiple disorders are likely to experience greater severity and duration of sleep related hypoventilation than are patients with either disorder alone.

Clinical and Pathophysiological Subtypes

The clinical presentation varies with the underlying disorder responsible for the sleep related hypoventilation. Chronic obstructive pulmonary disease is characterized by generally fixed and not fully reversible lower airways obstruction, and includes chronic bronchitis, emphysema, cystic fibrosis, and bronchiectasis. Chronic bronchitis is a clinical entity defined by the presence of chronic productive cough for at least three months of the year, for at least two consecutive years, in the absence of other identifiable etiologies. Emphysema is characterized by destruction of lung tissue and the dilation of peripheral airspaces without evident fibrosis. Emphysema and chronic bronchitis often coexist. Alpha-1 antitrypsin deficiency is a genetic cause of chronic obstructive pulmonary disease. Both bronchiectasis and cystic fibrosis are characterized by lower airway inflammation and destruction of airways and lung parenchyma. Patients with chronic lower airways obstruction are increasingly predisposed to developing hypoventilation as the severity of the underlying lower airways obstruction increases.

Parenchymal lung disease associated with restrictive ventilatory dysfunction (e.g., interstitial lung disease) can also be associated with sleep related hypoventilation. Neurologic, neuromuscular, and chest wall disorders can produce hypoventilation due to an abnormal ventilatory pump (secondary to reduced muscle strength or anatomic distortion of the chest wall structures) that is unable to meet the ventilatory requirements for maintaining $PaCO_2$ at or below 45 mm Hg. In addition, some of these patients have reduced central neural chemoresponsiveness. Last, hypoxemia may be worsened

by the development of atelectasis or aspiration due to defective swallowing associated with some neurologic and neuromuscular conditions.

Demographics

The demographics of sleep related hypoventilation due to a medical disorder are a function of the prevalence, clinical characteristics, and degree of severity of the underlying conditions. Thus, prevalence may be higher in patients with greater perturbations of pulmonary function or neuromuscular weakness. Individuals with chronic hypercapnia during wakefulness will experience even greater decrements of alveolar ventilation during sleep.

Predisposing and Precipitating Factors

Greater impairments of respiratory function are associated with greater risk for sleep related hypoventilation and hypoxemia. However, there is no recognized threshold of pulmonary parenchymal or vascular disease severity that adequately predicts the risk of sleep related hypoventilation in individual patients. Reduced chemosensitivity may be present in some neuromuscular disorders. The use of central nervous system depressants, such as alcohol, anxiolytics, and hypnotics, may further worsen respiratory impairment. Patients who are hypercapnic and hypoxemic during wakefulness will generally become even more so during sleep, in particular REM sleep, but the relationship between wake SaO_2/$PaCO_2$ and sleep related desaturation is not sufficiently strong to have substantial predictive value in individual patients.

Familial Patterns

Genetic patterns for many of the disorders are not known. Alpha-1 antitrypsin deficiency is a genetic disorder characterized by defective production of the enzyme inhibitor; severe forms of deficiency can lead to emphysema. Genetic causes of bronchiectasis include primary ciliary dyskinesia and cystic fibrosis. Muscular dystrophies are genetically inherited. The familial patterns of sleep related hypoventilation due to these disorders reflect those of the underlying inherited conditions.

Onset, Course, and Complications

Onset and course of the hypoventilation parallels the presence and severity of the underlying medical or neurological disorders that impair respiration although substantial variability in course is observed even within the same underlying condition. Many affected individuals with severe hypercapnia and hypoxemia develop respiratory impairment, pulmonary hypertension, heart failure, cardiac arrhythmias, and neurocognitive dysfunction. Polycythemia is common in those with chronic hypoxia. Although the risk of increased morbidity and mortality appears to increase with worsening sleep

related hypoventilation, the specific relationship between sleep related hypoventilation and morbidity and mortality is not well defined. Many patients respond to assisted ventilation, whereas hypercapnia may worsen with oxygen therapy alone.

Pathology and Pathophysiology

Pulmonary parenchymal diseases are characterized by altered lung volumes (e.g., reduced functional residual capacity) and abnormal ventilation/perfusion relationships, which can result in hypercapnia and hypoxemia during wakefulness. Decreased lung volume is associated with reduced oxygen reserves that increase the risk of hypoxemia. In addition, sleep may be associated with an altered pattern of ventilatory-muscle activation, particularly during REM sleep when, due to reduced activation of the intercostal and accessory muscles, there is a disproportionate ventilatory burden placed on the diaphragm. This may lead to hypoventilation in patients with chest wall abnormalities or in those with chronic obstructive pulmonary disease. In the latter, lung hyperinflation creates a mechanical disadvantage to the diaphragm. Many neurologic and neuromuscular disorders are associated with impaired respiratory mechanics and reduced CO_2 chemosensitivity. Finally, daytime hypoxemia, if sufficiently severe, may place the patient near or on the steep portion of the oxyhemoglobin dissociation curve, where even relatively small decrements in arterial oxygen tension result in large decrements in oxyhemoglobin saturation. Thus, sleep related hypoventilation in these patients may have a relatively great impact on oxyhemoglobin saturation.

Objective Findings

The characteristic polysomnographic finding is demonstration of sleep related hypoventilation (by arterial $PaCO_2$, transcutaneous PCO_2, or end-tidal PCO_2). Sustained oxygen desaturation during sleep that is unexplained by discrete apnea and hypopnea events is common but is not sufficient to establish a diagnosis of sleep related hypoventilation. Intermittent arousals associated with hypoxemia may be observed. Many medical and neurologic disorders are associated with significant sleep disturbances and changes in sleep architecture, including prolonged sleep onset latency, reduced sleep efficiency, and decreased sleep stages N3 and REM, may be present. Obstructive and central apneas, when present, will further disturb sleep and accentuate sleep related oxyhemoglobin desaturation. Daytime arterial blood gases may be normal or show hypoxia and hypercapnia. Chronic hypoxia (especially when present during the day as well as at night) can be associated with polycythemia. Electrocardiography, chest radiography, and echocardiography may demonstrate evidence of pulmonary hypertension.

In patients with neuromuscular weakness or restrictive chest wall disorders spirometry shows a restrictive ventilatory dysfunction with the forced vital capacity (FVC) often

less than 50% of predicted. However, significant nocturnal desaturation can occur with FVC values greater than 50% of predicted.

Differential Diagnosis

The differential diagnosis includes all disorders which can give rise to hypoventilation during sleep. This includes *OHS*, *use of medications or substances that can suppress respiratory drive*, and *congenital* or *idiopathic central alveolar hypoventilation syndromes*. *OSA* and *CSA* can be distinguished from sleep related hypoventilation by the periodic alterations in airflow and accompanying periodic fluctuations in SaO_2. In contrast, oxygen desaturation due to sleep related hypoventilation is generally more sustained, usually several minutes or longer in duration. When more than one disorder is believed to be responsible for the ventilatory insufficiency during sleep, all pertinent diagnoses should be coded.

Unresolved Issues and Further Directions

Thresholds of impairments of ventilation and respiratory drive producing hypercapnia/hypoxemia need to be identified. The degree and duration of hypercapnia/hypoxemia necessary to produce adverse consequences, such as pulmonary hypertension, in individual patients is not well defined. The value of routinely measuring $PaCO_2$ during sleep in these patients is not clear. Additionally, because it is clinically impractical to routinely obtain arterial blood samples during sleep in most persons suspected of this disorder, other techniques of measuring CO_2 levels must be investigated. Little information is available regarding the effect of oxygen therapy or noninvasive ventilation on the course of the underlying disease. Studies are needed to determine the optimal time to initiate these interventions and the specific subpopulations of patients who will benefit most from these therapies.

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Sleep Related Hypoxemia Disorder

Sleep Related Hypoxemia

ICD-9-CM code: 327.26 ICD-10-CM code: G47.36

Alternate Names

Nocturnal oxygen (or oxyhemoglobin) desaturation, low nocturnal oxygen saturation, nocturnal hypoxemia, sleep related hypoxemia, sleep related oxygen desaturation.

Diagnostic Criteria

Criteria A and B must be met

A. PSG, OCST or nocturnal oximetry shows the arterial oxygen saturation (SpO_2) during sleep of ≤ 88% in adults or ≤ 90% in children for ≥ 5 minutes.
B. Sleep related hypoventilation is not documented.[1]

Notes

1. If sleep related hypoventilation is documented (as measured by arterial blood gas, transcutaneous PCO_2, or end-tidal CO_2 sensors), the disorder is classified as sleep related hypoventilation.
2. OSA or CSA may be present, but these are not believed to be the major cause of hypoxemia.
3. Physiological causes, if known, should be indicated (e.g., shunt, ventilation-perfusion [V/Q] mismatch, low mixed venous oxygen, and/or high altitude).

Essential Features

Significant hypoxemia during sleep is present and is believed to be secondary to a medical or neurological disorder. The presence of hypoxemia is not better explained by another sleep related breathing disorder (e.g., OSA). Although some amount of obstructive or central apnea may be present, these disorders are not thought to be primarily responsible for the hypoxemia during sleep. Some patients with sleep related hypoxemia also exhibit hypoxemia during wakefulness. Sleep related hypoventilation has not been documented (if so, a diagnosis of sleep related hypoventilation is made). The presentation of patients with sleep related hypoxemia varies with the underlying medical or neurological disorders. Chronic hypoxemia can arise from airway or parenchymal pulmonary disease, chest wall disorders, pulmonary hypertension, or neurologic and neuromuscular disorders. Acute exacerbations of respiratory disorders

can accentuate the severity of hypoxemia. Hypoxemia due to underlying lower airway obstructive disease, pulmonary parenchymal disease, vascular pathology, and other causes of hypoventilation is generally sustained (several minutes or longer), whereas sawtooth fluctuations of oxygen saturation (typically less than one minute) characterize hypoxemia due to OSA or CSA. Patients can either be asymptomatic or present with complaints of nocturnal dyspnea, impaired sleep quality, chest tightness, or fatigue. Polycythemia is often noted with severe chronic hypoxemia.

Associated Features

Consequences of chronic hypercapnia and hypoxemia include pulmonary artery hypertension, cor pulmonale, and neurocognitive dysfunction. Some of the disorders causing hypoxemia are prevalent diseases and not uncommonly overlap. Patients with multiple breathing disorders are likely to experience greater severity and duration of sleep related hypoxemia than are patients with a single disorder.

Clinical and Pathologic Subtypes

Specific variations in the sleep related findings have not been described for the various etiologies.

Demographics

The demographics of sleep related hypoxemia are a function of the prevalence, clinical characteristics and degree of severity of the underlying conditions. Thus, prevalence may be higher in patients with greater perturbations of pulmonary function or neuromuscular weakness. Individuals with chronic hypoxemia during wakefulness will experience even greater decrements of oxygenation during sleep.

Predisposing and Precipitating Factors

Greater impairments of respiratory function are associated with greater risk for sleep related hypoxemia. However, there is no recognized threshold of pulmonary parenchymal or vascular disease severity or extent of neuromuscular weakness that adequately predicts the risk of sleep related hypoxemia in individual patients. Patients who are hypoxemic during wakefulness will generally become even more so during sleep, especially REM sleep. Among the best predictors of sleep related hypoxemia are reduced baseline wake SaO_2 and hypercapnia. Patients with wake hypercapnia should be suspected of sleep related hypoxemia. However, the relationship between wake SaO_2/$PaCO_2$ and sleep related desaturation is not sufficiently strong to have substantial predictive value in individual patients.

Familial Patterns

Genetic patterns for many of the disorders are not known. Alpha-1 antitrypsin deficiency is a genetic disorder characterized by defective production of the enzyme inhibitor; severe forms of deficiency can lead to emphysema. Genetic causes of bronchiectasis include primary ciliary dyskinesia and cystic fibrosis. Muscular dystrophies are genetically inherited. The familial patterns of sleep related hypoxemia due to these disorders reflect those of the underlying inherited conditions.

Onset, Course, and Complications

Onset and course of sleep related hypoxemia parallel the presence and severity of the underlying medical or neurological disorders that impair respiration, although substantial variability in course is observed even within the same underlying condition. Many affected individuals with severe hypercapnia and hypoxemia develop respiratory impairment, pulmonary hypertension, heart failure, cardiac arrhythmias, and neurocognitive dysfunction. Polycythemia is common in those with chronic hypoxia. Higher rates of painful crises accompany hypoxemia in children with sickle cell disease. Although the risk of increased morbidity and mortality appears to increase with worsening sleep related hypoxemia, the specific relationship between sleep related hypoxemia and morbidity and mortality is not well defined. Many patients respond to oxygen therapy; in some, hypercapnia may worsen with oxygen therapy alone for hypoxia.

Pathology and Pathophysiology

Hypoxemia may arise from a shunt physiology, ventilation-perfusion [V/Q] mismatching, low mixed venous oxygen, and/or high altitude. Hypoventilation also gives rise to hypoxemia; however, when hypoventilation has been documented, a diagnosis of sleep related hypoventilation should be assigned, rather than sleep related hypoxemia. Pulmonary parenchymal diseases are characterized by altered lung volumes (e.g., reduced functional residual capacity) and abnormal ventilation/perfusion relationships, which can result in hypercapnia and hypoxemia during wakefulness. Decreased lung volume is associated with reduced oxygen reserves that increase the risk of hypoxemia. In addition, sleep may be associated with an altered pattern of ventilatory muscle activation, particularly during REM sleep when, due to reduced activation of the intercostal and accessory muscles, there is a disproportionate ventilatory burden placed on the diaphragm. This may lead to hypoventilation in patients with chest wall abnormalities or chronic obstructive pulmonary disease. In the latter, lung hyperinflation creates a mechanical disadvantage to the diaphragm. In sickle cell anemia, decreased oxyhemoglobin affinity may partly contribute to hypoxemia. Many neurologic and neuromuscular disorders are associated with impaired respiratory mechanics and reduced CO_2 chemosensitivity. Finally, daytime hypoxemia, if sufficiently severe, may place the patient

near or on the steep portion of the oxyhemoglobin dissociation curve where even relatively small decrements in arterial oxygen tension result in large decrements in oxyhemoglobin saturation. Thus, sleep related hypoventilation in these patients might have a relatively great impact on oxyhemoglobin saturation.

Objective Findings

Various patterns of oxygen desaturation (sustained, intermittent, or episodic) may be observed during sleep. The diagnosis is generally made on the basis of overnight oximetry (alone or as a component of PSG or OCST); less commonly, arterial blood gas measurements are indicated, especially if concomitant hypoventilation is suspected. PSG may demonstrate normal sleep architecture or frequent arousals, increased wakefulness after sleep onset and reduced sleep efficiency; however, the contribution of sleep related hypoxemia to the altered sleep architecture, if present, is uncertain. Daytime arterial blood gases may be normal or show hypoxia and hypercapnia. Nocturnal oximetry usually shows sustained periods of reduced arterial oxygen but clusters of more severe drops in the arterial oxygen saturation can occur every one to two hours due to worsening of breathing during REM sleep. A sawtooth pattern of briefer desaturations (typically less than one minute) suggests the presence of discrete events (apneas or hypopneas). Some sawtooth changes may be superimposed on low baseline oxygen saturation but are not the predominant pattern. Chronic hypoxia can be associated with polycythemia. Electrocardiography, chest radiography, and echocardiography may demonstrate evidence of pulmonary hypertension.

Differential Diagnosis

The differential diagnosis encompasses all disorders which can give to hypoxemia during sleep. This includes *pulmonary airway and parenchymal disorders*, *pulmonary vascular pathology*, *neuromuscular and chest wall disorders*, *OHS*, *use of medications or substances that can suppress respiratory drive*, and *congenital or idiopathic central alveolar hypoventilation syndromes*. *OSA* and *CSA syndromes* can be distinguished from sleep related hypoxemia by the periodic alterations in airflow and accompanying periodic fluctuations in SaO_2. In contrast, oxygen desaturation associated with sleep related hypoxemia is generally more sustained, usually several minutes or longer in duration. In cases when more than one disorder is believed to be responsible for the ventilatory insufficiency during sleep, all pertinent diagnoses should be coded.

Unresolved Issues and Further Directions

The degree and duration of hypercapnia/hypoxemia necessary to produce adverse consequences, such as pulmonary hypertension, in individual patients is not well defined. The value of routinely measuring arterial blood gases or SaO_2 during sleep

is not clear. With the exception of COPD, little information is available regarding the effect of oxygen therapy on the course of the underlying disease. Even less is understood regarding the consequences of isolated sleep related hypoxemia and the need for oxygen supplementation in patients with normal daytime wake oxygen levels. Studies are needed to determine the optimal time to initiate oxygen therapy and the specific subpopulations of patients who will benefit most from this intervention.

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Isolated Symptoms and Normal Variants

Snoring

ICD-9-CM code: 786.09 ICD-10-CM code: R06.83

Snoring is a respiratory sound generated in the upper airway during sleep that typically occurs during inspiration but may also occur in expiration; the snoring described here occurs without episodes of apnea, hypopnea, RERAs or hypoventilation. The intensity of snoring may vary and often will disturb the bed partner's sleep and even awaken the patient. Snoring in this context does not cause symptoms of daytime sleepiness or insomnia in the patient. This type of snoring has variously been referred to as habitual, primary or simple snoring.

Snoring is a cardinal symptom of obstructive sleep apnea. *A designation of habitual snoring cannot be made in those who exhibit symptoms (daytime sleepiness/fatigue or other related symptoms) or report possible breathing pauses, without objective measurement of breathing during sleep*. In addition, those individuals with snoring and comorbid cardiovascular disease (especially pulmonary or systemic hypertension, coronary artery disease, or atrial fibrillation) are at increased risk for the presence of OSA even in the absence of complaints of daytime sleepiness. Therefore, *PSG or OCST is required in order to effectively rule out OSA in such populations*. It should also be noted that patients who initially have isolated snoring may be at risk for developing OSA with aging or weight gain.

Occasional snoring is almost universal. Estimates on snoring vary widely depending on its definition. The incidence of snoring in children is reported to be 10% to 12%. The Wisconsin cohort study reports habitual snoring in about 24% of adult women and 40% of adult men. Prevalence of snoring increases with age in both sexes, except that the prevalence of reported snoring starts to decrease again in men after 70 years of age. Some have hypothesized that his may be due to decreased hearing acuity in older individuals.

Snoring is most common in adult men and is also linked to obesity. Nasal obstruction increases the risk of snoring. Ingestion of alcohol, muscle relaxants, narcotics, or other substances that decrease upper airway muscle tone predisposes an individual to snoring. Smoking, particularly in males, has also been shown to be a risk factor. Snoring has also been shown to increase during pregnancy. In children, an association has been reported between snoring and adenotonsillar hypertrophy. During snoring

there is vibration of the uvula and soft palate, although it may also involve the faucial pillars, pharyngeal walls, and lower structures. Snorers have been shown to have morphologic derangements of the palate consistent with neurogenic lesions. These are thought to be due to trauma from vibration. If PSG is performed, snoring tends to be loudest during stage N3 sleep or REM sleep.

Epidemiologic studies are difficult to interpret if sleep apnea was not excluded by PSG. Based on the current literature, habitual snoring in children may be associated with worse school performance, but conclusive evidence for this is lacking. Some studies have suggested that adult snorers may have a higher prevalence of cardiovascular disease, including hypertension, stroke, and ischemic heart disease. However, a large observational study in which all subjects underwent PSG found no increased risk of cardiovascular morbidity or mortality with habitual snoring. Of interest, one study found that snoring was associated with atherosclerosis of the carotid artery, but this has not been confirmed by other studies. As snoring tends to increase during pregnancy, the impact of snoring on maternal health is of great interest. A study found that pregnancy-onset habitual snoring (but not chronic [pre-conceptual] snoring) was associated with increased risk of gestational hypertension and preeclampsia. Further studies are needed in this area.

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Catathrenia

Catathrenia, also known as sleep related groaning, is included in the SRBD section because it appears to be associated with prolonged expiration, usually during REM sleep. However, some studies have documented catathrenia during NREM sleep. Typically, a deep inspiration is followed by prolonged expiration and a monotonous vocalization resembling groaning. The pattern is sometimes called bradypnea (low respiratory rate). The affected individual is usually unaware of the problem, but clinical evaluation is sought due to complaints of the bed partner or family members. The recurrent bradypneic episodes may resemble central apnea except that central apneas are not typically associated with vocalization. Catathrenia is thought to be rare and more common in men. Several episodes may occur nightly and often in clusters. The long-term consequences of catathrenia are unknown, but the disorder is primarily a social problem for the affected individual. The episodes of catathrenia are not associated with sleep talking or body movement. No association with psychiatric disorders has been demonstrated. The onset of catathrenia has recently been reported in patients taking sodium oxybate for narcolepsy with cataplexy. The clinical significance of this finding is unclear.

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Central Disorders of Hypersomnolence

Isolated Symptoms and Normal Variants

Adequate alertness is necessary for well-being and performance in modern society. Sleepiness predisposes an individual to developing serious performance decrements in multiple areas of function, as well as to potentially life-threatening domestic, occupational, and vehicular accidents. This section includes a group of disorders in which the primary complaint is daytime sleepiness not caused by disturbed nocturnal sleep or misaligned circadian rhythms. Other sleep disorders may be present, but they must be adequately treated before a diagnosis in this category can be established. In this nosology, the term hypersomnolence is used to describe the symptom of excessive sleepiness, whereas hypersomnia refers to specific disorders, such as idiopathic hypersomnia.

Daytime sleepiness is defined as the inability to stay awake and alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep. Sleepiness may vary in severity and is more likely to occur in sedentary, boring, and monotonous situations that require little active participation. Some patients are aware of increasing sleepiness before falling asleep, whereas others can fall asleep with little or no prodromal symptoms ("sleep attacks"). This group of patients sometimes can present following motor vehicle accidents attributable to sleepiness. In some forms of hypersomnolence, sleepiness is associated with large increases in total daily amount of sleep without any genuine feeling of restoration. In others, sleepiness can be alleviated temporarily by naps but reoccurs shortly thereafter. In young children, sleepiness may express itself as excessively long night sleep or with the recurrence of previously discontinued daytime napping. Children may

paradoxically present with inattentiveness, emotional lability, hyperactive behavior, or decreased performance in school. In most cases, excessive sleepiness is a chronic symptom. It must occur for at least three months prior to diagnosis.

The severity of daytime sleepiness can be quantified subjectively using severity scales such as the Epworth Sleepiness Scale and objectively using the Multiple Sleep Latency Test (MSLT). These measures do not always correlate with each other and must be used with appropriate clinical judgment. When applied in clinical settings, the MSLT is sensitive to sleep deprivation and circadian effects. It has not been validated as a diagnostic test in people who are habitually awake throughout the night and sleep during the day. Normal and abnormal ranges of sleep latencies have not been established when this test is administered at times other than the hours between 8:00 a.m. and 6:00 p.m.

Normative data are not available for children younger than six years.

The MSLT measures the physiological tendency to fall asleep in quiet situations. In the context of diagnosing central disorders of hypersomnolence, the MSLT should be conducted according to standardized procedures, as defined in the American Academy of Sleep Medicine (AASM) practice parameters. In particular, patients should be encouraged to sleep as much as possible during the week and, especially, during the night prior to the MSLT. Delaying wake-up time and subsequent MSLT start time may be appropriate in some patients with delayed sleep phase syndrome. It is strongly recommended that adequate sleep be documented by sleep log and, whenever possible, actigraphy for a period of one to two weeks prior to the MSLT. MSLT mean sleep latencies should be considered a continuum with values below five minutes generally considered as indicative of sleepiness and those over 10 minutes generally considered indicative of normal alertness. In this section, a mean MSLT sleep latency of less than eight minutes is used to define sleepiness for diagnostic purposes. This value has been shown to be the best cutoff in the context of diagnosing narcolepsy, with approximately 90% of patients with narcolepsy having a latency below this level. The presence of multiple sleep onset rapid eye movement periods (SOREMPs) during the MSLT is a more specific finding in narcolepsy than is a mean sleep latency less than or equal to eight minutes, although SOREMPs can also be seen in the presence of insufficient sleep, circadian rhythm disorders (including delayed sleep phase disorder or shift work), sleep related breathing disorders or, occasionally, normal subjects. The results of an MSLT should be carefully interpreted in the context of the patient's history and the complaint of daytime sleepiness.

The maintenance of wakefulness test is a measure of the ability to remain awake during the daytime in a darkened, quiet environment and is usually administered to assess response to treatment. It should not be used for diagnostic purposes.

A 24-hour continuous sleep recording or an actigraphic recording of at least one week is useful in the diagnosis of some patients with idiopathic hypersomnia. In all cases in which a diagnosis of hypersomnolence is to be made, a review of other sleep, medical, and psychiatric disorders, as well as substance and medication use, should be performed.

In this edition of International Classification of Sleep Disorders the preferred names of certain central disorders of hypersomnolence have been changed. In particular, narcolepsy has been divided into narcolepsy type 1 and narcolepsy type 2 rather than narcolepsy with and without cataplexy. This change is predicated on the concept that absence of hypocretin (orexin) is a fundamental marker of the most precisely defined category of the disorder. Because some patients without cataplexy will also have low cerebrospinal fluid (CSF) hypocretin-1 levels, the use of the term "narcolepsy with cataplexy" or "narcolepsy-cataplexy" is inappropriate. The change is not intended to imply that the presence or absence of cataplexy is unimportant clinically nor that measuring CSF hypocretin-1 levels is obligatory. The motivation behind the decision to eliminate the subcategories of idiopathic hypersomnia is discussed in the appropriate section. The decision to use Kleine-Levin syndrome as the preferred name in place of recurrent hypersomnia is based on data suggesting that the condition is fairly homogeneous, as well as the lack of definite evidence for other major subcategories of the disorder.

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Narcolepsy Type 1

ICD-9-CM code: 347.01 ICD-10-CM code: G47.411

Alternate Names

Hypocretin deficiency syndrome, narcolepsy-cataplexy, narcolepsy with cataplexy.

Diagnostic Criteria

Criteria A and B must be met

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.[1]

B. The presence of one or both of the following:

1. Cataplexy (as defined under Essential Features) *and* a mean sleep latency of ≤ 8 minutes and two or more sleep onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.[2]
2. CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤ 110 pg/mL or <1/3 of mean values obtained in normal subjects with the same standardized assay.

Notes

1. In young children, narcolepsy may sometimes present as excessively long night sleep or as resumption of previously discontinued daytime napping.
2. If narcolepsy type I is strongly suspected clinically but the MSLT criteria of B1 are not met, a possible strategy is to repeat the MSLT.

Essential Features

Narcolepsy type 1 is a disorder primarily characterized by excessive daytime sleepiness and signs of REM-sleep dissociation, the most specific of which is cataplexy. It has now been firmly established that narcolepsy type 1 is caused by a deficiency of hypothalamic hypocretin (orexin) signaling. Patients with low or undetectable concentrations of hypocretin-1 in the CSF compose a specific disease population with a single etiology and relatively homogenous clinical and polysomnographic features. Patients with sleepiness and low or absent CSF hypocretin-1 levels are classified as having narcolepsy type 1, even if they do not manifest cataplexy.

Excessive daytime sleepiness is the cardinal symptom, and often the most disabling. Patients with narcolepsy type 1 experience repeated daily episodes of an irrepressible need to sleep or lapses into sleep. Most patients awaken refreshed after a sleep episode but begin to feel sleepy again after variable times. Sleepiness is most likely to occur in monotonous situations that require no active participation; for example, watching television or riding in a car. Physical activity may temporarily suppress the urge to sleep. In some cases sleepiness manifests as sudden irresistible sleep "attacks" that may occur in unusual situations such as eating or walking. Often, such sleep attacks occur on a background of overall sleepiness. Even when seemingly awake, many narcolepsy patients have lapses in vigilance, sometimes in combination with automatic behavior, such as writing gibberish or interrupting a conversation with a completely different topic. Sleepiness generally has a serious impact on the ability of the patient to function in educational, social, and occupational situations.

Because patients are rarely examined during an attack of cataplexy, its presence needs to be established based on the clinical interview alone. Cataplexy is defined as more than one episode of generally brief (< 2 minutes), usually bilaterally symmetrical sudden loss of muscle tone with retained consciousness. The episodes are precipitated by strong emotions, usually positive, with almost all patients reporting some episodes precipitated by emotions associated with laughter. The finding of transient reversible loss of deep tendon reflexes during an attack, if observed, is a strong diagnostic finding. In children (and rarely adults), cataplexy may present close to disease onset as facial (or generalized) hypotonia with droopy eyelids, mouth opening, and protruded tongue, or gait unsteadiness, which clearly are not related to emotion. Facial and masticatory movements may occur. In children, anticipation of a reward is a common precipitant. It is important to use child-appropriate contexts and language when trying to elicit a history of cataplexy in children.

The cataplexy phenotype differs widely between patients, ranging from sporadic partial attacks triggered by laughter, to frequent complete attacks of collapse brought about by a variety of emotions. In the vast majority of attacks, cataplexy is bilateral, although patients sometimes report one side of the body to be more affected than the other. Partial attacks can be very subtle and sometimes only recognized by experienced observers such as the patient's partner. Neck weakness, producing head drop, is a common complaint, whereas facial weakness may lead to sagging of the jaw and dysarthria. Respiratory muscles are not involved although patients sometimes describe shortness of breath when symptomatic. Attacks start abruptly and usually build up over several seconds, especially in attacks producing complete peripheral weakness and collapse. Positive motor phenomena are not uncommon, with muscle twitching

or small jerks, particularly of the face. Although many emotions can potentially lead to cataplexy, those associated with mirth are usually the most potent. Laughing out loud, telling a joke, and making a witty remark are typical examples. The frequency of cataplexy is variable, ranging from less than one attack per month to more than 20 attacks per day. Cataplexy is generally short-lived, lasting a matter of seconds, with the vast majority of attacks lasting less than two minutes. However, if a particular trigger continues, consecutive attacks may merge together to form what seems to be one long episode. Sudden withdrawal of anticataplectic medication, especially antidepressants, can result in "status cataplecticus" in which long-lasting attacks happen virtually continuously.

Associated Features

In addition to sleepiness and cataplexy, patients with narcolepsy type 1 often report several other symptoms, none of which are specific for the disorder. Many patients report disruption of nocturnal sleep, which can sometimes be of major concern. Although sleep onset is rarely a problem, an inability to maintain continuous sleep is very common. 33% to 80% of narcolepsy patients have hypnagogic hallucinations and/or sleep paralysis. Hypnagogic hallucinations are defined as vivid dreamlike experiences occurring at the transition from wake to sleep. Typically, hypnagogic hallucinations have a multimodal or "holistic" character, often combining visual, auditory, and tactile phenomena. Hypnopompic hallucinations are similar but occur at sleep to wake transitions. Sleep paralysis describes the disturbing temporary inability to move voluntary muscles at sleep-wake transitions. Despite being awake and conscious of the sleeping environment, it is impossible for subjects to move their limbs or even open their eyes. The experience may last for several minutes and can be very distressing. Other symptoms may include ptosis, blurred vision, and diplopia, presumably as a result of sleepiness.

Epidemiological studies have shown that obesity is a common symptom of narcolepsy. Around disease onset, an unexplained increase in body weight is often observed. Obesity (defined as a body mass index ≥ 30 kg/m^2) occurs more than twice as often in narcoleptic populations as in control groups. An increased frequency of several other sleep abnormalities has been described in narcolepsy, including sleep talking, periodic limb movements of sleep, sleep disordered breathing, and REM sleep behavior disorder. There is an increased prevalence of depressive symptoms, although there are conflicting reports on how often these symptoms qualify as a clinical depression. Recent studies point to a high level of anxiety disorders in patients with narcolepsy, with panic attacks or social phobias in about 20%. More than half of patients report severe fatigue, which can be distinct from sleepiness.

Clinical and Pathophysiological Subtypes

Narcolepsy type 1 due to a medical condition: This condition is primarily associated with central nervous system (CNS) disorders, including autoimmune or paraneoplastic disorders associated with anti-Ma2 or antiaquaporin4 antibodies, and tumors or other lesions of the hypothalamus. In addition, undetectable hypocretin-1 levels have been reported in association with sleepiness after severe head trauma. The condition must fulfill criteria for narcolepsy type 1 and be attributable to another medical disorder.

Narcolepsy without cataplexy with low CSF Hcrt-1 levels: Narcolepsy type 1 should be diagnosed, even in the absence of cataplexy, if diagnostic criteria A and B2 are fulfilled.

Demographics

Narcolepsy with cataplexy occurs in 0.02% to 0.18% of the United States and western European populations. A lower prevalence has been reported in Israel, whereas narcolepsy with cataplexy may be slightly more common in Japan (0.16% to 0.18%). Both sexes are affected, with a slight preponderance of males.

Predisposing and Precipitating Factors

Several unproven precipitating factors have been suggested in case reports, including head trauma, sustained sleep deprivation, unspecified viral illness, and sudden changes in sleep-wake patterns. Several studies have pointed to seasonal patterns in the onset of narcolepsy, which may point to a specific environmental trigger. Recent studies have shown an increase in antibodies against beta-hemolytic streptococcus, which were strongest around onset of narcolepsy and decreased with disease duration, suggesting that streptococcal infections may constitute an environmental trigger. There have been reports of narcolepsy type 1 occurring after vaccination against H1N1 associated influenza, but a definite causal association has not yet been established. Tribbles homolog 2 antibodies, found in some patients with autoimmune uveitis, have been described in 14% to 26% of narcolepsy patients, but the significance is uncertain.

Familial Patterns

At the genetic level, narcolepsy with cataplexy is closely associated with the human leukocyte antigen (HLA) subtypes DR2/DRB1*1501 and DQB1*0602. These two subtypes are always found together in whites and Asians, but in blacks, DQB1*0602 is more specifically associated with narcolepsy. Almost all patients with cataplexy are positive for DQB1*0602, compared with 12% to 38% of the general population who have this HLA subtype. Other subtypes also have less striking associations. For example, DQB1*0301 is associated with increased susceptibility to narcolepsy,

whereas subtypes such as DQB1*0501 and DQB1*0601, are protective in the presence of DQB1*0602. Genomewide studies have found associations between narcolepsy and polymorphisms in T cell receptor alpha, tumor necrosis factor (TNF)-alpha 2, and TNF receptor 2 as well as the purinergic receptor P2Y11 genes.

There is a low prevalence of familial cases; the risk of narcolepsy type 1 in first-degree relatives of affected individuals is approximately 1% to 2%. When compared to the population prevalence, this indicates a tenfold to fortyfold increase in risk. This increased risk cannot be explained solely by HLA gene effects, suggesting the existence of other genetic factors. Multiplex families with more than two affected members are uncommon. In most cases, normal CSF hypocretin levels have been found in these families, and the association with HLA DQB1*0602 is much weaker compared to sporadic narcolepsy. So far, only a single case of narcolepsy type 1 has been described in association with a preprohypocretin mutation.

Onset, Course, and Complications

Onset usually occurs after five years of age and most typically between ages 10 and 25 years. However, a bimodal distribution in the age at onset has been described in some populations with a first peak occurring at adolescence (age 15 years) and a second at the age of 35 years. Recent studies highlight the fact that narcolepsy, and especially cataplexy, in young children may present somewhat differently, resulting in delayed diagnosis and erroneously high estimates of age of onset.

Sleepiness is usually the first symptom to manifest. Cataplexy most often occurs within one year of onset but in rare cases, may precede the onset of sleepiness or commence up to 40 years later. Hypnagogic hallucinations, sleep paralysis, and disturbed nocturnal sleep often manifest later in the course of the disease.

When left untreated, narcolepsy type 1 is often socially disabling and isolating. Patients have a tendency to fail in school and are often dismissed from their jobs. Driving may be avoided for fear of a motor vehicle accident. The inability to sleep at night may further contribute to a loss of control these patients have over their schedule. Depression and weight gain also are common.

In most cases, symptoms gradually develop over several years. When the clinical picture has fully developed, there are usually only minor fluctuations in severity. Cataplexy may lessen with age, or occasionally increase in frequency and severity.

Developmental Issues

In recent years, increasing attention has been given to the clinical presentation of narcolepsy in childhood. Narcolepsy with cataplexy is infrequent prior to the age of four years. In addition, the clinical presentation in children may be different from that of adults. In young children, sleepiness may be difficult to assess, and may express itself as excessively long night sleep, or the recurrence of previously discontinued daytime napping. Moreover, children may paradoxically present with hyperactive behavior, behavioral problems or decreased performance in school. Inattentiveness, lack of energy, insomnia, bizarre hallucinations, or a combination thereof can lead to a psychiatric misdiagnosis of schizophrenia or depression. In this population, the presence of ancillary symptoms such as sleep paralysis or hypnagogic hallucinations may also be difficult to confirm, depending on the child's verbal ability. Precocious puberty and obesity may also develop around the time of symptom onset. REM sleep behavior disorder or REM sleep without atonia may also be manifest at the time of symptom onset.

Cataplexy may be very severe around disease onset and appear phenotypically different from typical episodes seen in adulthood. In addition to typical attacks triggered by positive emotions, children can also present with weakness involving the face, eyelids, and mouth not clearly associated with emotion. Together with tongue protrusion, this characteristic pattern has been termed a cataplectic facies. Children with cataplexy may also display positive motor phenomena, ranging from perioral dyskinetic or dystonic movements to frank stereotypies. In children, anticipation of reward may also be a precipitant.

The diagnosis of narcolepsy type 1 in children may be complicated because of difficulties performing the MSLT, and lack of normative values in children younger than six years. If the MSLT shows equivocal results, repeating it after a time interval may be helpful. Given these difficulties, CSF hypocretin-1 measurements are of particular value, as hypocretin-1 levels are low or undetectable very shortly after disease onset in children as well.

Pathology and Pathophysiology

It is now firmly established that narcolepsy type 1 is caused by deficiencies in hypocretin signaling, most likely due to a selective loss of hypothalamic hypocretin producing neurons. Several animal models lacking hypocretin neurotransmission demonstrate narcolepsy, indicating a causal relationship. The vast majority of patients (90% to 95%) with narcolepsy and cataplexy have undetectable or low (< 110 pg/mL) levels of hypocretin-1 in the CSF. Patients without cataplexy can be hypocretin deficient as well, although at a much lower frequency, and are thus also classified as narcolepsy

type 1. The strong HLA association in narcolepsy has led to the hypothesis that autoimmunity is a likely etiological mechanism, potentially explaining the selectivity of neuronal destruction in the hypothalamus. However, definitive proof for autoimmunity has not been obtained.

Objective Findings

Narcolepsy type 1 is essentially defined as a hypocretin deficiency syndrome, which is reflected in the need for objective measurements in the clinical criteria. This requirement is further driven by the fact that many patients require lifelong treatment with potentially addictive medications, underscoring the importance of objective confirmation of the diagnosis.

It is strongly recommended that the MSLT be preceded by at least one week of actigraphic recording with a sleep log to establish whether the results could be biased by insufficient sleep, shift work, or another circadian sleep disorder. In patients with narcolepsy type 1, the MSLT demonstrates a mean sleep latency of less than eight minutes and typically less than five minutes. Meta-analysis shows mean sleep latencies in narcoleptic patients with cataplexy of 3.1 ± 2.9 minutes. In addition, two or more SOREMPs must be present. Recent data suggest that a SOREMP within 15 minutes of onset of nocturnal sleep is a highly specific finding in the absence of another sleep disorder, but with low sensitivity. Therefore, the criteria for narcolepsy type 1 allow the "replacement" of one SOREMP in the MSLT with a SOREMP on the preceding polysomnogram. For the correct interpretation of MSLT findings, the recordings should be performed with the following conditions: (1) the patient must be free of drugs that influence sleep for at least 14 days (or at least five times the half-life of the drug and longer-acting metabolite), confirmed by a urine drug screen; (2) the sleep-wake schedule must have been standardized and, if necessary, extended to a minimum of seven hours in bed each night (longer for children) for at least seven days before polysomnography (preferably documented by sleep log and, whenever possible, actigraphy); and (3) nocturnal polysomnography should be performed on the night immediately preceding the MSLT to rule out other sleep disorders that could mimic the diagnostic features of narcolepsy type 1. Sleep time during polysomnography should be curtailed as little as possible with the goal of at least seven hours asleep. The overnight polysomnogram may demonstrate an increase in the amount of stage N1 sleep, and there may be a disruption of the normal sleep pattern, with frequent awakenings. REM sleep without atonia may be present.

Measuring CSF levels of hypocretin-1 is a highly specific and sensitive test for the diagnosis of narcolepsy type 1. Hypocretin-1 can be measured in crude CSF, using a

commercially available radioimmunoassay. When using the Stanford reference sample, values less than 110 pg/mL are highly specific. Alternatively, a laboratory may elect to obtain control data themselves, in which case a level of less than 33% of mean control values is considered abnormal. Issues concerning the standardization of CSF hypocretin measurements remain, but extensive protocols are available. Low CSF hypocretin values are occasionally observed in seriously ill patients with other disorders and should be interpreted within the clinical context.

HLA typing of narcoleptic patients with cataplexy almost always shows the presence of HLA DQB1*0602 (and DR2 or DRB1*1501 in whites and Asians), but this is not diagnostic for narcolepsy. Approximately 25% of the normal Caucasian population, 12% of the Japanese population, and 38% of the black population are positive for DQB1*0602. HLA typing could be considered when a spinal tap is contemplated to assess hypocretin-1 values: if the patient is HLA-negative, hypocretin-1 levels are most likely normal.

Differential Diagnosis

In the absence of cataplexy, narcolepsy type 1 can be diagnosed based on the presence of hypersomnolence and low CSF hypocretin-1 levels. When cataplexy is absent and CSF hypocretin-1 levels are normal or unknown, *narcolepsy type 2* should be diagnosed.

Cataplexy must be differentiated from cataplexy-like episodes that are occasionally observed in normal individuals. For example, feelings of muscle weakness are sometimes reported when healthy subjects laugh out loud. In genuine cataplexy, episodes most often occur with a significant frequency, and are associated with loss of muscle tone. Cataplexy should be differentiated from hypotension, transient ischemic attacks, drop attacks, akinetic seizures, neuromuscular disorders, vestibular disorders, psychological or psychiatric disorders, and sleep paralysis. Clear improvement with antidepressant medications may favor a diagnosis of cataplexy in difficult cases.

Sleepiness may be secondary to *obstructive sleep apnea*, *insufficient sleep syndrome*, *shift work*, *the effects of substances or medications*, or *other sleep disorders*. Many of these conditions can result in early onset REM sleep as well. When cataplexy is present, these disorders do not preclude a diagnosis of narcolepsy type 1. When there is a questionable history of cataplexy in such cases, either comorbid conditions should be adequately treated before performing an MSLT or CSF hypocretin-1 should be measured.

Idiopathic hypersomnia is differentiated from narcolepsy type 1 by the absence of cataplexy and the lack of two or more SOREMPs on the MSLT. In contrast with patients who have narcolepsy, patients with idiopathic hypersomnia generally have high sleep efficiency, sleep drunkenness, and long, unrefreshing naps.

In *insufficient sleep syndrome*, there is no cataplexy, and normalizing sleep time eliminates the daytime sleepiness. *Chronic fatigue syndrome* and *depression* may mimic narcolepsy but do not show the typical MSLT findings. *Malingering* and *substance abuse disorder* should be considered in patients who try to mislead the clinician in order to obtain stimulant medications.

Unresolved Issues and Further Directions

Ten percent of patients with narcolepsy with cataplexy have normal hypocretin-1 levels in the CSF, which suggests that CSF levels either do not perfectly reflect brain hypocretin neurotransmission or that narcolepsy with cataplexy can be caused by factors other than hypocretin deficiency. The cause of the hypocretin cell destruction remains unknown, although an autoimmune-mediated mechanism is suspected. Levels of hypocretin-1 have been reported in the blood of some subjects. The development of serum tests to determine hypocretin deficiency would provide a less invasive diagnostic approach.

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Narcolepsy Type 2

ICD-9-CM code: 347.00 ICD-10-CM code: G47.419

Alternate Names

Narcolepsy without cataplexy.

Diagnostic Criteria

Criteria A-E must be met

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.
B. A mean sleep latency of ≤ 8 minutes and two or more sleep onset REM periods (SOREMPs) are found on a MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.
C. Cataplexy is absent.[1]
D. *Either* CSF hypocretin-1 concentration has not been measured *or* CSF hypocretin-1 concentration measured by immunoreactivity is either > 110 pg/mL *or* > 1/3 of mean values obtained in normal subjects with the same standardized assay.[2]
E. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.

Notes

1. If cataplexy develops later, then the disorder should be reclassified as narcolepsy type 1.

2. If the CSF Hcrt-1 concentration is tested at a later stage and found to be either ≤ 110 pg/mL or < 1/3 of mean values obtained in normal subjects with the same assay, then the disorder should be reclassified as narcolepsy type 1.

Essential Features

Narcolepsy type 2 is characterized by excessive daytime sleepiness and abnormal manifestations of REM sleep on polysomnography/MSLT. Cataplexy is absent, although some atypical sensations of weakness triggered by unusual emotions such as stress and anger may be reported. Refreshing daytime naps are characteristic.

An essential feature of the diagnosis is the presence of a mean sleep latency less than or equal to eight minutes and two or more SOREMPs on an MSLT (or one SOREMP on an MSLT and one on the preceding nocturnal polysomnogram). The presence of CSF hypocretin-1 concentrations ≤ 110 pg/mL or less than one third of mean values obtained in normal subjects with the same assay excludes the diagnosis, but most patients with narcolepsy type 2 will not have undergone CSF examination.

Associated Features

Sleep paralysis, hypnagogic hallucinations, or automatic behavior may be present. Memory lapses, automatic behavior, ptosis, blurred vision, and diplopia may occur in association with sleepiness. REM sleep behavior disorder and nonrapid eye movement (NREM) parasomnias may occur. Nocturnal sleep disruption with frequent awakenings may be present.

Clinical and Pathophysiological Subtypes

Narcolepsy type 2 due to a medical condition: This condition fulfills criteria for narcolepsy type 2 and is attributable to another medical disorder. Neurologic disorders associated with narcolepsy type 2 include tumors or sarcoidosis of the hypothalamus, autoimmune or paraneoplastic disorders associated with anti-Ma-2 or anti-aquaporin-4 antibodies, multiple sclerosis, myotonic dystrophy, Prader-Willi syndrome, Parkinson disease, and head trauma. In disorders associated with both sleep apnea and narcolepsy type 2, such as myotonic dystrophy or Prader-Willi syndrome, a diagnosis of narcolepsy type 2 should only be made if abnormal MSLT findings persist after the sleep apnea is adequately treated. In all cases, especially with complex problems such as head trauma, clinical judgment should be used to determine if the development of narcolepsy was a mere coincidence or was triggered by the event or disorder.

Demographics

The exact prevalence of narcolepsy type 2 is uncertain. Cases of narcolepsy without cataplexy represent 15% to 25% of the clinic narcoleptic population. A population-based study suggested a higher percentage (36%), corresponding to a point prevalence of 20.5/100,000. Population-based studies have shown that approximately 4% to 9.5% of adults may have multiple SOREMPs during random MSLTs, but shift workers and subjects with sleep deprivation or sleep apnea were included in the studies. Although both sexes can be affected, the prevalence may be slightly higher in men. The age of onset mirrors that of narcolepsy type 1.

Predisposing and Precipitating Factors

As discussed below, about 24% of patients with narcolepsy but no cataplexy will have low CSF Hcrt-1 levels and almost all of these will be positive for the HLA DQB1*0602 antigen. These patients probably share a common pathogenesis with narcolepsy with cataplexy and should be classified as narcolepsy type 1. Underlying genetic and environmental factors associated with other patients with narcolepsy type 2 are unknown. Environmental precipitating factors are suspected from case reports but have never been proven to trigger narcolepsy without cataplexy. Among the most commonly reported triggers are head trauma and unspecified viral illnesses.

Familial Patterns

The detailed genetic pattern of narcolepsy type 2 is unknown. Relatives of patients with narcolepsy type 1 may be more likely to experience partial narcolepsy symptoms compatible with the diagnosis of narcolepsy type 2.

Onset, Course, and Complications

Onset typically occurs during adolescence. In about 10% of patients, cataplexy will develop later in the course of the disease, necessitating a change in diagnosis to narcolepsy type 1. Most of these patients will, if tested, have absent or intermediate levels of CSF Hcrt-1. In a cohort of patients with narcolepsy without cataplexy in whom CSF Hcrt-1 status was known, 33% of those with low levels later developed cataplexy, compared with 18% with intermediate levels and only 1% with normal levels. When left untreated, narcolepsy type 2 is socially disabling and isolating. Patients have a tendency to fail in school and are often dismissed from their jobs. Driving may be avoided for fear of a motor vehicle accident. The inability to sleep at night may further contribute to a loss of control these patients have over their schedule. Depression and weight gain also are common.

Developmental Issues

Children with narcolepsy type 2 will typically present with a reappearance of regular daytime napping after naps had been discontinued. In all pediatric cases, one should consider the possibility of an evolving disorder with the development of cataplexy over time. Once the patient develops clear cataplexy, the diagnosis should be changed to narcolepsy type 1. Limited information is available on narcolepsy type 2 prior to adolescence. Descriptions of the experience of sleep paralysis or hypnagogic hallucinations are very difficult to evoke in young patients, and normative data are not available for the MSLT in children younger than six years of age. In peripubertal children and adolescents, the diagnosis is often challenging. The most common causes of short sleep latencies, often with multiple SOREMPs on the MSLT, are chronic sleep deprivation and delayed sleep phase disorder. Behavioral problems may be associated with the onset of the disorder, and symptoms may be hidden by the patient. Inattentiveness, lack of energy, insomnia, bizarre hallucinations, or a combination thereof can lead to a psychiatric misdiagnosis of schizophrenia or depression. If the MSLT shows equivocal results, repeating it after a time interval may be helpful, as SOREMPs often emerge later in children.

Pathology and Pathophysiology

Narcolepsy type 2 is most likely a heterogeneous disorder. Approximately 24% of narcoleptic patients without cataplexy have a low CSF Hcrt-1 concentration, and another 8% have intermediate levels (> 110 pg/mL but ≤ 200 pg/mL). The CSF Hcrt-1 status of most patients with narcolepsy type 2 is unknown (those patients who are known to have absent CSF Hcrt-1 levels are classified as narcolepsy type 1). Therefore, there will be a subgroup of about one fourth to one third of narcolepsy type 2 patients who will have hypocretin deficiency, presumably from loss of the hypocretin-producing neurons. This group of patients cannot be accurately separated clinically or by laboratory tests (other than CSF Hcrt-1 level) from the majority of patients without cataplexy who have normal CSF Hcrt-1 levels. Although those with low CSF Hcrt-1 levels have a younger age of onset and their MSLT shows shorter mean sleep latency with more SOREMPs in comparison with those with normal levels, there is too much overlap between the groups for these differences to be helpful diagnostically in individual patients. One hundred percent of patients with low CSF Hcrt-1 levels are positive for HLA DQB1*0602. About 26% of patients with normal levels are also HLA positive, a percentage not higher than that seen in the normal population. The underlying pathophysiology of the remainder of patients who have normal CSF Hcrt-1 levels is unknown. It is possible some may have partial hypocretin deficiency severe enough to cause sleepiness but not severe enough to result in cataplexy or low CSF Hcrt-1 levels. However, support for this hypothesis is lacking in that there are no major

differences in clinical or polysomnographic findings in those positive or negative for HLA DQB1*0602. In the only postmortem study of a case of narcolepsy without cataplexy (CSF Hcrt-1 status unknown), the number of hypocretin cells was decreased but not as much as in cases of narcolepsy with cataplexy.

Objective Findings

It is strongly rcommended that the MSLT be preceded by at least one week of actigraphic recording with a sleep log to establish whether the results could be biased by insufficient sleep, shift work, or another circadian sleep disorder. The MSLT demonstrates a mean latency of less than eight minutes, typically less than five minutes, with two or more SOREMPs or one SOREMP together with a SOREMP on the preceding polysomnogram. Meta-analysis shows mean sleep latencies in narcoleptic patients with cataplexy of 3.1 ± 2.9 minutes. Recent data suggest that a SOREMP within 15 minutes of onset of nocturnal sleep is a highly specific finding in the absence of another sleep disorder, but with low sensitivity. Therefore, the criteria for narcolepsy type 2 allow the "replacement" of one SOREMP in the MSLT with a SOREMP on the preceding polysomnogram. For the correct interpretation of MSLT findings, the recordings should be performed with the following conditions: (1) the patient must be free of drugs that influence sleep for at least 14 days (or at least five times the half-life of the drug and longer-acting metabolite), confirmed by a urine drug screen; (2) the sleep-wake schedule must have been standardized and, if necessary, extended to a minimum of seven hours in bed each night (longer for children) for at least seven days before polysomnography (preferably documented by sleep log and, whenever possible, actigraphy); and (3) nocturnal polysomnography should be performed on the night immediately preceding the MSLT to rule out other sleep disorders that could mimic the diagnostic features of narcolepsy type 2. Sleep time during polysomnography should be curtailed as little as possible, with the goal of at least seven hours asleep. The overnight polysomnogram may demonstrate an increase in the amount of stage N1 sleep, and there may be a disruption of the normal sleep pattern, with frequent awakenings. REM sleep without atonia may be present.

About 45% of narcolepsy type 2 cases have been reported to be HLA DQB1*0602 positive, compared with 12% to 38% of controls. Whereas essentially all patients who have low CSF Hcrt-1 levels will be positive, about 25% of those with normal levels will also be positive. Assuming that 24% of patients with narcolepsy but no cataplexy will have low CSF Hcrt-1 levels, the probability that an HLA- positive patient will have low Hcrt-1 levels is only 0.56. Therefore the HLA status of a patient cannot be used to diagnose narcolepsy type 2 nor to predict with high probability the patient's CSF Hcrt-1 levels. However, if lumbar puncture is contemplated to measure CSF

Hcrt-1 levels, HLA typing should be performed first; if the patient is HLA negative, CSF Hcrt-1 levels will almost certainly be normal and the lumbar puncture will be unnecessary.

Approximately 24% of narcoleptic patients without cataplexy have a low CSF Hcrt-1 concentration and another 8% have intermediate levels (> 110 pg/mL but ≤ 200 pg/mL). If the CSF Hcrt-1 levels of such patients are known to be low, they are classified as narcolepsy type 1, but the CSF Hcrt-1 status will not be known for most of these patients. Possible indications for considering measuring CSF Hcrt-1 levels as a diagnostic procedure would be the presence of disorders such as obstructive sleep apnea or the use of psychotropic medications that may complicate interpretation of an MSLT.

Differential Diagnosis

Narcolepsy type 1 is diagnosed if cataplexy is present or the CSF hypocretin levels are known to be low even in the absence of cataplexy. Patients with *idiopathic hypersomnia* may have mean sleep latencies on MSLT similar to those of narcolepsy type 2, but have fewer than two SOREMPs on MSLT and the preceding polysomnogram combined. In contrast to narcolepsy, patients with *idiopathic hypersomnia* generally have high sleep efficiency, sleep drunkenness, and long, unrefreshing naps. Sleepiness may be secondary to *obstructive sleep apnea (OSA)*, *insufficient sleep syndrome*, *shift work*, *the effects of substances or medications*, or *other sleep disorders*. Many of these conditions can result in early-onset REM sleep, so their clinical and polysomnographic exclusion is essential before a diagnosis of narcolepsy type 2 is made. However, the presence of other sleep disorders does not preclude a diagnosis of narcolepsy type 2 if daytime sleepiness and REM abnormalities persist after adequate treatment of the initial disorder. *Chronic fatigue syndrome* and *depression* may mimic narcolepsy but do not show the typical MSLT findings. *Malingering* and *substance abuse disorder* should be considered in patients who try to mislead the clinician in order to obtain stimulant medications.

Unresolved Issues and Further Directions

Excluding the minority of patients with definite hypocretin deficiency, the underlying biology of narcolepsy without the presence of cataplexy is unknown. It is not established whether narcolepsy type 2 is a homogeneous or heterogeneous condition. It is uncertain whether or not some patients have partial hypocretin deficiency not identifiable from CSF measurements. Further advances in classification will depend on answers to these unknowns. Further studies on the natural history of narcolepsy type 2 are needed to determine the cause of the hypersomnolence and the risk of development of cataplexy over time.

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Idiopathic Hypersomnia

ICD-9-CM code: 327.11 ICD-10-CM code: G47.11

Alternate Names

Idiopathic CNS hypersomnolence.

Diagnostic Criteria

Criteria A-F must be met

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.[1]

B. Cataplexy is absent.

C. An MSLT performed according to standard techniques shows fewer than two sleep onset REM periods or no sleep onset REM periods if the REM latency on the preceding polysomnogram was less than or equal to 15 minutes.[2]

D. The presence of at least one of the following:

   1. The MSLT shows a mean sleep latency of ≤ 8 minutes.
   2. Total 24-hour sleep time is ≥ 660 minutes (typically 12–14 hours)[3] on 24-hour polysomnographic monitoring (performed after correction of chronic sleep deprivation), *or* by wrist actigraphy in

association with a sleep log (averaged over at least seven days with unrestricted sleep).[4]

E. Insufficient sleep syndrome is ruled out (if deemed necessary, by lack of improvement of sleepiness after an adequate trial of increased nocturnal time in bed, preferably confirmed by at least a week of wrist actigraphy).

F. The hypersomnolence and/or MSLT findings are not better explained by another sleep disorder, other medical or psychiatric disorder, or use of drugs or medications.

Notes

1. Severe and prolonged sleep inertia, known as sleep drunkenness (defined as prolonged difficulty waking up with repeated returns to sleep, irritability, automatic behavior, and confusion) and/or long (> 1 hour), unrefreshing naps are additional supportive clinical features.
2. A high sleep efficiency (≥ 90%) on the preceding polysomnogram is a supportive finding (as long as sleep insufficiency is ruled out).
3. The total 24-hour sleep time required for diagnosis may need to be adapted to account for normal changes in sleep time associated with stages of development in children and adolescents as well as for variability across cultures in all age groups.
4. Occasionally, patients fulfilling other criteria may have an MSLT mean sleep latency longer than 8 minutes and total 24-hour sleep time shorter than 660 minutes. Clinical judgment should be used in deciding if these patients should be considered to have idiopathic hypersomnia (IH). Great caution should be exercised to exclude other conditions that might mimic the disorder. A repeat MSLT at a later date is advisable if the clinical suspicion for IH remains high.

Essential Features

IH is characterized by excessive daytime sleepiness that occurs in the absence of cataplexy, is accompanied by no more than one SOREMP on MSLT and preceding polysomnogram combined, and is not adequately explained by another disorder. Other disorders causing sleepiness must be carefully considered and excluded, especially insufficient sleep syndrome. Objective evidence of hypersomnolence must be demonstrated by an MSLT showing a mean sleep latency of ≤ 8 minutes or by polysomnography or wrist actigraphy showing a total 24-hour sleep time of ≥ 660 minutes. A prolonged and severe form of sleep inertia, historically known as sleep drunkenness, consists of prolonged difficulty waking up with repeated returns to sleep, irritability, automatic

behavior, and confusion. It is reported in 36% to 66% of patients with IH in different series. Subjects typically do not easily awaken to alarm clocks and frequently use special devices or procedures to wake up. Naps are generally long, often more than 60 minutes, and described as unrefreshing by 46% to 78% of patients. Sleep efficiency on polysomnogram is usually high (mean 90% to 94%). Self-reported total sleep time is longer than in controls and is ≥ 10 hours in at least 30% of patients.

Associated Features

Associated symptoms which suggest a dysfunction of the autonomic nervous system may be present. These symptoms include headache, orthostatic disturbance, perception of temperature dysregulation, and peripheral vascular complaints (Raynaud-type phenomena with cold hands and feet). Sleep paralysis and hypnagogic hallucinations may also be reported, but the frequency is uncertain (4% to 40% in different series).

Clinical and Pathologic Subtypes

The 2005 2nd edition of the International Classification of Sleep Disorders divided IH into two disorders: IH with long sleep time, and IH without long sleep time. IH is likely a heterogeneous condition, the pathophysiology of which is currently unknown. However, recent studies suggest that a division of the disorder based on the length of nocturnal sleep lacks validity. Comparison of patients with ≥ 10 hours of sleep to those with < 10 hours show no differences in Epworth Sleepiness Scale scores, MSLT mean sleep latencies, or percentage with sleep drunkenness, unrefreshing naps, hypnagogic hallucinations, or sleep paralysis. The only reported differences are that the group with long sleep is somewhat younger and thinner, with lower Horne-Ostberg scores and marginally higher sleep efficiency. If MSLT mean sleep latencies are not used as a diagnostic criterion, the distribution of latencies is unimodal, suggesting no separate subtypes. In addition, an actigraphy study has shown that patients with IH tend to overestimate their sleep time by a mean of 0.99 hours, thus making the fundamental criterion for distinguishing between patients with long and shorter sleep inaccurate. Clinicians may wish to continue to note sleep duration as an important clinical feature, but the caveats discussed above should be clearly considered. Any future separation of IH into distinct conditions must await advances in understanding the underlying biology.

Demographics

Prevalence and incidence of IH are not known. Some studies have suggested a higher prevalence in women.

Predisposing and Precipitating Factors

In contrast to narcolepsy, the disorder is not known to be HLA associated, and no consistent precipitating factor has been identified.

Familial Patterns

A familial predisposition to hypersomnia has been reported but rigorous studies have not been performed.

Onset, Course, and Complications

The mean age of onset of IH in different series is 16.6–21.2 years. Once established, the disorder is generally stable in severity and long lasting, although a spontaneous remission rate of 14% has been reported in one series. Complications are mostly social and professional, and include poor work or school performance, reduced earnings, and loss of employment.

Developmental Issues

IH frequently develops in adolescence. Exclusion of other causes of hypersomnolence in that age group, including delayed sleep-wake phase disorder, obstructive sleep apnea, insufficient sleep syndrome, and use of recreational drugs, is essential. Early in the development of narcolepsy, SOREMPs may not be present on MSLT; therefore, some patients may need to be reclassified later as narcolepsy type 2. If the 24-hour total sleep time is used to confirm the diagnosis of IH in a child or adolescent, normal values may need to be adapted to account for changes in sleep time associated with stages of development.

Pathology and Pathophysiology

The pathophysiology of IH is unknown. Neurochemical studies measuring monoamine metabolites in the CSF have been inconclusive. CSF hypocretin-1 concentrations in patients with IH are normal. CSF histamine levels have been reported to be low in patients with narcolepsy and IH, but a recent study did not confirm these findings.

Objective Findings

Polysomnographic monitoring generally demonstrates NREM and REM sleep in expected proportions with normal REM latency. Total sleep time is often prolonged. Sleep apnea should be either absent or adequately treated before diagnosing this disorder, with special attention paid to excluding significant respiratory effort related arousals. The MSLT should not show more than one SOREMP (or none if a SOREMP was observed on the preceding night's polysomnogram (PSG)). The mean sleep latency on

the MSLT is usually shorter than in controls but longer than in most patients with narcolepsy, averaging 8.3 and 7.8 minutes in two large studies.

In patients with MSLT mean latencies > 8 minutes, prolonged sleep monitoring should be performed by polysomnography (24 hours) or wrist actigraphy (7 days with unrestricted sleep) after correction of sleep deprivation, exclusion of other sleep disorders, and discontinuation of sedating medication as required for an MSLT (see Narcolepsy–Objective Findings). Total 24-hour sleep time in adults (major sleep episode plus naps) must be ≥ 660 minutes (note that the use of 24-hour PSG monitoring for the diagnosis of IH has been validated against controls, but the use of seven days of actigraphic monitoring still awaits validation).

Differential Diagnosis

IH may be confused with *OSA*, especially when respiratory-related arousals (rather than apneas or hypopneas) are present. *Narcolepsy type 2* is distinguished from IH by the presence of two or more sleep onset REM periods on the MSLT or preceding PSG. *Insufficient sleep syndrome* must be carefully excluded by extending the patient's sleep before testing. Historical information, physical examination, and, if indicated, laboratory testing including brain imaging should help rule out *hypersomnolence due to a medical disorder*. In particular, *posttraumatic hypersomnolence*, *residual hypersomnolence following adequate treatment of sleep apnea*, and *sleep fragmentation due to pain* may mimic IH. *Hypersomnolence due to a medication or substance* must be considered and ruled out by discontinuation of possible causative agents, if clinically appropriate. *Hypersomnia associated with a psychiatric disorder* should be considered in patients with a psychiatric condition, most typically depression. The complaint of excessive sleepiness and prolonged sleep may be rather similar to that of patients with IH, except that it may vary from day to day and is often associated with poor sleep at night. The MSLT in hypersomnia associated with a psychiatric disorder does not demonstrate a short mean sleep latency. *Chronic fatigue syndrome* is characterized by persistent or relapsing fatigue that does not resolve with sleep or rest. Patients clearly complain of fatigue rather than excessive daytime sleepiness, and the mean MSLT sleep latency is normal. *Long sleepers* feel fully refreshed and do not experience daytime sleepiness if they are allowed to sleep as long as they need, in contrast with patients with IH who continue to feel sleepy regardless of prior sleep duration.

Unresolved Issues and Future Directions

There is a paucity of knowledge regarding the neurobiology of IH. Further research in this area, as well as more precise characterization of clinical characteristics and treatment response, is required.

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Kleine-Levin Syndrome

ICD-9-CM code: 327.13 ICD-10-CM code: G47.13

Alternate Names

Recurrent hypersomnia, periodic hypersomnolence.

Diagnostic Criteria

Criteria A-E must be met

A. The patient experiences at least two recurrent episodes of excessive sleepiness and sleep duration, each persisting for two days to five weeks.
B. Episodes recur usually more than once a year and at least once every 18 months.
C. The patient has normal alertness, cognitive function, behavior, and mood between episodes.
D. The patient must demonstrate at least *one* of the following during episodes:
    1. Cognitive dysfunction.
    2. Altered perception.
    3. Eating disorder (anorexia or hyperphagia).
    4. Disinhibited behavior (such as hypersexuality).
E. The hypersomnolence and related symptoms are not better explained by another sleep disorder, other medical, neurologic, or psychiatric disorder (especially bipolar disorder), or use of drugs or medications.

Essential Features

Kleine-Levin syndrome is characterized by relapsing-remitting episodes of severe hypersomnolence in association with cognitive, psychiatric, and behavioral disturbances. A typical episode lasts a median 10 days (range, 2.5–80 days), with rare episodes lasting several weeks to months. The first episode is often triggered by an infection or alcohol intake, with further episodes recurring every 1–12 months (median three months) for years. During episodes, patients may sleep as long as 16 to 20 hours per day, waking or getting up only to eat and void (incontinence is not observed). They remain rousable, but are irritable if prevented from sleeping. When they are awake during episodes, most patients are exhausted, apathetic, confused, and slow in speaking and answering. Anterograde amnesia is typical. Almost all report a dreamlike, altered perception of the environment (derealization). Less commonly, patients eat ravenously (66%, although one third eat less), are hypersexual (53%, principally men), childish, depressed (53%, predominantly women), and anxious at being left alone and seeing strangers, and experience hallucinations and delusions (30%). Patients are remarkably normal between episodes with regard to sleep, cognition, mood, and eating. The disease typically resolves after a median of 14 years, except in adult-onset cases, when the course may be more prolonged. The simultaneous occurrence of all these symptoms is the exception rather than the rule, with hypersomnolence being more characteristic at the disease onset and during the first part of the episodes, and disinhibited behaviors being evident during only a few episodes. In occasional cases, isolated recurrent hypersomnolence may be the only symptom. Amnesia, transient dysphoria, or elation with insomnia may signal the termination of an episode.

Associated Features

Physical examination is unremarkable, except for general psychomotor slowing. Social and occupational impairment during attacks is often severe, with teenagers bedridden for days, but can be variable depending on the frequency, severity, and duration of episodes.

Clinical and Pathophysiological Subtypes

Menstrual-related Kleine-Levin syndrome (alternate name: menstrual-related hypersomnia): This descriptor is used when episodes are exclusively associated with menstruation (occurring just before or during menses), a condition reported in only 18 women worldwide. Hypersomnolence episodes in these cases have been associated with compulsive eating in 65%, sexual disinhibition in 29%, and depressive mood in 35%. Episodes last 3 to 15 days and recur less than three times a year. One boy with Kleine-Levin syndrome is reported to have a sister affected by menstrual-related hypersomnolence. Menstrual-related hypersomnia may be a variant of Kleine-Levin

syndrome, although response to contraceptive doses of estrogen and progesterone, reported in some cases, suggests a reproductive endocrine disturbance.

Demographics

Kleine-Levin syndrome is rare, with a prevalence estimated around 1 to 2 cases per million. Roughly 500 cases have been reported to date in the literature, from all countries in which the disease has been investigated. The disease starts during the second decade in 81% of patients, with a male/female ratio of 2:1. Adults and younger children may also be affected.

Predisposing and Precipitating Factors

Birth and developmental problems, as well as Jewish heritage, are risk factors for developing the syndrome. The frequency of the HLA DQB1*02 was increased compared with controls in a retrospective, multicenter series of 30 patients with Kleine-Levin syndrome, but not in another larger prospective series (n = 108). A flu-like illness or an infection of the upper airway (and more rarely gastroenteritis) is often reported immediately prior to the onset of the first episode, and more rarely before relapses. Other less frequently reported triggering events include alcohol consumption, head trauma, travel, or exposure to anesthesia.

Familial Patterns

Familial cases of Kleine-Levin syndrome are found in 5% of patients, including twins, parent-child, siblings, and uncle-nephew associations. There is no increased history of mood disorders in family members of patients.

Onset, Course, and Complications

Early adolescence (second decade) is the usual age of onset. The course of Kleine-Levin syndrome is characterized by recurrent episodes of severe sleepiness, lasting up to several weeks, with normal functioning between episodes. Several long-term studies suggest an often-benign course, with episodes lessening in duration, severity, and frequency over a median course of 14 years. Male sex, age at onset younger than 12 years or older than 20 years, as well as the presence of hypersexuality during episodes, predict longer disease duration. Complications are mainly social and occupational. In rare cases, subjects have been reported to choke while eating voraciously, to have suicidal thoughts, or to be involved in a car accident. A reduced long-term working memory capacity following episodes was reported in eight patients with Kleine-Levin syndrome.

Developmental Issues

Adolescents are affected in most cases. However, the onset of the condition has been reported in children as young as four years.

Pathology and Pathophysiology

Postmortem examination of the central nervous system has been performed in only four cases, with inconsistent findings. One subject showed significant perivascular lymphocytic infiltrations in the hypothalamus, amygdala, and the grey matter of the temporal lobes; a second demonstrated similar infiltrations in the thalamus; and a third in the diencephalon and the midbrain with a suggestion of mild localized encephalitis. In the fourth case, a smaller locus coeruleus and decreased pigmentation in the substantia nigra were reported. Magnetic resonance imaging was unremarkable. In contrast, functional brain imaging studies during episodes are frequently abnormal, showing hypometabolism in the thalamus, hypothalamus, mesial temporal lobe, and frontal lobe. Some of these abnormalities persist during asymptomatic periods in half of the patients. An autoimmune basis for the disorder is suggested clinically (onset occurs during adolescence, often in conjunction with an infection) and by the occasional association with HLA DQB1*02.

Objective Findings

Routine electroencephalograms obtained during episodes have shown general slowing of background electroencephalographic activity and often paroxysmal—0.5-2.0-second—bursts of bisynchronous, generalized, moderate- to high-voltage 5- to 7-Hz waves. Polysomnography studies are often difficult to interpret, and results are dependent on the duration of recording (overnight vs. 24-hour monitoring) as well as the timing (at the beginning versus the end of episodes or at onset of the disease or later in its course). Twenty-four-hour polysomnography demonstrates prolonged total sleep time (a mean 11–12 hours), and 18 hours or more in some reports. During nocturnal polysomnography in 17 children, nighttime slow wave sleep percentage was decreased during the first half of the episodes, and REM sleep decreased during the second half. Results of the MSLT are highly dependent on the subjects' willingness to comply with the procedure, and may either be normal or abnormal, showing short latencies or multiple SOREMPs. CSF cytology and protein are normal. CSF levels of hypocretin-1 were within normal range in 16 patients, although intraepisodic levels are lower than interepisodic levels. Computed tomography scans and magnetic resonance imaging are normal. Brain functional imaging is abnormal in most cases, with hypoperfusion of the left or right temporal and frontal lobes as well as the diencephalon. These abnormalities are present during the episode of hypersomnolence and sometimes between episodes. Hormone levels are normal, as are 24-hour secretory patterns.

Differential Diagnosis

Recurrent waxing and waning episodes of sleepiness may be secondary to *structural insults of the central nervous system*. *Tumors within the third ventricle* (such as

colloid cysts, pedunculated astrocytomas, or, in some cases, craniopharyngiomas) may produce intermittent obstructions of ventricular flow, leading to headaches, vomiting, vague sensorial disturbances, and a paroxysmal impairment of alertness. *Encephalitis*, *hyperammonemic encephalopathy*, *multiple sclerosis*, *head trauma*, *porphyria*, *Lyme disease*, *basilar migraine*, and *complex partial status epilepticus* less frequently mimic symptoms of Kleine-Levin syndrome. Recurrent episodes of sleepiness also are reported in the context of psychiatric disorders, such as *depression*, *bipolar disorder*, *seasonal affective disorder*, and *somatoform disorder*. However, the onset and offset of symptoms are less abrupt than in Kleine-Levin syndrome and persist to some extent between episodes. Other differential diagnoses include *excessive sleepiness due to a medication or substance*, *OSA*, *narcolepsy*, *IH*, and *insufficient sleep*. In these disorders, however, the complaint of excessive sleepiness occurs daily and is usually not recurrent or periodic. There is no evidence that Kleine-Levin syndrome occurs as a result of a seizure disorder.

Unresolved Issues and Future Directions

The pathophysiology of this disorder is not known. Evidence to date suggests that a localized but multifocal encephalopathy occurs during episodes of Kleine-Levin syndrome, as functional imaging and electroencephalography (EEG) slowing indicate thalamic, temporal, and frontal lobe involvement. The cause of these episodic abnormalities may be genetic, autoimmune, inflammatory, or metabolic.

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Hypersomnia Due to a Medical Disorder

ICD-9-CM code: 327.14 ICD-10-CM code: G47.14

Alternate Names

Not applicable.

Diagnostic Criteria

Criteria A-D must be met

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.
B. The daytime sleepiness occurs as a consequence of a significant underlying medical or neurological condition.
C. If an MSLT is performed, the mean sleep latency is ≤ 8 minutes, and fewer than two sleep onset REM periods (SOREMPs) are observed.[1]
D. The symptoms are not better explained by another untreated sleep disorder,[2] a mental disorder, or the effects of medications or drugs.

Notes

1. In the subtype of residual hypersomnolence after treatment of obstructive sleep apnea, the MSLT mean latency may be > 8 minutes.
2. Should criteria for narcolepsy be fulfilled, a diagnosis of narcolepsy type 1 or type 2 due to a medical condition should be used rather than hypersomnia due to a medical condition.
3. In patients with severe neurological or medical disorders in whom it is not possible or desirable to perform sleep studies, the diagnosis can be made by clinical criteria.

Essential Features

Patients with this disorder have excessive nocturnal sleep, daytime sleepiness, or excessive napping that is attributable to a coexisting medical or neurological disorder. Daytime sleepiness may be of variable severity and may resemble that of narcolepsy (i.e., refreshing naps) or idiopathic hypersomnia (i.e., long periods of unrefreshing sleep). Sleep paralysis, hypnagogic hallucinations, or automatic behavior may be present, but if the patient has cataplexy, the MSLT shows two or more SOREMPs, or CSF Hcrt-1 levels are low, then narcolepsy (type 1 or type 2) due to a medical condition should be diagnosed. In patients with both sleep related breathing disorders and hypersomnia due to a medical disorder, the latter diagnosis should be made only if the hypersomnolence persists after adequate treatment of the sleep disordered breathing. Hypersomnia due to a medical disorder is only diagnosed if the medical condition is

judged to be directly causing the excessive sleepiness. Hypersomnolence has been described in association with a large range of conditions, including metabolic encephalopathy, head trauma, stroke, brain tumors, encephalitis, systemic inflammation (e.g., chronic infections, rheumatologic disorders, cancer), genetic disorders, and neurodegenerative diseases.

Associated Features

Not applicable or known.

Clinical and Pathophysiological Subtypes

Many medical conditions can cause hypersomnolence.

Hypersomnia secondary to Parkinson disease: Significant hypersomnolence documented by MSLT has been reported in some cases of Parkinson disease. Hypersomnia in Parkinson disease may be due to insufficient control of nocturnal symptoms, resulting in insufficient sleep and daytime sleepiness. If so, the diagnosis should be insomnia disorder. Cases of hypersomnolence that are due to the side effects of dopaminergic agents should be coded as hypersomnia due to a medication or substance. In other cases, however, hypersomnolence is likely of central origin and should be classified in this section. Parkinson disease patients with an MSLT profile consistent with narcolepsy should be coded as narcolepsy due to a medical condition.

Posttraumatic hypersomnia: Hypersomnolence appears to be common after traumatic brain injury (TBI), with one meta-analysis suggesting a frequency of 28% of TBI patients. In some cases this may be caused by injury to the hypocretin/orexin neurons or other wake-promoting neural systems. However, the prevalence of sleep related breathing disorder (SRBD) in patients with head trauma is high (frequency 23% to 25%). The nature of the relationship between TBI and OSA remains undefined. Therefore, control of other potential sleep disorders is necessary prior to making a diagnosis of hypersomnia due to a medical disorder (posttraumatic hypersomnia).

Genetic disorders associated with primary central nervous system somnolence: Genetic disorders such as Niemann Pick type C disease and Norrie disease have been associated with daytime somnolence. Prader-Willi syndrome, myotonic dystrophy, Moebius syndrome, and fragile X syndrome are other examples of centrally mediated sleepiness. A number of genetic disorders have been reported to be associated with both sleep disordered breathing and hypersomnolence (e.g., myotonic dystrophy and Prader-Willi syndrome). In these cases, hypersomnia due to a medical disorder should be diagnosed only if the excessive sleepiness is still present after adequate treatment of

the SRBD. Smith-Magenis syndrome is a neurodevelopmental disorder characterized by dysmorphic facial features, behavioral disturbance with onset in early childhood, daytime somnolence, and night awakenings in association with reversal in the timing of the melatonin secretion pattern (i.e., the serum levels of melatonin are high during the daytime and low at night).

Hypersomnia secondary to brain tumors, infections, or other central nervous system lesions: Strokes, infections, tumors, sarcoidosis, or neurodegenerative lesions of the brain, especially in the hypothalamus or rostral midbrain, may produce daytime sleepiness. In patients with brain tumors, the sleepiness may be due to the tumor itself or the effects of treatment.

Hypersomnia secondary to endocrine disorder: Hypothyroidism is the most recognized example of this condition.

Hypersomnia secondary to metabolic encephalopathy: Hepatic encephalopathy, chronic renal insufficiency, adrenal or pancreatic insufficiency, exposure to toxins, and certain inherited metabolic disorders in childhood may result in hypersomnolence.

Residual hypersomnia in patients with adequately treated OSA: Some patients with SRBDs report persistent sleepiness despite apparently adequate amounts of sleep and optimal treatment of their sleep apnea and other known sleep disorders. They may have moderately elevated Epworth Sleepiness Scale scores, but most have mean sleep latencies > 8 minutes on MSLT. They also report more fatigue, apathy, and depression. It is essential that sleep disordered breathing be fully treated for at least three months, and that control of the SRBD be confirmed by: (1) a download of positive airway pressure (PAP) machine compliance data demonstrating optimal usage (preferably at least 7 hours a night); and (2) a polysomnogram demonstrating elimination of essentially all sleep disordered breathing. Other causes of sleepiness, such as insufficient sleep syndrome, psychiatric disorders, or hypersomnolence related to medications or drugs must be eliminated. Animal studies have suggested this residual sleepiness could be caused by hypoxic injury to monoamine systems. Obesity itself may also contribute, and more research is needed to understand the underlying mechanism.

Demographics

Demographics reflect those of the underlying condition.

Predisposing and Precipitating Factors

Predisposing and precipitating factors reflect those of the underlying condition.

Familial Patterns

Familial patterns reflect those of the underlying condition.

Onset, Course, and Complications

Onset, course, and complications reflect those of the underlying condition.

Developmental Issues

Daytime naps are normal in children younger than 3-4 years; thus, it is difficult to differentiate physiologic napping from hypersomnolence in children younger than this age. Inattentiveness, mood swings, and learning difficulties often accompany childhood daytime sleepiness. Reference values for the MSLT in children differ from those of adults, and this issue should be considered during the evaluation process. Special attention should be paid to genetic disorders in children.

Pathology and Pathophysiology

Pathology and pathophysiology reflect those of the underlying condition.

Objective Findings

Nocturnal polysomnography may show normal or moderately disturbed sleep. In patients with a metabolic encephalopathy, EEG abnormalities may be present, such as an increase in the amount of slow wave sleep. MSLT must show fewer than 2 SOREMPs and usually will show a mean sleep latency less than eight minutes. If clinically significant sleep disordered breathing or periodic limb movements are present, they should be treated prior to diagnosing hypersomnia due to a medical disorder.

Differential Diagnosis

See the differential diagnosis in previous hypersomnolence sections. The major challenge in establishing a diagnosis of hypersomnia due to a medical disorder is determining whether the associated medical or neurological disorder is truly causing the hypersomnolence.

Unresolved Issues and Future Directions

This area is understudied. Multiple complex neurological, metabolic, endocrine, and medication-related interactions may be present. Further studies are needed to define the reciprocal relationships between sleep disorders and other diseases.

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Hypersomnia Due to a Medication or Substance

ICD-9-CM code: 292.85 (drug-induced); 291.82 (alcohol-induced)
ICD-10-CM code: F11-F19 (see table in Appendix B for detailed coding instructions)

Alternate Names

Hypersomnia due to substance abuse, hypersomnia due to stimulant withdrawal, hypersomnia due to sedative abuse, toxic hypersomnia, toxic encephalopathy.

Diagnostic Criteria

Criteria A-C must be met

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep.
B. The daytime sleepiness occurs as a consequence of current medication or substance use or withdrawal from a wake-promoting medication or substance.
C. The symptoms are not better explained by another untreated sleep disorder, medical or neurological disorder, or mental disorder.

Essential Features

Patients with this disorder have excessive nocturnal sleep, daytime sleepiness, or excessive napping that is attributable to sedating medications, alcohol, or drugs of abuse. This diagnosis also includes hypersomnolence associated with withdrawal from amphetamines and other drugs. If narcolepsy or hypersomnolence existed prior to stimulant abuse, the diagnosis of hypersomnia due to a medication or substance should not be used.

Associated Features

Associated features reflect those of the medications or substances responsible.

Clinical and Pathological Subtypes

Hypersomnia due to sedating medications: Sedation is a common side effect of many prescription medications including benzodiazepines, nonbenzodiazepine hypnotics, opioids, barbiturates, anticonvulsants, antipsychotics, anticholinergics, and some antidepressants and antihistamines. Sleepiness also can occur with some dopamine agonists such as pramipexole or ropinirole, and with many antiseizure medications. Though less common, sleepiness can also occur with nonsteroidal anti-inflammatory drugs, some antibiotics, antispasmodics, antiarryhthmics, and beta-blockers. Over-the-counter medications, such as valerian and melatonin, can produce sedation. Excessive sleepiness is especially common when these drugs are used in elderly patients or those with multiple medical conditions, or in combination. Some tolerance to the sedative effects can occur with time.

Hypersomnia due to substance abuse: Daytime sleepiness can occur with abuse of alcohol, benzodiazepines, barbiturates, gamma hydroxybutyrate, opiates, and marijuana.

Hypersomnia due to stimulant withdrawal: Daytime sleepiness is common with abrupt discontinuation of stimulants. In chronically heavy amphetamine users, sleepiness is most severe in the first week of withdrawal and can persist for up to three weeks; individuals may have an increase in total sleep and daytime napping, but sleep may seem fragmented and nonrestorative. Significant depression often accompanies the hypersomnolence. Infrequently, sleepiness may be a residual complaint in those who have used stimulants in the past but have been abstinent for many years. In people who regularly consume coffee or other sources of caffeine, discontinuation can produce sleepiness, fatigue, and inattentiveness for two to nine days.

Demographics

Patients of any age can experience sleepiness from sedating medications. Stimulant abuse and the consequent sleepiness during withdrawal are most common in adolescents and young adults.

Predisposing and Precipitating Factors

Sleepiness from sedating medications may be more common in older patients and in those with multiple medical problems.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

Onset, course, and complications reflect those of the medications or substances responsible.

Pathology and Pathophysiology

Not applicable or known.

Objective Findings

Polysomnography is generally unnecessary unless a concomitant sleep disorder is suspected. Polysomnography and MSLT results vary depending on the specific substance in question and the timing of the most recent intake. With stimulant withdrawal, nocturnal polysomnography may show normal sleep, whereas the MSLT typically demonstrates a short mean sleep latency with or without multiple SOREMPs. A urine toxicology screen may be positive for the suspected substance. The diagnosis is often confirmed if symptoms resolve after the causal agent is removed.

Differential Diagnosis

Major sleep disorders that are associated with excessive sleepiness, especially *SRBDs, periodic limb movement disorder*, *narcolepsy*, *IH*, and *insufficient sleep syndrome* should be ruled out. A urine drug screen should routinely accompany an MSLT as the use of or withdrawal from some medications or substances may affect MSLT test results.

Although many psychotropic medications may result in daytime sleepiness, it is important for clinicians to recognize that many psychiatric disorders also are associated with increased prevalence of other sleep disorders (e.g., insomnia, SRBD, circadian disorders, and movement disorders). Although sedative effects of the psychotropic agents

may contribute to sleepiness, clinicians must maintain a high index of suspicion for other sleep related etiologies. When other sleep disorders are identified, multiple diagnoses may be appropriate.

Unresolved Issues and Future Directions

Sedatives can worsen sleep related breathing disorders, and more research is needed to understand and manage this interaction.

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Hypersomnia Associated with a Psychiatric Disorder

ICD-9-CM code: 327.15 ICD-10-CM code: F51.13

Alternate Names

Hypersomnia not due to substance or known physiological condition, nonorganic hypersomnia, pseudohypersomnia, or pseudonarcolepsy.

Diagnostic Criteria

Criteria A-C must be met

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.
B. The daytime sleepiness occurs in association with a concurrent psychiatric disorder.
C. The symptoms are not better explained by another untreated sleep disorder, a medical or neurological disorder, or the effects of medications or drugs.

Essential Features

Patients with hypersomnia associated with a psychiatric disorder may report excessive nocturnal sleep, daytime sleepiness, or excessive napping. In addition, they often feel their sleep is of poor quality and nonrestorative. Patients are often intensely focused on their hypersomnolence, and psychiatric symptoms may become apparent only after prolonged interviews or psychometric testing. Associated psychiatric conditions include mood disorders, conversion or undifferentiated somatoform disorder, and less frequently other mental disorders such as schizoaffective disorder, adjustment disorder, or personality disorders.

Associated Features

Poor work attendance, spending full days in bed several times a week, or abruptly leaving work because of a perceived need to sleep are common symptoms. Patients may also have social withdrawal, apathy, and feelings of low energy.

Clinical and Pathological Subtypes

Hypersomnia associated with mood disorder: Hypersomnolence in the context of depression is a frequent feature of atypical depression and bipolar II disorder (recurrent major depressive episodes with hypomanic episodes). In seasonal affective disorder, daytime fatigue, loss of concentration, increased appetite for carbohydrates, and weight gain are reported. MSLT results are usually normal, but long hours spent in bed are reported.

Hypersomnia associated with a conversion disorder or somatic symptom disorder: Pseudohypersomnia or pseudonarcolepsy, sometimes with pseudocataplexy, has been described.

Demographics

Hypersomnia associated with a psychiatric disorder accounts for 5% to 7% of hypersomnolence cases. Women are more susceptible than men, and the typical age range is between 20 and 50 years. In patients with major depression, the prevalence of hypersomnolence ranges from 5% to over 50% depending on how hypersomnolence is defined. Hypersomnolence affects over 50% of patients with seasonal affective disorder.

Predisposing and Precipitating Factors

Not applicable or known.

Familial Patterns

Not known, except for the familial patterns of certain psychiatric disorders (e.g., bipolar II disorder).

Onset, Course, and Complications

The mean age of onset is usually in the third decade in both sexes. With major depression, hypersomnolence may persist even after the depressive episode improves, and persistent hypersomnolence is associated with increased risk of recurrent depression. Complications are mostly social and occupational.

Developmental Issues

Hypersomnolence occurs in 10% to 20% of children with major depression, sometimes in combination with insomnia, but sleep quality appears normal. Although sleep problems may develop at any stage of depression, they are most pronounced during the acute phase. Children and adolescents with depression who manifest either insomnia or hypersomnolence generally manifest more pronounced symptoms, such as anhedonia and weight loss.

Pathology and Pathophysiology

The underlying cause is unknown. Although patients with this disorder report sleepiness, sleep studies reveal little or no evidence of increased propensity to sleep. In some patients, fragmented nighttime sleep may contribute to their daytime sleepiness. Because of uncertainty about the nature of the relationship, the term "hypersomnia *associated with* a psychiatric disorder" is preferred to "hypersomnia *due to* a psychiatric disorder."

Objective Findings

Nocturnal polysomnography typically shows a prolonged total time in bed with fragmented sleep. Sleep latency is prolonged, wake time after sleep onset is increased, awakenings may be frequent and prolonged, and sleep efficiency is low. REM sleep latency may be shortened in the case of untreated depression. Sleep latencies on the MSLT are often within normal limits, a result contrasting with the subjective complaint of daytime sleepiness and an elevated score on the Epworth Sleepiness Scale. 24-hour continuous sleep-recording studies typically show considerable time spent in bed during day and night, a behavior sometime referred to as clinophilia. Psychiatric interviews and evaluations are essential to diagnose the underlying psychiatric condition.

Differential Diagnosis

As there are no definitive tests for diagnosing hypersomnolence associated with a psychiatric disorder, it is essential to rule out other common causes of sleepiness such as *insufficient sleep*, *sedation from medications or substances*, *SRBD*, *periodic limb movement disorder*, and *IH*. *Chronic fatigue syndrome* is characterized by persistent or relapsing fatigue that does not resolve with sleep or rest, but the main complaint is usually fatigue rather than sleepiness. Insufficient sleep syndrome is associated with excessive daytime sleepiness, impaired concentration, and lowered energy level, but a detailed history of the subject's current sleep schedule reveals chronic sleep deprivation.

Unresolved Issues and Future Directions

The lack of concordance between subjective and objective findings raises multiple issues. It is unclear to what extent these patients are objectively sleepy or, instead, suffer from decreased energy and lack of interest that confines them to bed. More research is needed to create an effective definition of hypersomnolence in this population and to develop tools for measuring it. Finally, future efforts should define the mechanism through which some patients express their psychiatric symptoms as excessive sleepiness.

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Insufficient Sleep Syndrome

ICD-9-CM code: 307.44 ICD-10-CM code: F51.12

Alternate Names

Behaviorally induced insufficient sleep syndrome, insufficient nocturnal sleep, chronic sleep deprivation, sleep restriction.

Diagnostic Criteria

Criteria A-F must be met

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep or, in the case of prepubertal children, there is a complaint of behavioral abnormalities attributable to sleepiness.
B. The patient's sleep time, established by personal or collateral history, sleep logs, or actigraphy[1] is usually shorter than expected for age.[2]
C. The curtailed sleep pattern is present most days for at least three months.
D. The patient curtails sleep time by such measures as an alarm clock or being awakened by another person and generally sleeps longer when such measures are not used, such as on weekends or vacations.
E. Extension of total sleep time results in resolution of the symptoms of sleepiness.
F. The symptoms are not better explained by another untreated sleep disorder, the effects of medications or drugs, or other medical, neurologic, or mental disorder.

Notes

1. If there is doubt about the accuracy of personal history or sleep logs, then actigraphy should be performed, preferably for at least two weeks.
2. In the case of long sleepers, reported habitual sleep periods may be normal based on age. However, these sleep periods may be insufficient for these patients.

Essential Features

Insufficient sleep syndrome occurs when an individual persistently fails to obtain the amount of sleep required to maintain normal levels of alertness and wakefulness. The individual is chronically sleep deprived as a result of failure to achieve necessary sleep time due to reduced time in bed. There is a U-shaped relationship between age and average sleep time, with the minimum in middle-aged individuals. Examination reveals unimpaired or above-average ability to initiate and maintain sleep, with little or no psychopathology. Physical examination reveals no medical explanation for the patient's sleepiness. A detailed history of the sleep pattern reveals a substantial disparity between the need for sleep and the amount actually obtained. The significance of this disparity often goes unappreciated by the patient. Sleep time that is markedly extended on weekend nights or during holidays compared to weekday nights is also suggestive of this disorder. A therapeutic trial of a longer major sleep episode can reverse the symptoms. In individuals with physiologic sleep requirements significantly in excess of seven to eight hours, reported "average" amounts of sleep (e.g., seven hours/night) may, in fact, be insufficient. Additional symptoms such as sleep paralysis and hypnagogic hallucinations may occur.

Associated Features

Depending upon chronicity and extent of sleep loss, individuals with this condition may show irritability, concentration and attention deficits, reduced vigilance, distractibility, reduced motivation, anergia, dysphoria, fatigue, restlessness, uncoordination, and malaise. Secondary symptoms may become the main focus of the patient, serving to obscure the primary cause of the difficulties. Psychologically and somatically normal individuals who chronically obtain less sleep than they physiologically require typically experience daytime sleepiness. Situational factors such as demands of the family and work schedule may, on occasion, make it very difficult to obtain adequate sleep.

Clinical and Pathophysiologic Subtypes

Not applicable or known.

Demographics

Insufficient sleep syndrome affects all ages and both sexes. It may be more frequent in adolescence, when sleep need is high, but social pressure and tendency to delay sleep often lead to chronic restricted sleep. Cultural factors may also influence sleep duration, with students from different countries reporting sleep time varying between six and eight hours per night.

Predisposing and Precipitating Factors

Social and psychological factors may impact nocturnal sleep length and daytime sleepiness. Cultural habits such as the *siesta* may enhance evening alertness at the expense of reducing nocturnal sleep efficiency. Also, the evening preference chronotype predisposes to complaints of insomnia and insufficient sleep. The association of eveningness with insufficient sleep persists after controlling for variables such as sex, age, and sleep duration.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

This condition results in increased daytime sleepiness, concentration problems, lowered energy level, and malaise. If unchecked, insufficient sleep syndrome may predispose to depression and other psychological difficulties, as well as poor work performance and withdrawal from family and social activities. Abuse of stimulants may also occur. Traffic accidents or injury at work may result.

Developmental Issues

Insufficient sleep syndrome is a common problem in adolescents. It should be differentiated from delayed sleep phase disorder, the effects of recreational drug use, and school avoidance behavior. Increased predisposition to substance use and accidents in teens may be consequent to insufficient sleep.

Pathology and Pathophysiology

Symptoms are due to normal physiological and psychological responses to sleep deprivation. Sleep restriction studies in normal volunteers have shown that even mild sleep restriction (for example, six hours of nocturnal sleep per night) results in a corresponding decrease in performance and increased sleepiness. Sleep restriction to four hours per night (i.e., extension of wakefulness to 20 hours per day) will likely lead to greater buildup of homeostatic sleep drive during the waking hours and greater likelihood of impaired performance on a psychomotor vigilance task. The effects of sleep deprivation on neurobehavioral performance measures may vary with the nature of the task being considered.

In some long sleepers, it is important to be aware that extending sleep to nine or more hours often results in improved performance. The diagnosis of insufficient sleep syndrome may be especially difficult to make in subjects who have a physiologic need for unusually large amounts of sleep.

Objective Findings

Actigraphy combined with sleep diaries maintained for a 2- to 3-week period may be helpful by documenting total time in bed, sleep latency, total sleep time, and sleep efficiency. Polysomnography and MSLT are not required to establish a diagnosis of insufficient sleep syndrome. Rather, sleep time is extended first, and the patient is reevaluated. If a therapeutic trial with a longer sleep episode eliminates the symptoms, insufficient sleep syndrome is diagnosed.

Polysomnography, when performed, reveals reduced sleep onset latency, and high (greater than 90%) sleep efficiency. When extended sleep is permitted, prolonged sleep time with slow wave rebound may be seen. Noting a disparity between reported sleep at home and observed total sleep time in the sleep laboratory can be helpful. The MSLT reveals excessive sleepiness, with stage N1 sleep occurring in most naps, with short sleep latency. Stage N2 sleep occurs in more than 80% of MSLT naps. SOREMPs can occur.

Differential Diagnosis

Insufficient sleep syndrome may be confused with *narcolepsy* or *other hypersomnolence disorders* because an abnormal MSLT (even with two SOREMPs) can be observed as the result of acute or chronic sleep deprivation. The confusion may be most frequently encountered in adolescents or young adults. The differential diagnosis of insufficient sleep syndrome includes numerous other conditions that may result in daytime sleepiness or shortening of nocturnal sleep duration. These include other *central disorders of hypersomnolence*, *long sleeper* or *short sleeper*, *SRBD*, *circadian rhythm sleep disorders*, *insomnia disorder*, *affective disorder*, and *periodic limb movement disorder*.

Unresolved Issues and Future Directions

The correlation between subjectively reported sleepiness, performance-test decrements, and MSLT-measured sleepiness after sleep deprivation is poor. Short sleepers often have a higher NREM sleep pressure, as measured by EEG delta power, than long sleepers, even if they do not complain of daytime sleepiness. There is interindividual susceptibility to sleep deprivation, with some people being consistently more tired and experiencing greater performance decrement after even a mild degree of sleep deprivation.

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Isolated Symptoms and Normal Variants

Long Sleeper

A long sleeper is an individual who consistently sleeps substantially more in 24 hours than does the typical person of his or her age group. For adults, the usually accepted figure is 10 hours or more, but many epidemiologic studies have used sleep times of 8–10 hours. For children and adolescents, the entity should be considered if sleep time is more than two hours longer than age-specific norms. Sleep, although long, is basically normal in architecture and physiology. Sleep efficiency and timing are normal. A consistent daily pattern, documented by a carefully kept sleep log (preferably confirmed by actigraphy), showing 10 or more hours of sleep per night over a minimum of seven days is desirable for the identification of the long sleeper. In general, long sleepers seek medical help when they develop sleepiness as a result of being forced to curtail their sleep time to less than their required amounts. Usually, the long sleep pattern began in childhood, is well established by early adolescence, and persists throughout life. Many long sleepers, because of occupational or educational demands, function with reasonable success on nine hours of sleep per night during the work or school week, with increases to 12 or more hours on weekends and holidays.

About 2% of men and 1.5% of women report sleeping at least 10 hours per night. Epidemiologic studies have consistently found an increased mortality (and sometimes increased body mass index, lower glucose tolerance, higher prevalence of type 2 diabetes and coronary heart disease) associated with long sleep, compared to average-duration sleep, but it is not clear whether most of the subjects were naturally long sleepers or had disorders resulting in excessive duration of sleep. In subjects older than 60 years, sleep duration longer than 9.5 hours is associated with male sex, low education, no physical exercise, and more physical diseases. Long (> nine hours) sleep duration has a high heritability (44%) and concordance between monozygotic twins, which is higher if they live together. Genomewide studies favor a polygenic origin of sleep duration, with influence of clock and other genes (DEC2, K+ channel regulatory proteins genes). Long sleepers presumably represent the extreme high end of the normal sleep duration continuum.

Long sleepers, like short sleepers, have normal absolute amounts of stage N3 sleep, unless there is chronic sleep restriction preceding polysomnography, in which case the absolute amount of N3 stage is increased. Amounts of stages N2 and REM sleep are somewhat higher than normal. The individual has no problem with time distortion or ability to be accurate about the quantity or quality of sleep. Assuming that individuals

have obtained their usual sleep amounts for several nights before the procedure, no sleepiness is evident on the MSLT. It is important to differentiate the long sleeper from patients with narcolepsy, idiopathic hypersomnia, sleep disordered breathing, or medical causes of hypersomnolence. Many pathologic causes of increased sleep have an acute or subacute onset, may not be present since childhood, and rarely show the stable course of the long sleeper. Nevertheless, differentiation from pathologic conditions of hypersomnolence may be difficult in the child or adolescent because the normal continuum of sleep duration is somewhat higher in these age groups than in adults. The correct determination is often made by exclusion of specific diagnostic features associated with other conditions and by the absence of complaints concerning the quality of the individual's awake-state functioning when adequate sleep is obtained (e.g., during prolonged holidays). In particular, the differentiation of a genuine long sleeper from a patient with idiopathic hypersomnia may be difficult. In the genuine long sleeper, sleeping long hours is refreshing, and sleepiness disappears when long hours of nocturnal sleep are enforced.

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Circadian Rhythm Sleep-Wake Disorders

Circadian rhythms are endogenous, near-24-hour biological rhythms that exist in all living organisms. The internal near-24-hour circadian clock is entrained or synchronized to the 24-hour light-dark cycle. In humans, the endogenous period of the circadian oscillation is genetically determined and typically is slightly longer than 24 hours. In order to maintain entrainment, the endogenous rhythm must be reset each day to the 24-hour clock time. For optimal sleep, the actual sleep time should match the timing of the circadian rhythm of sleep and wake propensity. Therefore, a recurrent or chronic pattern of sleep and wake disturbance may result from disruption of the internal circadian timing system or a misalignment between the timing of the individual's circadian sleep-wake propensity and the 24-hour social and physical environments (e.g., sleep episodes scheduled entirely or in part during a phase of circadian alertness promotion). As used herein, a circadian rhythm sleep-wake disorder (CRSWD) is defined by the following criterion: The disorder is caused by alterations of the circadian time-keeping system, its entrainment mechanisms, or a misalignment of the endogenous circadian rhythm and the external environment.

Most CRSWDs arise when a substantial misalignment exists between the internal rhythm and the required timing of the patient's school, work, or social activities. Therefore, measurement of endogenous circadian timing is important for the accurate diagnosis of CRSWDs. In addition to the history, multiple tools are available to assess sleep-wake patterns. Sleep log and actigraphy are essential instruments in the evaluation of CRSWDs and should be conducted for at least seven days, preferably for 14 days, to capture work and non-work days. Circadian chronotype (Morningness-Eveningness Questionnaires) and physiological measures of endogenous circadian timing (salivary or plasma dim light melatonin onset and urinary 6-sulfatoxymelatonin) also can provide important diagnostic information. Circadian chronotype is a reflection of an individual's optimal timing of sleep and wake propensity, as well as other

physiological and mental functions. Several questionnaires can be used to assess chronotype of "eveningness" or "morningness" (e.g., Munich Chronotype Questionnaire, or Morningness-Eveningness Questionnaire).

The most common presenting symptoms of CRSWDs are difficulty initiating and maintaining sleep, and excessive sleepiness, but their impact extends to adverse health outcomes, impairments in social, occupational and educational performance, and safety concerns. Important advances have been made in the identification of clinical CRSWD subtypes, particularly in the area of pediatrics. However, the challenge remains to develop more precise and clinically practical tools to improve diagnostic accuracy for CRSWDs.

General Criteria for Circadian Rhythm Sleep-Wake Disorder

Criteria A-C must be met

A. A chronic or recurrent pattern of sleep-wake rhythm disruption primarily due to alteration of the endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the sleep-wake schedule desired or required by an individual's physical environment or social/work schedules.
B. The circadian rhythm disruption leads to insomnia symptoms, excessive sleepiness, or both.
C. The sleep and wake disturbances cause clinically significant distress or impairment in mental, physical, social, occupational, educational, or other important areas of functioning.

All disorders described in the ensuing section imply a sleep difficulty that meets each of the above criteria. The specific features that characterize each type of CRSWD are included within the individual diagnostic criteria.

Delayed Sleep-Wake Phase Disorder

ICD-9-CM code: 327.31 ICD-10-CM code: G47.21

Alternate Names

Delayed sleep phase syndrome, delayed sleep phase pattern, motivated delayed sleep phase disorder.

Diagnostic Criteria

Criteria A-E must be met

A. There is a significant delay in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidenced by a chronic or recurrent complaint by the patient or a caregiver of inability to fall asleep and difficulty awakening at a desired or required clock time.
B. The symptoms are present for at least three months.
C. When patients are allowed to choose their ad libitum schedule, they will exhibit improved sleep quality and duration for age and maintain a delayed phase of the 24-hour sleep-wake pattern.
D. Sleep log and, whenever possible, actigraphy monitoring for at least seven days (preferably 14 days) demonstrate a delay in the timing of the habitual sleep period. Both work/school days and free days must be included within this monitoring.
E. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Notes

1. Standardized chronotype questionnaires are useful tools to assess the chronotype of eveningness and morningness. Individuals with this disorder typically score as evening types. This tool can also be useful in determining whether an eveningness circadian preference contributes to sleep initiation difficulties among those who do not meet full criteria for the disorder.
2. Demonstration of a delay in the timing of other circadian rhythms, such as melatonin (measured by dim light melatonin onset or urinary 6-sulfatoxymelatonin sampled across a 24-hour period), is desirable to confirm the delayed circadian phase.

Essential Features

Delayed sleep-wake phase disorder (DSWPD) is characterized by habitual sleep-wake timing that is delayed, usually more than two hours, relative to conventional or socially acceptable timing. Affected individuals complain of difficulty falling asleep at a socially acceptable time, as required to obtain sufficient sleep duration on a school or work night. Once sleep onset occurs, it is reportedly of normal duration. These individuals also experience difficulty arising at a socially acceptable wake time, as required to prepare for school or work. When allowed to follow his or her preferred schedule, the patient's timing of sleep is delayed.

Associated Features

Individuals with DSWPD may demonstrate excessive sleep inertia (extreme difficulty awakening and confusion) in the morning as a result of curtailed sleep time and awakening during a circadian phase of high sleep propensity. Individuals with this disorder as well as normal sleepers with evening chronotypes may have increased rates of mental disturbances, such as Diagnostic and Statistical Manual of Mental Disorders (DSM) Axis I disorders or symptoms (e.g., mood disorders or depressive symptoms). In some individuals with DSWPD, there may be an overlap with non-24-hour sleep-wake disorder, or an alternation between symptoms of the two disorders. Attempts to cope with the inability to fall asleep earlier may result in the development of insomnia disorder. Individuals may use alcohol, sedatives, hypnotics, or stimulant substances to alleviate symptoms of insomnia and excessive sleepiness, thereby perpetuating their underlying sleep disorder.

Clinical and Pathophysiological Subtypes

Motivated delayed sleep-wake phase disorder is a subtype typically composed of adolescents who have little intrinsic motivation to successfully complete treatment and thereby resume a normal lifestyle (regular school attendance, developmentally appropriate peer interactions, etc). A history of mood or anxiety disorder (especially school phobia and separation and social anxiety) or other factors (e.g., learning disabilities, attention deficit hyperactivity disorder) are often present and may motivate the patient (sometimes unconsciously) to avoid a return to normal adolescent activities, especially regular school attendance. It is not uncommon that ill-defined medical issues (e.g., chronic fatigue, recurrent mononucleosis episodes, pain syndromes) trigger the onset or complicate the course of the disorder. Important clues, in addition to the existence of premorbid mental disorders, include exaggerated presenting symptoms (e.g., "can't wake up even if I throw cold water on him") and failure to comply with basic straightforward treatment recommendations (e.g., refusal or inability to stop napping during the day).

Although social, psychological, and environmental factors may play a significant role in the development of delayed sleep-wake phase, International Classification of Sleep Disorders, 3rd Edition has chosen to list only a single delayed sleep-wake phase diagnosis, with the recognition that most cases reflect variable chronobiologic and behavioral contributions.

Demographics

The exact prevalence of DSWPD in the general population is unknown. The condition is more common among adolescents and young adults, with a reported prevalence of 7% to 16%. It is estimated that DSWPD is seen in approximately 10% of patients presenting in sleep clinics with recurrent insomnia complaints. There have been no studies assessing racial/ethnic differences in DSWPD.

Predisposing and Precipitating Factors

Most individuals with DSWPD are evening chronotypes. Many adolescents experience a biological endogenous shift towards later bedtimes beginning around puberty. Genetic factors such as polymorphism in the circadian clock gene *hPer3* are associated with DSWPD. Environmental factors, including decreased exposure to light during the phase advance region of the phase response curve (PRC) (i.e., in the morning on days with early wake times) or increased exposure to bright light during the phase delay portion of the PRC (i.e., late in the evening) may exacerbate the delayed circadian phase. Individuals may have increased sensitivity in the phase delay region or decreased sensitivity in the phase advance region of the phase response curve to light. Maladjustment to changes in work and social schedules, travel across time zones, and shift work can precipitate this disorder. Individuals may consume excessive caffeine and other stimulants, which may further delay sleep onset and thus exacerbate the delayed sleep time.

Social and behavioral factors play an important role in the development and maintenance of the delayed sleep patterns for many affected individuals. Personal, social, and occupational activities that continue into the late evening may perpetuate and exacerbate the sleep phase delay. In adolescents, the role of school avoidance, social maladjustment, and family dysfunction should be considered as contributing factors. Individuals with a psychiatric disorder, such as a mood disorder (major depression or bipolar disorder), severe obsessive-compulsive disorder, attention deficit hyperactivity disorder, or other neurodevelopmental disorders may have a delayed sleep phase.

Familial Patterns

A positive family history has been reported in approximately 40% of individuals with DSWPD. In one pedigree, DSWPD was suggested to segregate as an autosomal dominant trait. Polymorphisms in *hPer3*, arylalkylamine *N*-acetyltransferase, human leukocyte antigen, and Clock have been suggested to be associated with DSWPD.

Onset, Course, and Complications

A delayed sleep pattern typically begins during adolescence. Onset in early childhood is also described, especially in familial cases; the onset may follow psychological, medical, or environmental stressors. Without treatment, DSWPD is a chronic condition that may last into late life. However, with increasing age across adulthood, the timing of the sleep-wake cycle may advance, thereby decreasing the propensity to delayed sleep phase. Phototherapy, as well as behavioral and pharmacologic treatments, can advance the timing of sleep hours, but there is usually a continual tendency and preference for delayed sleep hours, and recurrence is high. Use of alcohol, sedatives, hypnotics, or stimulants to treat symptoms of insomnia and sleepiness during normal waking hours may lead to substance abuse.

Developmental Issues

DSWPD may be encountered in any age group but is especially prevalent among adolescents and young adults. In addition to the clinical features described elsewhere, DSWPD may present in older children and adolescents with chief complaints of truancy, repeated school absences, chronic tardiness and/or school failure, rather than sleep complaints per se. In severe cases, school attendance is completely curtailed and the patient may have failed to attend school regularly for many months. Extreme difficulty in morning awakening, requiring intensive parental involvement, may also be the presenting concern. An increased risk of motor vehicle accidents has been associated with delayed sleep onset and resultant insufficient sleep in adolescents; thus, the occurrence of a car crash or "near-miss" incident should alert the clinician to probe for additional evidence of circadian pathology. Adolescents may also present primarily with mood complaints (depression, suicidal ideation). Chronic insomnia is commonly associated with and may be the chief presenting complaint in adolescents with DSWPD as a result of repeated attempts and failures to achieve sleep onset at their desired bedtime.

In younger children, the condition may be associated with delays in other markers of circadian phase, including the typical presleep surge in alertness referred to as the "forbidden zone" or "second wind phenomenon." Thus, especially in younger children, DSWPD may present primarily as bedtime resistance, as caregivers attempt to establish bedtimes that directly conflict with the child's circadian-mediated readiness for sleep.

Several pediatric populations appear to have an increased vulnerability to DSWPD and sleep disturbances, likely of multifactorial etiology. These include children with attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Several studies have examined melatonin onset in children with ADHD and reported significant delays in comparison with typically developing children, as well as successful treatment with melatonin. Children with ASD have a high prevalence (up to 80%) of sleep disturbances, including delayed sleep onset, night and early morning awakenings, and irregular sleep patterns, at least some of which appear associated with circadian abnormalities. These children reportedly have a number of alterations in melatonin synthesis, levels, amplitude, and patterns of secretion.

Little is known about the natural history of the clinical entity of DSWPD in the pediatric population, including the impact of various treatment modalities, the likelihood of spontaneous resolution of symptoms, or long-term consequences.

There is increasing evidence to suggest that the evening chronotype is associated in both children and adolescents with a number of adverse consequences, including decreased health-related quality of life, higher rates of behavioral/emotional problems including depression and suicidality, decreased sleep duration and increased daytime sleepiness, more sleep complaints, impairments in academic functioning, and increased likelihood of substance use. Thus, eveningness may confer an increased risk for physical and mental health problems.

Pathology and Pathophysiology

The exact mechanisms responsible for DSWPD are unknown. An abnormal interaction between the endogenous circadian rhythm and the sleep homeostatic process that regulates sleep and wakefulness may play an essential role in the pathophysiology of DSWPD. Early studies reported an altered phase relationship between the sleep-wake cycle and circadian phase, whereas more recent studies have failed to support this finding. In these patients, sleep onset, sleep offset, and phase of circadian markers such as core body temperature and melatonin are delayed relative to clock time when compared with controls. Although this condition may be predominantly due to a misalignment between circadian timing and the external environment, alterations in the length of the circadian period or an altered homeostatic process (indicated by decreased sleep propensity in response to sleep deprivation) also may be contributing factors. In children and adults, voluntary behaviors such as staying awake late at night and waking up late in the morning or afternoon may result in an abnormal relationship between the endogenous circadian rhythm and the sleep homeostatic process that regulates sleep and wakefulness. Delayed bedtimes and wake times may increase exposure to bright

light in the late evening (a delay signal for the circadian clock) and decrease exposure to light in the early morning (an advance signal for the circadian clock), thereby promoting and perpetuating the delay in the circadian sleep phase. Given a sufficient discrepancy between early and late wake times, early wake times may be associated with bright light exposure during the maximal phase delay region, perpetuating the circadian phase delay and the disorder. Individuals may have alterations in sensitivity to the phase shifting effects of light. For example, partial sleep deprivation encountered with this disorder can also attenuate the ability to phase-advance the circadian system, further perpetuating the delayed circadian phase.

Objective Findings

Recordings of sleep logs and actigraphy over an interval of at least seven (and preferably fourteen) consecutive days demonstrate delayed sleep onset and sleep offset (typically greater than two hours) relative to socially acceptable times. Though clock times may be culture dependent, for many affected individuals sleep onset is typically delayed until 1:00 a.m. to 6:00 a.m., (though may be earlier based on age and developmental status), and wake time occurs in the late morning or afternoon. Daily demands and schedules may result in an earlier than desired wake-up time during work or school days, but a delay in bedtime and wake-up time is almost always seen during free days and vacation. Polysomnography (though not routinely indicated nor required for the diagnosis), when performed at preferred (delayed) sleep times, is essentially normal for age. If a conventional bedtime and wake-up time are enforced, however, polysomnographic recording may show prolonged sleep latency and decreased total sleep time. Laboratory measures of circadian timing generally show the expected phase delay in the timing of the nadir of the core body temperature rhythm and dim-light melatonin onset (DLMO). Several questionnaires are useful in assessing the chronotype, the degree of eveningness or morningness (e.g., "Morningness-Eveningness Questionnaire," "Munich Chronotype Questionnaire"). Individuals with DSWPD, typically score high as evening types, though normal sleepers can also score high on eveningness. Elevations are expected in self-report of daytime sleepiness, such as on the Epworth Sleepiness Scale.

The results of polysomnography and other diagnostic tools in younger age groups are similar to those seen in adults. Actigraphy and/or sleep logs are useful in the diagnosis of DSWPD in the pediatric population. Several validated instruments are available for assessing phase preference in the pediatric and adolescent populations. These include the Children's Chronotype Questionnaire (CCTQ) (parent-report), the Morningness-Eveningness Scale for Children (self-report), and the Morningness-Eveningness Questionnaire for Children and Adolescents. These

surveys have been used to assess chronotype in the pediatric population and may be useful in clinical settings.

Differential Diagnosis

Delayed sleep-wake phase disorder must be distinguished from "normal" sleep patterns, particularly in adolescents and young adults who maintain delayed schedules regularly or intermittently, without distress or impaired functioning. DSWPD must be distinguished from other causes of difficulty initiating sleep, including *chronic insomnia disorder*. In DSWPD, sleep initiation and maintenance are improved when the patient is allowed to sleep on the preferred schedule. When individuals with DSWPD must arise before the desired wake time, excessive sleep inertia and excessive daytime sleepiness may be evident. *Other forms of excessive daytime sleepiness*, from which this must be distinguished, do not generally exhibit the pronounced circadian pattern and do not abate with alterations in the sleep-wake schedule. The development of DSWPD may be influenced by alterations in circadian physiology as well as behavioral factors.

Inadequate sleep hygiene and *insufficient sleep syndrome* must also be considered in the differential.

Unresolved Issues and Further Directions

There is limited knowledge of the underlying pathophysiology of DSWPD. Recent evidence suggests that alteration in the homeostatic regulation of sleep and alertness may play an important role. The intrinsic circadian period may be abnormally long. Recent advances in the understanding of the molecular basis for the generation and entrainment of circadian rhythms, together with the identification of a familial form of DSWPD, will lead to improved understanding of the mechanisms responsible for this condition, as well as targeted, evidence-based therapies.

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Advanced Sleep-Wake Phase Disorder

ICD-9-CM code: 327.32 ICD-10-CM code: G47.22

Alternate Names

Advanced sleep phase type, advanced sleep phase disorder, advanced sleep phase syndrome.

Diagnostic Criteria

Criteria A-E must be met

A. There is an advance (early timing) in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidenced by a chronic or recurrent complaint of difficulty staying awake until the required or desired conventional bedtime, together with an inability to remain asleep until the required or desired time for awakening.
B. Symptoms are present for at least three months.
C. When patients are allowed to sleep in accordance with their internal biological clock, sleep quality and duration are improved with a consistent but advanced timing of the major sleep episode.

D. Sleep log and, whenever possible, actigraphy monitoring for at least seven days (preferably 14 days) demonstrate a stable advance in the timing of the habitual sleep period. Both work/school days and free days must be included within this monitoring.
E. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Notes

1. Standardized chronotype questionnaires are useful tools to assess the chronotype of eveningness and morningness. Individuals with advanced sleep phase score as morning types.
2. Demonstration of an advance (typically greater than two hours) in the timing of other circadian rhythms such as DLMO or urinary 6-sulfatoxymelatonin is desirable to confirm the advanced circadian phase.

Essential Features

Advanced sleep-wake phase disorder (ASWPD) is characterized by a stable advance (earlier timing) of the major sleep episode, such that habitual sleep onset and offset occur typically two or more hours prior to required or desired times. Affected individuals complain of early morning or maintenance insomnia and excessive evening sleepiness. When affected individuals are allowed to maintain an advanced schedule, sleep quality and quantity are improved.

Associated Features

Individuals with ASWPD may experience chronic partial sleep loss due to early morning and maintenance insomnia, particularly if sleep is resisted during early evening.

Clinical and Pathophysiological Subtypes

Familial patterns are discussed below.

Demographics

The prevalence of ASWPD in the general population is unknown. In one large survey study involving middle-aged adults (40-64 years), the population prevalence was estimated at 1%, although it is unclear what proportion of these subjects would deem their schedule to be significantly troublesome so as to warrant clinical attention. Until the identification of familial cohorts (see below), only four cases were described in the literature. There is no known sex difference.

Predisposing and Precipitating Factors

Advanced age appears to be a risk factor. Among a cohort aged 20 to 59 years, older age was associated with increased morningness, which was determined to be a significant mediator of numerous age-sleep relationships. A patient's ability to sleep at an abnormal circadian phase (phase tolerance) also impacts the degree to which adverse symptoms are experienced, and this adaptability varies among individuals. Conflicting results have been obtained with respect to the relationship between age and phase tolerance, with some suggesting that age decreases phase tolerance, and others suggesting that age may actually be protective. Methodological differences preclude direct comparisons of the investigations, as do wide variations in the age groups studied. Genetic factors also can influence the development of the condition, as has been definitively demonstrated among select familial cohorts (see Pathology and Pathophysiology section). Environmental influences may precipitate, maintain, or exacerbate the advanced circadian phase, but this has not been proven. ASWPD has been reported in children with neurodevelopmental disorders. In particular, studies in children with autism spectrum disorders and Smith-Magenis syndrome have shown profound alterations in melatonin secretion profiles, which may manifest as a phase advance with very early morning waking.

Familial Patterns

Various groups have described kindreds with familial ASWPD. These cases may be characterized by an earlier age of onset. It is not clear whether the familial or non-familial variety of the condition is more common.

Onset, Course, and Complications

Repetitive attempts to resume sleep with awakenings may result in the development of a comorbid chronic insomnia disorder. Individuals may use alcohol, other sedatives, and/or stimulants to alleviate symptoms, potentially exacerbating the underlying sleep/wake disorder. The impact on caregivers of children with neurodevelopmental disorders and ASWPD may be particularly profound.

Developmental Issues

ASWPD is most frequently encountered among older age groups. An early age of onset of ASWPD should prompt further probing for a familial pattern. Caregivers may report that a child wakes "too early" in the morning, which is disruptive to the household routine and may curtail parental sleep. This is particularly true for younger children, who may require adult supervision once they are awake. However, this complaint regarding the waking pattern is often more related to unrealistic caregiver expectations regarding an "appropriate" wake time for a young child and/or a developmentally

inappropriate early bedtime resulting in prolonged time in bed, rather than to a true advance in sleep onset and offset. In some cases, children are motivated to wake up earlier than desired because they are reinforced for this behavior by parental attention or the opportunity to watch television or utilize other media upon waking. The complaint that a child "falls asleep too early" in the evening, especially in adolescence, is rare and should raise concerns regarding the possibility of chronically insufficient sleep and/or a sleep disorder resulting in increased sleep needs. The rarity of observations of advanced sleep onset and offset times among young children may also be due in part to societal expectations of earlier bed and wake times for this age group; thus, a misalignment with circadian preference is less likely.

Pathology and Pathophysiology

Possible etiologies include: (1) an alteration in the ability of the circadian clock to phase delay; (2) a dominant phase advance region of the light phase response curve to entraining agents; (3) altered strength of entraining agents, such as light exposure at the appropriate circadian time (voluntarily or involuntarily induced); or (4) a shortened endogenous circadian period of the pacemaker. Among these proposed mechanisms, only the latter has been definitively demonstrated among select familial ASWPD subjects. Genetic analyses revealed a missense mutation in a casein kinase (*CK1ε*) binding region of a Period gene (*hPer2*), culminating in hypophosphorylation by *CK1ε* in vitro. Hypophosphorylation of the Period protein results in promotion of its transcription and, ultimately, a decrease in the period length of the clock. However, genetic heterogeneity is apparent within familial ASWPD, as demonstrated by the fact that other cohorts from this same study and another study did not reveal mutations in *hPer2*. A separate report of a Japanese familial ASWPD cohort described a missense mutation in a different casein kinase gene (*CKIδ*), which also resulted in decreased enzymatic activity in vitro. Yet another group described associations between *hPer1* and *hPer2* polymorphisms and extreme morningness circadian preferences (questionnaire-based), in the absence of discrete ASWPD.

Objective Findings

Among patients with familial ASWPD, laboratory measures to determine the phase of circadian rhythms reliably show the expected phase advance in the timing of the nadir of the temperature rhythm and the dim light melatonin onset, in comparison with unaffected controls. Among those with nonfamilial ASWPD, a wider range of timing of circadian markers is found, with some values approaching those of unaffected controls.

Polysomnography (though not routinely indicated nor required for the diagnosis), when performed at preferred (advanced) sleep times, is essentially normal for age. If

a conventional bedtime and wake-up time is enforced, however, polysomnographic recording may show short sleep latency and early awakening with curtailment of total sleep time.

Differential Diagnosis

ASWPD must be distinguished from "normal" sleep patterns, particularly among the elderly or very young, who often maintain advanced schedules without distress or impaired functioning. ASWPD must also be distinguished from other causes of early awakening, including *chronic insomnia disorder*. *Poor sleep hygiene* practices, particularly evening napping among the elderly, and *irregularity of the sleep-wake schedule* should also be considered. The possibility of a "free-running" (nonentrained) circadian rhythm also merits consideration, but patients with this condition are most commonly blind and report only periodic complaints of insomnia depending on the relative relationship between the internal rhythm and that of the light/dark cycle. *Major depressive disorder* is a common cause of early awakening that must be considered. These patients do not typically manifest the early evening sleepiness that is characteristic of ASWPD. As with any sleep disturbances that persists over time, insomnia can develop secondarily. The Horne-Östberg questionnaire (or other chronotype questionnaire) may assist in determining the contribution of a morningness circadian preference to the presenting sleep/wake complaint. The presence of more than one contributing variable seems to be the norm, and each entity needs to be treated accordingly.

Unresolved Issues and Further Directions

The existing literature suggests that clinicians are unlikely to encounter patients with stringently defined ASWPD. Until the identification of familial cohorts, only four cases were described. Various treatment trials also support this contention with demonstration of objectively conventional sleep and wake times despite study entry based on subjective reports of advanced sleep phase. Select studies of patients with *sole* complaints of maintenance insomnia/early-morning awakenings have demonstrated marked advances (earlier timing) of physiologically measured circadian rhythms. The absence of the early evening sleepiness complaint may be due to the fact that the timing of sleep onset can be more readily modified than wake time, and is likely to be more actively resisted due to its propensity to conflict with social or family obligations. Alternatively, evening sleep that occurs prior to entering the bed/bedroom may not be reported as such. If it is definitively demonstrated that the evening sleepiness complaint is not present or is not prominent, the term *advance-related sleep complaints* may be used in lieu of ASWPD. If this broader term is used, the condition is observed more commonly (~7% of respondents in a study of individuals aged 40-64 years). There is limited knowledge of the pathophysiology of ASWPD (or advance-related sleep

complaints) beyond those associated with select cases of familial ASWPD. Increased use of physiologic circadian assessments will require the development of normative values to guide practitioners. Knowledge gaps are even more prominent within pediatric and adolescent populations.

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Irregular Sleep-Wake Rhythm Disorder

ICD-9-CM code: 327.33 ICD-10-CM code: G47.23

Alternate Names

Irregular sleep-wake cycle disorder, irregular sleep-wake rhythm type.

Diagnostic Criteria

Criteria A-D must be met

A. The patient or caregiver reports a chronic or recurrent pattern of irregular sleep and wake episodes throughout the 24-hour period, characterized by symptoms of insomnia during the scheduled sleep period (usually at night), excessive sleepiness (napping) during the day, or both.
B. Symptoms are present for at least three months.
C. Sleep log and, whenever possible, actigraphy monitoring for at least seven days, preferably 14 days, demonstrate no major sleep period and multiple irregular sleep bouts (at least three) during a 24-hour period.
D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Essential Features

Irregular sleep-wake rhythm disorder (ISWRD) is characterized by lack of a clearly defined circadian rhythm of sleep and wake. The chronic or recurring sleep-wake pattern is temporally disorganized so that sleep and wake episodes are variable throughout the 24-hour cycle. Individuals have symptoms of insomnia and excessive sleepiness, depending on the time of day and their particular sleep-wake pattern.

Associated Features

ISWRD is more commonly observed in neurodegenerative disorders, such as dementia, and in children with developmental disorders. Individuals typically present with insomnia or excessive sleepiness, depending on the time of day. Sleep and wake episodes across the 24-hour cycle are fragmented, with the longest sleep bout being typically less than four hours. Individuals or caregivers report frequent naps throughout the daytime. Total sleep time across the 24 hours may be normal for age.

Clinical and Pathophysiological Subtypes

Older adults with Alzheimer disease who experience sundowning may represent a clinical subtype with more severe sleep fragmentation and lower circadian rhythm amplitude than those who do not experience sundowning.

Demographics

Demographic patterns generally parallel those of associated risk factors such as neurodevelopmental and neurodegenerative disorders.

Predisposing and Precipitating Factors

Neurodegenerative disorders such as Alzheimer disease, Parkinson disease, and Huntington disease increase the risk for ISWRD. Children with developmental disorders also are at increased risk for ISWRD.

Poor sleep hygiene and lack of exposure to external synchronizing agents such as light, activity, and social schedules may be predisposing as well as precipitating factors involved in the development of ISWRD, particularly in the institutionalized elderly.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

Onset of the condition may occur at any age. Little is known regarding the course and complications of ISWRD in adults. Due to the multiple awakenings and, in the elderly, nocturnal wandering, falls can be an indirect complication. In addition to the patient's sleep-wake dysfunction, the caregiver's sleep is often disrupted. The sleep and wake disruption associated with ISWRD is a common cause of institutionalization.

Developmental Issues

Caregivers may report that a child with ISWRD has difficulty falling asleep at the desired bedtime or "falls asleep too early" in the evening, wakes "too early" or has difficulty waking in the morning, and/or exhibits developmentally inappropriate napping behavior during the day. Parents may complain that their child sleeps too much or too little or at inappropriate times. Attempts to keep the child awake during the day, especially during sedentary activities, are often unsuccessful. The key characteristics that distinguish ISWRD from other sleep complaints or circadian sleep wake disorders are the lack of prolonged consolidated sleep periods, the often seemingly random distribution in sleep periods across the 24-hour day, and the marked day-to-day and week-to-week variability with little in the way of a clearly predictable major sleep-wake pattern. The impact on caregivers' sleep and daytime functioning is likely to be particularly profound.

There may be phenotypes of ISWRD in children, with differences regarding symptom presentation and severity and chronicity that are related to the underlying condition.

For example, it is possible that children with chronic neurologic conditions such as autism or chromosomal syndromes characterized by developmental delays may have a more intractable and treatment resistant pattern compared with children with more self-limited conditions (e.g., postconcussion).

Although ISWRD appears to be rare in typically developing children, it may be environmentally or behaviorally induced. This may be seen in children with irregular or fragmented sleep and wake schedules because of a chaotic household. Children with developmental disorders are at increased risk for ISWRD. For example, children with autism, Asperger syndrome, or pervasive developmental disorder not otherwise specified often have highly irregular sleep patterns. In addition, these children often have circadian rhythm abnormalities which are both more severe and chronic and they are at increased risk for relapse.

Both ISWRD and non-24-hour sleep-wake rhythm disorder are also common in Angelman syndrome, a neurodevelopmental disorder associated with an abnormality of chromosome 15q11-q13, and have been reported in children with Williams syndrome, a neurodevelopmental genetic disorder characterized by physical abnormalities and a distinctive cognitive profile with intellectual disabilities and learning difficulties. Studies in children and adults with autism spectrum disorders and in children with Smith-Magenis syndrome have shown profound alterations in melatonin secretion profiles. Smith-Magenis syndrome is a developmental disorder caused by an abnormality in the short (p) arm of chromosome 17. It is characterized by mild to moderate intellectual disability, distinctive facial features, sleep disturbances, and behavioral problems. Decreased concentrations of melatonin and its metabolites and daytime elevation and abnormal rhythm/decreased amplitude of melatonin secretion have been reported in these populations. These findings may be due to polymorphisms in melatonin enzymes synthesis or variants in genes coding for melatonin receptors. Other postulated mechanisms for circadian rhythm disturbances, particularly ISWRD, in these populations include clock gene polymorphisms and decreased levels of entrainment by social/environmental cues.

There may also be medical conditions that predispose typically developing children and adolescents to ISWRD. These include traumatic brain injury and chronic fatigue syndrome. Brain tumor survivors, especially patients who have experienced disruption in the hypothalamic-pituitary axis, may have an increased prevalence of circadian rhythm disorders, including ISWRD.

There is very little literature on ISWRD in the pediatric population; prevalence, sex, and racial/ethnic differences are unknown. Little is known about the natural history

of the clinical entity of ISWRD in the pediatric population, including the impact of various treatment modalities, the likelihood of spontaneous resolution of symptoms, or long-term consequences. The impact on caregivers of children with neurodevelopmental disorders and ISWRD may be particularly profound.

The prevalence of ISWRD increases with advancing age, but it is likely that age-related increase in neurodegenerative disorders, rather than aging per se, explains this relationship.

Pathology and Pathophysiology

The etiology of ISWRD is likely multifactorial. Anatomic or functional abnormalities of the circadian clock can result in an arrhythmic pattern of rest and activity. Decreased exposure to environmental-entraining agents, such as light and structured physical and social activities (common in institutionalized elderly, and children with developmental disorders), also can contribute to the development of an irregular sleep-wake cycle.

Objective Findings

In addition to a careful sleep history, sleep log and actigraphy monitoring show the expected lack of a clearly defined circadian rhythm of the sleep-wake cycle, which, instead, is characterized by multiple irregular sleep and wake bouts throughout the 24-hour period. The use of sleep log and actigraphy is indicated for the identification of irregular sleep wake rhythm. The irregular sleep-wake pattern is defined as having multiple sleep bouts (typically 2–4 hours) during a 24-hour period. The pattern may vary from day to day, thus monitoring for at least seven days and preferably 14 days may be needed to differentiate the irregular pattern from other circadian rhythm sleep-wake disorders.

Polysomnography is not required to establish the diagnosis. Polysomnography may be useful for the diagnosis of other comorbid sleep disorders. Monitoring of other circadian rhythms, such as core body temperature and melatonin for at least 24 hours, may also show a loss of clear circadian rhythmicity or a low amplitude rhythm.

Differential Diagnosis

Poor sleep hygiene and *voluntary maintenance of irregular sleep schedules* should be distinguished from irregular sleep-wake pattern. Individuals with irregular sleep-wake rhythms may present with complaints of insomnia. Careful analysis of sleep logs or actigraphy will demonstrate multiple irregular periods of sleep throughout the 24-hour cycle. In both adults and children, other causes of sleep fragmentation and daytime

napping, including *comorbid medical and psychiatric disorders*, *other sleep disorders*, or *medication* should be identified and treated.

Unresolved Issues and Further Directions

There is limited knowledge of the pathophysiology and natural history, response to treatment, and complications of the disorder in adults and children. Further research into the relative contribution of alterations in environmental synchronizing agents, such as light and activity, versus a dysfunction of the endogenous circadian clock in the development of irregular sleep and wake patterns will lead to improved understanding of this condition.

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Non-24-Hour Sleep-Wake Rhythm Disorder

ICD-9-CM code: 327.34 ICD-10-CM code: G47.24

Alternate Names

Free-running disorder, nonentrained disorder, hypernychthemeral syndrome.

Diagnostic Criteria

Criteria A-D must be met

A. There is a history of insomnia, excessive daytime sleepiness, or both, which alternate with asymptomatic episodes, due to misalignment between the 24-hour light-dark cycle and the non-entrained endogenous circadian rhythm of sleep-wake propensity.
B. Symptoms persist over the course of at least three months.
C. Daily sleep logs and actigraphy for at least 14 days, preferably longer for blind persons, demonstrate a pattern of sleep and wake times that typically delay each day, with a circadian period that is usually longer than 24 hours.
D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Notes

1. Patients may present with a progressively delaying sleep-wake pattern and intermittent insomnia and excessive sleepiness. Individual symptoms will depend on when an individual tries to sleep in relation to the circadian rhythm of sleep-wake propensity. The magnitude of the daily delay will depend on the endogenous circadian period, and may range from less than 30 minutes (when the period is close to 24 hours) to more than an hour (when the period is longer than 25 hours).
2. The symptomatic episode will typically begin with a gradual increase in sleep latency and delayed sleep onset. As the sleep propensity rhythm shifts into the daytime, patients will have difficulty falling asleep at night and staying awake during the day. As the sleep-wake propensity rhythm drifts further, patients will eventually complain of late afternoon and evening sleepiness and naps as well as an early sleep onset time and short sleep latency.
3. Other circadian rhythms, such as the DLMO or urinary 6-sulfatoxy-melatonin rhythm obtained at two time points 2-4 weeks apart (i.e., to allow sufficient time for the drift to be apparent) is desirable to confirm the nonentrained rhythm.

Essential Features

Non-24-hour sleep-wake disorder (N24SWD) is characterized by symptoms of insomnia or excessive sleepiness that occur because the intrinsic circadian pacemaker is not entrained to a 24-hour light/dark cycle. The non-24-hour period can be shorter or, more typically, longer than 24 hours. Because the endogenous circadian rhythm is not aligned to the external 24-hour environment, symptoms will depend on when an individual tries to sleep in relation to the circadian rhythm of sleep and wake propensity. Individuals typically present with episodes of difficulty falling asleep or staying asleep, excessive sleepiness or both, alternating with short asymptomatic periods. The severity of individual sleep-wake symptoms can be variable. Starting with the asymptomatic period when the individual's endogenous rhythm is aligned to the external environment and required sleep-wake times, sleep latency will gradually increase and the individual will complain of sleep-onset insomnia. As the sleep phase continues to drift so that maximal endogenous sleep propensity is now in the daytime, individuals will have trouble staying awake during the day (exhibiting multiple daytime naps) and complain of sleepiness.

Associated Features

Most individuals with nonentrained circadian rhythms are totally blind, and the failure to entrain circadian rhythms is related to the lack of photic input to the circadian pacemaker. A small proportion of totally blind people may retain functional circadian photoreception and entrained rhythms if their blindness is due exclusively to an outer retina disorder (rod and cone layer) with retention of functional, intrinsically photosensitive retinal ganglion cells and the retinohypothalamic pathway. Some blind people may also be able to entrain to nonphotic cues (e.g., the timing of physical activity), producing entrainment at an adverse phase in some cases. In sighted people, social and behavioral factors also play an important role in the development and maintenance of the disorder, as there is an increased incidence of psychiatric disorders. Occasionally, the disorder is associated with developmental intellectual disability or dementia. In sighted individuals, there is often a history of delayed sleep phase, and decreased exposure to light and structured social and physical activity. Some sighted individuals with N24SWD also demonstrate increased sleep duration.

Demographics

It is thought that over half of totally blind individuals have non-24-hour circadian rhythms; 50% to 80% of blind individuals complain of sleep disturbances. The prevalence, sex, and racial/ethnic differences of N24SWD in adults and children are unknown.

Predisposing and Precipitating Factors

Total blindness is the most common predisposing condition. In sighted people, the disorder can be induced by certain environmental conditions, such as decreased or inappropriately timed exposure to circadian entraining agents, particularly light. Delayed sleep-wake phase disorder may predispose to N24SWD in sighted persons. The condition has developed after chronotherapy for DSWPD. This disorder has also been reported in adults following traumatic brain injury.

Familial Patterns

Not applicable or known.

Developmental Issues

Caregivers may report that a child has difficulty falling asleep at the desired bedtime or "falls asleep too early" in the evening, wakes "too early" or has difficulty waking in the morning and staying awake during the day. Parents may complain that their child sleeps too much or too little or at inappropriate times. The key characteristics that distinguish N24SWD from other sleep complaints or circadian sleep wake disorders are twofold: (1) the predictable pattern of misalignment between the child's sleep patterns and the light-dark 24-hour cycle (progressive delay in sleep onset-offset across days to weeks); and (2) periods of apparent "symptom remission" during those transient intervals when the child's circadian sleep-wake propensity coincides with the desired bed and wake times. The impact on caregivers' sleep and daytime functioning is often profound.

Although N24SWD is extremely rare in typically developing or sighted children, it has been reported with some frequency in children with intellectual disabilities and blindness. For example, children with optic nerve hypoplasia due to a variety of underlying causes, especially those children with hypoplastic corpus callosum and comorbid severe intellectual and visual impairments, have been reported to have features of N24SWD. N24SWD has also been described in pediatric patients with Rett syndrome (a genetic disorder occurring almost exclusively in girls, characterized by severe developmental regression, language delays, and limited social interactions), autism spectrum disorders, and Angelman syndrome, a neurodevelopmental disorder associated with an abnormality of chromosome 15q11-q13. The common mechanism in all of these disorders is postulated to be lack of entrainment to the 24-hour day that results from the failure to perceive and/or attend to social/environmental zeitgebers (time cues). There have also been several case reports which describe the emergence of N24SWD in intellectually normal sighted children or adolescents who have limited or inappropriate exposure to environmental and other entraining cues (e.g., decreased

light during the day and/or excessive light exposure in the evening). These individuals are likely to have significant psychiatric impairments that predispose them to avoidance of social interactions (e.g., anxiety) or medical conditions that involve enforced prolonged periods of inactivity (traumatic brain injury, chronic fatigue).

Little is known about the natural history of the clinical entity of N24SWD in the pediatric population, including the impact of various treatment modalities, the likelihood of spontaneous resolution of symptoms, or long-term consequences.

There may be varying phenotypes of N24SWD in children, with differences in regard to symptom presentation, severity, and chronicity that are related to the underlying condition. For example, it is likely that children with chronic neurologic conditions such as blindness or neurodevelopmental disabilities have a more intractable and treatment resistant pattern compared to children with more self-limited conditions (e.g., traumatic brain injury).

Onset, Course, and Complications

Onset may occur at any age in blind individuals, coincident with loss of light perception, and, in congenitally blind children, onset can occur from birth or during infancy. If untreated, the course is chronic. Attempts to regulate sleep and wake times may involve the use of alcohol, sedatives-hypnotics, and stimulants, which in turn can exacerbate the underlying sleep disorder. Depressive symptoms and mood disorders can be comorbid conditions, particularly in sighted patients. The adverse effects on school or work performance, as well as other psychosocial complications, due to a lack of predictable sleep and wake times and excessive daytime sleepiness, are key motivations for seeking treatment.

Pathology and Pathophysiology

The intrinsic period of the human circadian pacemaker is usually longer than 24 hours and requires daily input from the environment to maintain synchrony to the 24-hour day. The light-dark cycle is the most important environmental time cue (zeitgeber) in humans (as in other species), although nonphotic time cues also play a role in normal entrainment. A lack of photic input to the circadian pacemaker is clearly the cause of nonentrained rhythms in totally blind people. It has been suggested that, in sighted individuals, a systematic delay due to inadequate exposure to light may contribute to the development of N24SWD. In addition, the disorder may be caused by an extremely prolonged endogenous circadian period that is outside of the range for entrainment to the 24-hour cycle or by an alteration in the response of the circadian clock to the entraining effects of light.

Objective Findings

Sleep studies yield different results depending on the degree of synchrony between sleep times and the circadian pacemaker at the time when the sleep study is performed. Recording of sleep log and actigraphy over prolonged periods (at least 14 days, but ideally longer in blind individuals) demonstrate the lack of a stable relationship between the timing of the sleep-wake cycle and the 24-hour day. When sleep schedules follow the endogenous circadian propensity for sleep and wake, sleep onset and wake times are typically delayed each day. Serial measurements of circadian rhythms, such as melatonin, usually show a progressive daily delay of the phase of the rhythm consistent with a period that is longer than 24 hours.

Clinical and Pathophysiologic Subtypes

Totally blind patients with N24SWD are clinically different than sighted patients. In sighted patients with N24SWD, the circadian period is often 25 hours or longer, whereas in totally blind patients with the disorder, the circadian period follows an average period length which is often closer to 24 hours and rarely may be shorter than 24 hours.

Differential Diagnosis

Some individuals with severe *DSWPD* may demonstrate progressive delay of their sleep period by 30 minutes or more for several days, and their symptoms may be confused with N24SWD.

Behavioral factors and psychiatric disorders, as well as medical and neurological disorders (especially blindness, but also dementia or mental retardation), may play a role in the development of N24SWD. In many of these cases, however, multiple physiologic, behavioral, and environmental factors contribute to the condition. In the majority of these cases, the disorder should be coded as N24SWD. This includes non-24-hour sleep-wake patterns that are associated with blindness.

Unresolved Issues and Further Directions

There is only limited knowledge of the underlying pathophysiology of sighted persons with N24SWD. The primary risk factor in sighted persons appears to be a long circadian period that is beyond the range of entrainment to a 24-hour cycle or a progressive delay due to inappropriate exposure to light. This risk may explain the overlap between DSWPD and N24SWD. Future studies are needed to understand the role of genetic predisposition, environmental or social cues and traumatic brain injury in the development of N24SWD, and to delineate other health consequences of the condition. There are substantial knowledge gaps regarding the prevalence, pathophysiology, clinical

presentation, natural history, effective treatment strategies, and prognosis of N24SWD in children and adolescents compared with adults.

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Shift Work Disorder

ICD-9-CM code: 327.36 ICD-10-CM code: G47.26

Alternate Names

Shift work sleep disorder.

Diagnostic Criteria

Criteria A-D must be met

A. There is a report of insomnia and/or excessive sleepiness, accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps the usual time for sleep.
B. The symptoms have been present and associated with the shift work schedule for at least three months.
C. Sleep log and actigraphy monitoring (whenever possible and preferably with concurrent light exposure measurement) for at least 14 days (work and free days) demonstrate a disturbed sleep and wake pattern.
D. The sleep and/or wake disturbance are not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, poor sleep hygiene, or substance use disorder.

Essential Features

Shift work disorder is characterized by complaints of insomnia or excessive sleepiness that occur in association with work hours that occur, at least in part, during the usual sleep episode. There are several types of shift-work schedules, including evening shifts, night shifts, early morning shifts, rotating shifts, split shifts, on-call overnight duty, and long duration work shifts that include work hours at night. The sleep disturbance is most commonly reported in association with night shifts, early morning shifts, and rotating shifts. Total sleep time is typically curtailed by one to four hours, and sleep quality is perceived as unsatisfactory in night, early morning, and rotating shift workers as well as in those who work long-duration shifts. In addition to impairment of performance at work, reduced alertness may also be associated with consequences for safety during the work schedule and on the commute to and from work. The sleep disorder occurs despite attempts to optimize environmental conditions for sleep. The condition usually persists only for the duration of the shift work schedule. However, in some individuals, the sleep disturbance may persist beyond the duration of shift work.

Associated Features

Early morning work shifts starting between 4:00 a.m. and 7:00 a.m. can also be associated with complaints of difficulty in sleep initiation as well as difficulty awakening.

Permanent evening shifts may be primarily associated with sleep maintenance difficulty. Excessive sleepiness usually occurs during work shifts (mainly night, early morning, and rotating shifts), often accompanied by the need to nap and by impaired mental ability due to the reduced alertness. Reduced alertness and increased fatigue throughout the waking period may be associated with reduced performance capacity, and with consequences for safety. Also, major portions of free time may have to be used for recovery of sleep, resulting in adverse social consequences. When compared with shift workers without shift work disorder, patients with shift work disorder report greater mood problems, such as impatience, avoidance of interaction with coworkers, a higher risk of depression, impaired social functioning, and lower coping skills. Patients with shift work disorder also have a higher risk of subjective health complaints, ulcers, and substance abuse. Risk for sleepiness-related errors and accidents are highest at night, especially in the early morning hours. Drowsy driving accident risk is highest in the morning hours when night shift workers commute home and early morning workers commute to work.

Clinical and Pathophysiological Subtypes

There are substantial individual differences in the ability to adjust to shift work. However, mechanisms underlying these individual differences are not known.

Requirement of extended work hours, such as on-call overnight duty and long-duration work shifts that include work hours at night, represents a specific clinical subtype. In addition to the circadian misalignment (having to work during the night), sleep loss and fatigue associated with prolonged continuous work may increase the severity of excessive sleepiness and performance impairments.

Demographics

The prevalence of shift work disorder depends on the prevalence of shift work in the population. It has been estimated that approximately 20% of the workforce in industrialized countries is employed in a job that requires shift work. Although the actual prevalence of clinically significant sleep disturbance and excessive daytime sleepiness due to work schedules is unknown, the total number of night-shift workers suggests that an estimated prevalence of 2% to 5% of the general population is reasonable. The prevalence of shift work disorder among rotating- and night-shift workers has been estimated to be between ~10% and 38%. These figures do not, however, include individuals with early morning or split shift work, which may be other at-risk groups. There is no known sex or racial difference in vulnerability.

Predisposing and Precipitating Factors

Depending on the type of shift, circadian preference may influence the ability to adjust to or tolerate shift work. For example, individuals described as morning types obtain shorter daytime sleep after a night shift. Persons with comorbid medical, psychiatric, and other sleep disorders such as sleep apnea and individuals with a strong need for stable hours of sleep may be at particular risk. Social pressures before and after a work shift also contribute to short sleep durations in shift workers (e.g., social interactions with family and friends, domestic obligations, a second job, and leisure activities). Social pressures also diminish the desire or willingness to maintain a consistent daytime sleep schedule on days off, thereby reducing the likelihood of circadian adjustment.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

The condition is closely linked to work schedules and typically remits when the major sleep episode is scheduled at a conventional time. Because there are so many different work schedules, ranging from an occasional overnight shift to regular night work, the course is quite variable. Because shift work is often combined with extended hours of duty, fatigue can be a complicating factor. Circadian adaptation is often counteracted by exposure to light at the wrong time of the day and the tendency of most workers to resume full daytime activities and nighttime sleep during weekends and vacations. It has been hypothesized that in some individuals, the condition may lead to chronic sleep disturbances. Complications may include exacerbation of gastrointestinal, metabolic, reproductive, neoplastic, and cardiovascular disorders. Disruptions of social and family life are frequent. Drug and alcohol dependency may result from attempts to improve the sleep and wakefulness disturbances produced by shift work. Fatigue and excessive sleepiness due to the combination of sleep loss and circadian misalignment pose important safety concerns. The level of alertness required of the worker, in addition to the intensity of symptoms, needs to be taken into account when evaluating the disorder. For example, the threshold for intervention may be lower for workers whose performance is critical for personal or public safety (for example, health care workers or nuclear power plant or public transport operators).

Developmental Issues

Not applicable or known.

Pathology and Pathophysiology

The condition is thought to be directly related to circadian misalignment and sleep loss. The sleep disturbance is generated by a circadian alerting process that corresponds with the time that the worker needs to sleep. The excessive sleepiness during the night and early morning appears to be partly related to cumulative sleep loss and partly due to a decreased circadian alerting signal that corresponds with the work time and the commute to and from work. Tolerance to night work varies considerably and may involve differences in the degree of circadian adaptation ("clock resetting") to a night-work, day-sleep schedule. Alternatively, tolerance may be related to individual differences in response to circadian and homeostatic influences on sleep and wakefulness regulation. Environmental and social factors may exacerbate sleep loss associated with shift work schedules.

Objective Findings

The condition can usually be diagnosed by history. Sleep logs and actigraphy are recommended to demonstrate a disrupted sleep-wake pattern consistent with shift work disorder. Polysomnographic recordings, while not required for the diagnosis, are useful if the etiology of the sleep disturbance is in question (for example to rule out sleep apnea or narcolepsy). Polysomnography during a typical daytime sleep episode after a work shift also can be useful to determine the severity of the sleep disruption, although this is undertaken almost exclusively for research studies of shift work disorder. Polysomnography may demonstrate impaired sleep quality, with prolonged sleep latency, sleep maintenance difficulty, or shortened total sleep time, depending on the timing of the sleep episode in relation to the underlying phase of the circadian timing system. The sleep episode may be fragmented, with frequent arousals and awakenings. The Multiple Sleep Latency Test (MSLT) may demonstrate excessive sleepiness during the time of the work shift. If available, measures of the unmasked melatonin rhythm are useful to indicate the degree of circadian misalignment.

Differential Diagnosis

The excessive sleepiness should be differentiated from that caused by other primary sleep disorders such as *obstructive sleep apnea* or *narcolepsy*. *Insufficient sleep* related to conflicting daytime activities (for example, child care) or from environmental interference with sleep (for example, daytime noise) often contributes to sleepiness. Sometimes patients with *DSWPD* may adopt a night-work schedule that is more congruent with their sleep preferences. Insomnia and excessive sleepiness may also suggest other persistent circadian rhythm sleep-wake disorders. However, historical information on the relation between the occurrence of disturbed sleep and work-hour distribution should provide sufficient information to indicate the correct diagnosis. Increasing

frustration, negative expectations, and poor sleep hygiene may predispose the person to the development of coexisting *chronic insomnia disorder* that could persist beyond the shift work schedule (i.e., shift work may represent a precipitating event that leads to chronic problems with insomnia). Drug and alcohol abuse or dependency may result from efforts to treat the sleep disturbance.

Unresolved Issues and Further Directions

Although there is sufficient information regarding the prevalence of shift work in industrialized populations, less information is available regarding the actual prevalence of shift work disorder and its impact on health and safety. Further research is needed to improve the definition of what constitutes shift work disorder, to develop diagnostic tools for shift work disorder, to determine the prevalence of shift work disorder using diagnostic criteria, to elucidate the burden of shift work disorder over and above that which may be due to shift work in general, to investigate mechanisms underlying the health and safety consequences of shift work disorder, and to determine which shift workers are at greatest risk of shift work disorder. Furthermore, there is limited information on the role of age, sex, and circadian chronotype on the vulnerability to shift work disorder.

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Jet Lag Disorder

ICD-9-CM code: 327.35 ICD-10-CM code: G47.25

Alternate Names

Jet lag, time zone change syndrome, jet lag syndrome, jet lag type.

Diagnostic Criteria

Criteria A-C must be met

A. There is a complaint of insomnia or excessive daytime sleepiness, accompanied by a reduction of total sleep time, associated with transmeridian jet travel across at least two time zones.
B. There is associated impairment of daytime function, general malaise, or somatic symptoms (e.g., gastrointestinal disturbance) within one to two days after travel.
C. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Essential Features

Jet lag disorder is characterized by a temporary mismatch between the timing of the sleep and wake cycle generated by the endogenous circadian clock and that of the sleep and wake pattern required by a change in time zone. Individuals complain of disturbed sleep, sleepiness and fatigue, and impaired daytime function. The severity and duration of symptoms is dependent on the number of time zones traveled, the ability to sleep while traveling, exposure to appropriate circadian times cues in the new environment, tolerance to circadian misalignment when awake during the biological night, and the direction of the travel. Eastward travel (requiring advancing circadian rhythms and sleep-wake hours) is usually more difficult to adjust to than westward travel.

Associated Features

In addition to sleep disturbance and decreased daytime alertness, associated features may include general malaise and gastrointestinal symptoms. Numerous other variables related to travel, such as sleep loss, decreased mobility, and alcohol and/or caffeine intake, contribute to the overall fatigue. Daytime sleepiness can lead to memory difficulties, problems concentrating, driving and flying, and to impaired decision-making. Sleepiness, sleep disturbance and circadian misalignment associated with jet lag may also impair athletic performance. Effects of jet lag not only affect travelers, but also can have significant consequences for airline pilots and flight attendants.

Clinical and Pathophysiological Subtypes

There are individual differences in the ability to adjust to rapid shifts in time zones; however, specific clinical subtypes have not been identified.

Demographics

Jet lag affects all age, sex, and racial groups. Limited available data suggest that older individuals may experience fewer jet lag symptoms compared with younger individuals. However, the data have limitations and further research is needed to better define the relationship between age and the development of jet lag disorder.

There are no studies on the prevalence of jet lag disorder.

Predisposing and Precipitating Factors

Disturbed sleep and/or shortened sleep duration before and during travel contribute to jet lag symptoms. Prolonged uncomfortable sitting positions, air quality and pressure, stress, and excessive caffeine and alcohol consumption may increase the severity of insomnia and impaired alertness and function associated with transmeridian travel.

Eastward travel often leads to difficulties with sleep onset as attempts to sleep are made at an earlier internal circadian time when the travelers' biological clock is promoting alertness (i.e., biological day). Difficulty awakening and daytime sleepiness and fatigue occur because wake time also occurs at an earlier biological time when the circadian clock is still promoting sleep (i.e., during the travelers' biological night).

Westward jet travel often leads to sleepiness and fatigue in the evening hours of the new time zone as the internal circadian clock of the traveler is promoting sleep (i.e., biological night). Sleep disturbance in the new time zone is typically manifest as a sleep maintenance issue with early morning awakenings and difficulty returning to sleep because the internal circadian clock of the traveler is promoting wakefulness during the sleep episode (i.e., biological day).

Basic circadian science principles suggest that inappropriately timed exposure to light and darkness during and immediately after jet travel can shift the circadian clock in the wrong direction, thereby increasing the duration of jet lag symptoms. Time at destination upon arrival may also influence jet lag symptoms with fewer symptoms reported following midday arrivals after eastward travel.

An individual's innate circadian preference may also confer a greater or lesser ability to adjust to a particular time shift, but this finding has not been systematically assessed.

Jet lag is often reported to be worse after eastward than westward travel. Westward travel may generally be easier because the genetically determined period of the circadian clock in humans is on average longer than 24 hours. A circadian period longer than 24 hours is associated with a circadian drive or physiological tendency for bed and wake times to be later, thus making it easier to shift the circadian clock during westward travel to more delayed sleep and wake times. However, 20% to 25% of humans have circadian periods that are near to, or shorter than, 24 hours, and these individuals may find it easier to adapt to eastward travel.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

Jet lag is usually a temporary condition. Symptoms begin approximately one to two days after air travel across at least two time zones and are self-limited. The severity and duration of symptoms are usually in proportion to the number of time zones traveled and the direction of travel. It is estimated that it takes one day per time zone for circadian rhythms to adjust to the local time. However, if traveling more than six time zones, circadian rhythms may shift in the opposite direction, resulting in a prolonged period of adjustment that may last up to several weeks and increased severity of jet-lag symptoms. Exposure to light at inappropriate times may prolong the time of adjustment by shifting the circadian rhythms in the opposite direction. Menstrual and reproductive problems have been associated with frequent transmeridian travel in female airline personnel. Poor sleep hygiene practices may perpetuate sleep/wake complaints, and repetitive failed attempts to initiate or maintain sleep at desired times may predispose to the development of insomnia disorder.

Developmental Issues

The effect of age on the development or severity of jet lag disorder symptoms is unknown.

Pathology and Pathophysiology

The symptoms of jet lag disorder are due to both desynchronization of endogenous circadian rhythms with local time and sleep disturbance. The severity of symptoms can be influenced by the environment and behaviors of the traveler. Factors inherent to jet travel, including prolonged time spent sitting in a confined space, ability to sleep on long-haul flights, decreased physical activity, and a low oxygen environment, may influence severity.

Objective Findings

Objective laboratory testing usually is not indicated. When performed, polysomnography or actigraphy shows disturbed sleep and a loss of a normal sleep-wake pattern or a mismatch between the timing of sleep and wakefulness with the desired sleep-wake pattern of the local time.

Differential Diagnosis

A thorough history and physical examination should be performed to exclude other mental, physical, or sleep disorders. Somatic complaints of gastrointestinal symptoms may indicate an underlying medical condition. When jet lag symptoms persist, increasing frustration, negative expectations, and poor sleep hygiene may predispose the individual to the development of *chronic insomnia disorder*.

Unresolved Issues and Further Directions

Understanding mechanisms of individual differences in vulnerability and tolerance to disturbed sleep and wakefulness during jet lag is necessary. Development of effective and practical strategies to combat jet-lag symptoms and improve sleep, performance and safety are needed.

It is unknown how expression of the disorder varies across the life span.

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Circadian Sleep-Wake Disorder Not Otherwise Specified (NOS)

ICD-9-CM code: 327.30 ICD-10-CM code: G47.20

Patients who meet all of the general diagnostic criteria for a CRSWD but do not meet criteria for one of the specific types of circadian rhythm sleep-wake disorders are classified here. This diagnosis is intended primarily for patients with alterations in circadian sleep-wake patterns due to underlying medical, neurologic, and psychiatric disorders. The underlying neurological, psychiatric, or medical condition is typically the precipitating factor. Patients may present with a variety of symptoms, including disturbed nocturnal sleep and excessive sleepiness. The sleep-wake pattern may range from alterations in the phase of the sleep-wake cycle to irregular sleep-wake pattern. Recordings of sleep logs and actigraphy over a period of at least seven days, preferably for 14 days or longer, demonstrate sleep onsets and sleep offsets that may be delayed or advanced relative to conventional times, irregular or non-24-hour.

Sleep-wake disturbances are common in patients with neurodegenerative disorders (Alzheimer disease, Parkinson disease, Huntington disease), as well as neurodevelopmental disorders. Sleep-wake disturbances associated with these disorders may exhibit some features of irregular sleep-wake patterns, but do not have a consistent pattern of at least three sleep periods per day. The particular features of this disorder vary with the type of underlying medical, psychiatric, or neurological condition. The disruption of the sleep-wake cycle has been implicated in the etiology of sundowning and nocturnal wandering in older adults with dementia. Patients with Parkinson disease may exhibit various types of circadian-rhythm alterations. In addition, motor fluctuations can exhibit marked diurnal fluctuation in patients with Parkinson disease.

Parasomnias

Parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep. Parasomnias may occur during non-rapid eye movement sleep (NREM), rapid eye movement sleep (REM), or during transitions to and from sleep.

Parasomnias encompass abnormal sleep related complex movements, behaviors, emotions, perceptions, dreams, and autonomic nervous system activity. Parasomnias are clinical disorders because of the resulting injuries, sleep disruption, adverse health effects, and untoward psychosocial effects. The clinical consequences of the parasomnias can affect the patient, the bed partner, or both.

Human consciousness consists of three essential states: Wake, NREM sleep, and REM sleep. The three states are modulated by a host of influences including the degree of aminergic and cholinergic neurochemical bias, central nervous system (CNS) activation,

and the degree of endogenous versus exogenous input. Under normal physiologic conditions, which include homeostatic drive and circadian rhythmicity, the process of state declaration is maintained in a stable and predictable fashion throughout a 24-hour period. However, as the sleep-wake cycle oscillates, the normally distinct states of consciousness may be rendered into a state that is not fully declared, resulting in a temporary unstable state of dissociation. Thus, sleep and wake can be viewed as occurring on a spectrum rather than being entirely dichotomous states.

Parasomnias are the result of such state dissociation. Recent research has shown that combinations of one or more of these states do occur and may result in unstable states of altered consciousness manifesting as parasomnias. Disorders of arousal, such as sleepwalking, sleep terrors, and confusional arousals are an admixture of wakefulness and NREM sleep. Higher cognitive function is severely impaired, if not absent, while the potential for motor capacity has, for the most part, been retained. REM sleep behavior disorder (RBD) is an admixture of REM sleep coupled with waking or NREM sleep levels of tonic EMG activity. All three states may be present in the same individual as an overlap of disorders.

The comingling of basic states of consciousness is the result of different forms of pathophysiology. In disorders of arousal, no identifiable neuropathology is present, but functional changes in cerebral activity during NREM sleep are present, essentially resulting in a brain in which certain areas are deactivated (asleep) and others remain activated (awake). This CNS activation, with concomitant skeletal muscle and autonomic nervous system activation, is believed to reflect a functional disabling of, or damage to, brain areas usually responsible for the inhibition of these activities during sleep. Additionally, sleep inertia, sleep state instability, and locomotor/central pattern generators are thought to contribute to the occurrence of NREM parasomnias.

NREM disorders of arousal frequently appear to involve the disinhibition of "basic drive states" such as feeding, sex, and aggression. Here, it has been postulated that central pattern generators elicit primal fixed action patterns that would otherwise have been inhibited by the prefrontal cortex during wake. In this regard, aggression is typically abrupt in onset and characterized by apparent instinctual defensive posturing as opposed to behaviors that are complex and procedural. These can emerge in pathologic forms with the parasomnias, as seen with sleep related aggression and locomotion, sleep related eating disorder (SRED), and abnormal sleep related sexual behaviors.

In contrast, RBD often results from serious neuropathology. Initially, this neuropathology affects the area of the brain responsible for inhibiting muscle tone during REM sleep. As a result, dreams may be enacted. In the case of REM-related behaviors, the experience

and activity reflect the actual, often aggressive content of a dream. It is frequently possible to correlate observed movements with later descriptions of the dream. The initial appearance of RBD symptoms is often followed years later by the development of neurodegenerative disorders, particularly Parkinson disease and related synucleinopathies.

Abnormal sleep related movements comprise a separate category of disorders, which is detailed in the sleep related movement disorders section. Unlike the parasomnias, which typically entail more complex movements and behavior, the movement disorders encompass a broad range of predominantly simple motoric activities: myoclonic, repetitive, rocking, rhythmic, grinding, cramping, fragmentary, dystonic, or dyskinetic movements or tremors, which are not usually associated with dream mentation or experiential concomitants.

Parasomnias involve sleep related behaviors and experiences over which there is no conscious deliberate control. There are ten core categories of parasomnias listed in the International Classification of Sleep Disorders, 3rd Edition. Only one of the core categories, RBD, requires video-polysomnographic documentation as one of the essential diagnostic criteria. However, for most of the other parasomnias, polysomnographic monitoring can provide corroborative documentation in support of the clinical diagnosis.

Considerable advances have taken place in understanding the neurophysiologic aspects of abnormal arousals from slow wave sleep associated with the disorders of arousal. Advances in the clinical understanding of these NREM sleep parasomnias have occurred as well, particularly in regard to their prevalence and severity in adults. In regard to RBD, long-term delayed emergence of neurodegeneration has frequently been found in middle-aged and older adults following onset of RBD. When combined with thorough clinical interviews, video-polysomnography a powerful discriminating tool for identifying the cause of sleep related injury in adults.

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NREM-Related Parasomnias

Disorders of Arousal (From NREM Sleep)

This group of NREM-related disorders, which includes confusional arousals, sleep-walking, and sleep terrors, arise as a result of incomplete arousals from deep sleep. The conditions share: (1) similar genetic and familial patterns; (2) similar pathophysiology of partial arousals from deep sleep; and (3) similar priming by sleep deprivation and biopsychosocial stressors. Disorders of arousal are: (1) not secondary to psychiatric disorders; (2) not generally secondary to neuropathology or head injury; (3) associated with absent or minimal cognitive functioning; (4) associated with amnesia for the prior episode; and (5) may be triggered by sound, touch, or other stimuli.

General Diagnostic Criteria for Disorders of Arousal

Criteria A-E must be met

A. Recurrent episodes of incomplete awakening from sleep.[1]
B. Inappropriate or absent responsiveness to efforts of others to intervene or redirect the person during the episode.
C. Limited (e.g., a single visual scene) or no associated cognition or dream imagery.
D. Partial or complete amnesia for the episode.
E. The disturbance is not better explained by another sleep disorder, mental disorder, medical condition, medication, or substance use.

Notes

1. The events usually occur during the first third of the major sleep episode.
2. The individual may continue to appear confused and disoriented for several minutes or longer following the episode.

Confusional Arousals

ICD-9-CM code: 327.41 ICD-10-CM code: G47.51

Alternate Names

Elpenor syndrome.

Diagnostic Criteria

Criteria A-C must be met

A. The disorder meets general criteria for NREM disorders of arousal.
B. The episodes are characterized by mental confusion or confused behavior that occurs while the patient is in bed.
C. There is an absence of terror or ambulation outside of the bed.

Notes

1. There is typically a lack of autonomic arousal such as mydriasis, tachycardia, tachypnea, and diaphoresis during an episode.

Sleepwalking

ICD-9-CM code: 307.46 ICD-10-CM code: F51.3

Alternate Names

Somnambulism.

Diagnostic Criteria

Criteria A and B must be met

A. The disorder meets general criteria for NREM disorders of arousal.
B. The arousals are associated with ambulation and other complex behaviors out of bed.

Sleep Terrors

ICD-9-CM code: 307.46 ICD-10-CM code: F51.4

Alternate Names

Night terrors, pavor nocturnus.

Diagnostic Criteria

Criteria A-C must be met

A. The disorder meets general criteria for NREM disorders of arousal.
B. The arousals are characterized by episodes of abrupt terror, typically beginning with an alarming vocalization such as a frightening scream.
C. There is intense fear and signs of autonomic arousal, including mydriasis, tachycardia, tachypnea, and diaphoresis during an episode.

Essential Features

Disorders of arousal consist of complex behaviors that are usually initiated during partial arousals from slow wave (N3) sleep. Most episodes are brief, but they may last as long as 30 to 40 minutes in some children. Sleep talking and shouting may accompany these events. The eyes are usually open during an episode and, not uncommonly, are wide open with a confused "glassy" stare. The patient with a disorder of arousal may be very difficult to awaken and, when awakened, is often confused. There is usually amnesia for these episodes, although adults may remember fragments of episodes. Dream-like mentation is sometimes reported in adults. Other high-level cognitive functions such as attention, planning, social interaction, and intent are absent. Because disorders of arousal usually originate from slow wave sleep, they most often emerge in the first third or first half of the typical sleep period. They may occur during other times of increased slow wave sleep, such as during recovery sleep following sleep deprivation. They rarely arise from a daytime nap.

Disorders of arousal are encountered most commonly in children and typically resolve by puberty but may persist (or, infrequently, arise de novo) in adolescence or adulthood.

Confusional Arousals: Confusional arousals, unlike sleepwalking, occur with the patient in bed. When the patient leaves the bed, sleepwalking has been initiated. Confusional arousals often start with the individual sitting up in bed and looking about in a confused manner.

Sleepwalking: Sleepwalking episodes typically begin as confusional arousals. Sleepwalking episodes can also begin with the individual immediately leaving the

bed and walking or even "bolting" from the bed and running. Highly inappropriate, agitated, resistive, belligerent, or violent behavior can also occur. Behaviors can be simple and non–goal-directed, or complex and protracted, and may involve inappropriate sexual activity with oneself or an individual in close proximity such as a bed partner. The ambulation may terminate spontaneously, at times in inappropriate places, or the sleepwalker may return to bed, lie down, and continue to sleep without reaching conscious awareness at any point. The sleepwalking individual is disoriented in time and place, with slow speech, with severely diminished mentation, and blunted response to questions or requests. There is often prominent anterograde and retrograde memory impairment. Despite diminished external perception as a result of blockade of sensory input, the individual may appear to be awake during some or most of a disorder of arousal with reduced vigilance and impaired cognitive response.

Sleep Terrors: Sleep terrors differ from other disorders of arousal in that the events are often accompanied by a cry or piercing scream, accompanied by autonomic nervous system and behavioral manifestations of intense fear. There is often intense autonomic discharge, with tachycardia, tachypnea, flushing of the skin, diaphoresis, mydriasis, and increased muscle tone. The person usually sits up in bed; is unresponsive to external stimuli; and, if awakened, is confused and disoriented. However, bolting out of bed and running is not uncommon in adults and also can be associated with violent behaviors, particularly if attempts are made to block or restrain the individual. The sleep terror episode may be accompanied by incoherent vocalizations. Sometimes there is prolonged inconsolability associated with a sleep terror in children or adults.

Associated Features

Disorders of arousal are devoid of higher cognitive functions such as planning, memory from before an incident, formation of a memory during an incident, true social interaction, or recognition of others. Patients exhibiting disorders of arousal are not consciously aware and behaviors are often thought to be "automatic" in nature. Self-injury may occur as well as injury to others in close proximity.

Disorders of arousal, in particular sleepwalking, can involve normal, routine behaviors that are inappropriate only in regard to their timing. More often, however, sleepwalking involves inappropriate behaviors, such as urinating in a wastebasket, moving furniture around haphazardly, or climbing out a window. Sleepwalkers are sometimes able to navigate in familiar surroundings, but are prone to bumping into objects or falling down. A sudden arousal consistent with sleep terrors may segue rapidly into agitated sleepwalking and panicky running and other potentially dangerous behaviors. Self-injury is not unusual and when resulting in death has been given the term of

"parasomnia pseudosuicide." Cuts, bruises, and other injuries may occur—often to the surprise of the sleepwalker once awake. Sleepwalkers are reported to have a high tolerance for pain. Knife cuts, burns, and other self-injury sustained during sleepwalking may not awaken them.

Violence to others also can occur with adult sleepwalking, especially in men. The sleepwalker does not generally seek out the eventual victim of violence. More typically, a person attempting to block, grab, restrain, redirect or awaken a sleepwalker during an episode may be violently attacked, even if they are family members or friends. This may result in a form of primitive defensive aggression including pushing, hitting, kicking, or throwing objects. This pattern also has been reported in the sleep laboratory when technical personnel have attempted to return sleepwalking patients to bed. In extreme cases, victims have been stabbed with knives or blunt objects. Such inappropriate and antisocial behaviors have legal and forensic implications, as sleepwalkers have been arrested and charged with assault and battery, attempted homicide, homicide, and sexual assault with indecency.

The child with calm sleepwalking may quietly walk toward a light or to the parents' bedroom. Occasionally, children will walk toward a window or door or even go outside, with obvious attendant risk.

Clinical or Pathophysiological Subtypes

Sleep related abnormal sexual behaviors are primarily classified as confusional arousals in that they typically occur without any behaviors outside of the bed (or chosen sleeping accommodation), but have also been less commonly associated with sleepwalking. Other terms for this condition include "*atypical sexual behavior during sleep*," "*sexsomnia*," and "*sleep sex*." Sleep related abnormal sexual behaviors often have major interpersonal, clinical, and occasional criminal consequences. The set of abnormal sexual behaviors during disordered arousals includes prolonged or violent masturbation, sexual molestation and assaults (of minors and adults), initiation of sexual intercourse irrespective of the menstrual status of the bed partner (in contrast to waking intercourse for those individuals), and loud (sexual) vocalizations during sleep—followed by morning amnesia. The preponderance of patients have also been diagnosed with a NREM sleep parasomnia, most often confusional arousals alone but on occasion with sleepwalking, sleep related driving, or sleep related eating disorder. Obstructive sleep apnea (OSA) is another recognized precipitant of sleep related abnormal sexual behaviors.

The presence of an overlap disorder, in which RBD and a partial arousal disorder (sleepwalking or sleep terrors) are comorbid in a patient, may complicate diagnosis of

each condition. Careful review of history and use of polysomnography may facilitate identification of this presentation.

Demographics

There is no sex difference with disorders of arousals. They are especially prevalent among children and adults younger than 35 years. The prevalence rate of confusional arousals and sleepwalking are similar.

The prevalence of confusional arousals in children three to 13 years of age in a large population-based study was 17.3%. Lifetime prevalence of confusional arousals has recently been reported as 18.5% (16.1-20.9 confidence interval). The prevalence among adults older than 15 years is 2.9% to 4.2%.

The lifetime prevalence of sleepwalking is as high as 18.3%. A recent study of "nocturnal wandering" that likely included a large percentage of sleepwalkers reported a lifetime prevalence of 29.2%. A Swedish study of children aged 6-16 years found the incidence of sleepwalking to be 40%. Up to 4.3% of adults sleepwalk. In one series, one third of 54 adult patients with injurious sleepwalking (with or without night terrors) began sleepwalking after 16 years of age.

The prevalence of sleep terrors has not been studied as thoroughly. Prevalence rates of 1% to 6.5% in children and 2.2% in adults have been reported, with a virtually constant prevalence rate of 2.3% to 2.6% in the 15-year-old to 64-year-old age group, before falling to 1% in the older than 65 years age group. Other studies have reported the intermittent appearance of sleep terrors in 25% of children younger than five years.

Predisposing and Precipitating Factors

Disorders of arousal are most often evaluated in terms of predisposing, priming, and precipitating (triggering) factors. Most often a simultaneous co-occurrence of these factors is thought necessary in order for a disorder of arousal occur. However, the reason a disorder of arousal occurs on one night and not others is not fully understood.

A genetic predisposition has been hypothesized and several studies have identified different genetic loci and modes of inheritance (see Familial Pattern, below). In childhood, disorder of arousal can usually be considered an expected and normal developmental sleep phenomenon, apart from those cases with clinical consequences. However, disorders of arousal that persist beyond adolescence or begin in adulthood can often be problematic and may require clinical attention.

Many priming factors for disorders of arousal, in particular sleepwalking, have been identified. Sleep deprivation and situational stress are the most potent factors. Hyperthyroidism, migraines, head injury, encephalitis, stroke, and other conditions have also been reported much more rarely as potential priming factors.

OSA and other sleep related respiratory events are increasingly recognized precipitants of disorders of arousal in both children and adults. Treatment of these comorbid conditions may reduce or eliminate the occurrence of disorders of arousal. Disorders of arousal may also be triggered by environmental stimuli such as telephone calls, pagers, messaging from electronic devices, and a host of other stimuli. It is clinically important to note that first responders, physicians, and others on call may be vulnerable to such stimuli, increasing the potential for inappropriate responses and behavior.

Travel, sleeping in unfamiliar surroundings, febrile states in children, physical or emotional stress in adults, the premenstrual period in women, as well as the use of psychotropic medications such as lithium carbonate, phenothiazines, anticholinergic agents, and sedative/hypnotic agents have been associated with the onset of sleepwalking, but a causal relationship has yet to be established. Alcohol has been identified in previous reports as a potential sleepwalking trigger. However, the amnesia associated with disorders of arousal makes these reports unreliable. More recent evidence-based reviews have found no compelling relationship between alcohol and disorders of arousal. Internal stimuli, such as a distended bladder, or external stimuli, such as noise or light, can also precipitate episodes.

There is no significant association between childhood disorders of arousal and psychopathology. In adult sleepwalking, although a considerable number of patients may have a past or current history of nonpsychotic depressive and anxiety disorders, it does not appear that the psychiatric disorder and sleepwalking, in particular, are tightly linked. In addition, when the two conditions emerge in close temporal proximity, control of the psychiatric disorder often does not control the parasomnia, for which separate treatment is required.

Familial Pattern

Genetic factors appear to play an important role in all of the disorders of arousal. However, published research data exist primarily for patients who sleepwalk. Sleepwalking has a familial pattern. The rate of childhood sleepwalking increases in relation to the number of affected parents: 22% when neither parent has the disorder, 45% if one parent is affected, and 60% when both are affected. Population-based studies of monozygotic and dizygotic twins suggest that genetic factors play a role

in 65% of cases of sleepwalking. Different models of modes of inheritance including multifactorial, recessive with incomplete penetrance, and autosomal dominant trait with reduced penetrance have been proposed, based primarily on analysis of family histories. However, these finding are not sufficiently specific to be used for diagnostic testing. Further, the mechanisms by which a genetic predisposition for confusional arousal or other related disorders contributes to their occurrence are not known.

Onset, Course, and Complications

Confusional arousals most often appear in early childhood around the age of two years. This childhood form of confusional arousals is typically benign, but may cause concern in parents. Confusional arousals of early childhood diminish in occurrence after the age of five years.

Sleepwalking can begin as soon as a child is able to walk but may begin at almost any time in the life cycle, including as late as the seventh decade. Sleepwalking is often preceded by confusional arousals. Childhood sleepwalking usually disappears spontaneously around puberty but may persist into adolescence. Episodes can occur sporadically or with high frequency, such as multiple times nightly for several consecutive nights. Sleepwalking may occur for the first time in adulthood or may recur in adulthood during periods of sleep deprivation or stress.

Sleep terrors usually emerge in children aged four to 12 years (but can also emerge in adulthood) and tend to resolve spontaneously by early adolescence, as does sleepwalking. Social embarrassment over the sleep terrors can impair social relationships in children and adults. Serious or even lethal injuries can occur.

Developmental Issues

As noted above, disorders of arousal most often occur initially in childhood and decrease in occurrence steadily until young adulthood. However, they may occur for the first time in adulthood or reappear after many asymptomatic years, often related to stress, sleep deprivation, or development of another sleep disorder.

Pathology and Pathophysiology

The overwhelming majority of individuals with disorders of arousal do not have neurological or psychological pathology. There are rare reported cases of confusional arousals associated with brain lesions in areas subserving arousal, such as the posterior hypothalamus, midbrain reticular area, and periventricular gray matter. However, data from a single patient with confusional arousals suggest that they may be due to a functional abnormality in the brain that leaves some regions, such as hippocampus and

frontal associative cortices, asleep, while other parts of the brain such as motor, cingulate, insular, amygdala, and temporopolar cortices, are active or awake.

It is generally considered that disorders of arousal represent a dissociation of different regions of the brain in addition to activation of locomotor centers/central pattern generators, accompanied by sleep inertia and sleep state instability.

Objective Findings

Although not routinely indicated for the evaluation of typical, uncomplicated, and noninjurious parasomnias, polysomnographic studies demonstrate that disorders of arousal typically begin after an arousal from slow wave sleep, most commonly toward the end of the first or second episode of slow wave sleep. Occasionally, disorders of arousal can emerge from stage N2 sleep. Heart rate acceleration, increased muscle tone, and muscle twitching may rarely be observed before a slow wave sleep arousal.

Diagnostic polysomnography may note high-amplitude hypersynchronous delta waves and frequent arousals from slow wave sleep. However, these findings have a low specificity and have been reported to occur in other disorders such as OSA and in asymptomatic individuals. On rare occasions, polysomnography can provide support for the clinical diagnosis by documenting arousals from slow wave sleep accompanied by behaviors typical of confusional arousals. Out-of-bed behaviors are very rare in the sleep laboratory. Changes between the home and sleep laboratory environment, timing, habits, and other factors may serve to decrease the likelihood of sleepwalking in the laboratory. Time-synchronized video-polysomnographic (vPSG) recording is essential if polysomnography (PSG) is to be used as support for the diagnosis. However, a normal PSG does not rule out the diagnosis of a disorder of arousal. In adults in whom there are only one or two episodes per year, there is a very low likelihood of occurrence in the sleep laboratory. However, the sleep study may assist in ruling out disorders with similar presentations, such as RBD or nocturnal epilepsy. PSG may further be useful by identifying potential triggers, such as sleep related breathing disorder or periodic leg movements that are currently present. Provocative sleep studies using sleep deprivation and acoustic stimuli have been used for research purposes, with success. However, the sensitivity and specificity of these techniques for clinical purposes are unknown.

Postarousal EEG recordings in children and adults with sleepwalking often demonstrate a partial or virtually complete persistence of sleep, with diffuse, rhythmic delta activity; diffuse delta and theta activity; mixed delta, theta, alpha, and beta activity; or at times alpha and beta activity.

PSG also may be helpful in excluding the diagnosis of RBD by demonstration of normal muscle atonia in REM sleep (assuming adequate amounts of REM sleep are observed). Although the "macrostructure" of sleep (i.e., the cycling of various NREM and REM sleep stages and the relative distributions of these sleep stages) is generally preserved with sleepwalking, the "microstructure" of sleep can be perturbed. Power spectral analyses of slow wave activity in adult sleepwalkers have revealed several forms of slow wave sleep dysregulation, including high amounts of slow wave sleep fragmentation (particularly during the first NREM-REM sleep cycle), a significant increase in delta power just prior to an arousal, and increased slow wave activity across all NREM sleep cycles.

Differential Diagnosis

Disorders of arousal should be carefully distinguished from other disorders with similar presentations, but different pathophysiologies, courses, and treatments. Other disorders to be considered include *RBD*, *sleep related epilepsy*, *sleep related dissociative disorders*, *alcohol and drug related behaviors*, and *OSA*.

RBD typically presents as dream-enacting behaviors during the second half of the night and usually affects middle-aged men, but also can affect women and virtually any age group. Because sleepwalking in adults can also present as dream-enacting behaviors that emerge during any time of the night, vPSG may be necessary to distinguish sleepwalking from RBD. In contrast to disorders of arousal, signs of RBD, particularly tonic/phasic EMG activity during REM sleep, are almost always present during sleep studies. If sleepwalking (or sleep terrors) occurs with RBD in the same patient, both should be diagnosed. This has been referred to as a parasomnia overlap disorder.

Other sleep disorders, such as *OSA*, can precipitate disorders of arousal. Therefore, a careful history must be obtained to identify other sleep disorders. *Sleep related epilepsy* can manifest with wandering behavior or with frenzied walking or running. In adults, a diagnosis of *malingering* also should be considered. If a neurologic or medical disorder is identified as the precipitant of a disorder of arousal, then the sleepwalking should be diagnosed as *parasomnia due to a medical disorder*.

Disorders of arousal should not be diagnosed in the presence of *alcohol intoxication*. The behavior of the alcohol-intoxicated individual may superficially resemble that of the sleepwalker. However, the sleepwalker is typically severely cognitively impaired, but with only limited motor impairment. The alcohol-intoxicated individual's level of cognitive functioning may be reduced, but not absent, whereas motor behavior is often severely impaired. In alcoholic blackouts, where anterograde amnesia is, by definition,

the cardinal manifestation, it is important to note that outward motor behavior and cognitive function may not be impaired and may be perceived as normal. Thus, the importance of appreciating the neuroscience of alcoholic blackouts and its potential role in the explanation of unusual and bizarre nocturnal behaviors cannot be understated because these can mimic parasomnias. The former are exponentially more prevalent and thus should be given appropriate weight when attributing likely causation in cases with criminal allegations.

Unresolved Issues and Further Directions

With the development of sophisticated genetic testing and neuroimaging, direct research into the causes and mechanisms of disorders or arousals is anticipated. Further investigations that aid in the characterization of the pathophysiology are necessary. Further development of sleep laboratory-based techniques for provoking episodes of sleepwalking would improve diagnostic accuracy.

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Sleep Related Eating Disorder

ICD-9-CM code: 327.40 ICD-10-CM code: G47.59

Alternate Names

Sleep eating

Diagnostic Criteria

Criteria A-D must be met

A. Recurrent episodes of dysfunctional eating that occur after an arousal during the main sleep period.
B. The presence of at least one of the following in association with the recurrent episodes of involuntary eating:
    1. Consumption of peculiar forms or combinations of food or inedible or toxic substances.
    2. Sleep related injurious or potentially injurious behaviors performed while in pursuit of food or while cooking food.
    3. Adverse health consequences from recurrent nocturnal eating.
C. There is partial or complete loss of conscious awareness during the eating episode, with subsequent impaired recall.
D. The disturbance is not better explained by another sleep disorder, mental disorder, medical disorder, medication, or substance use.

Essential Features

SRED consists of recurrent episodes of involuntary eating and drinking during arousals from sleep, associated with diminished levels of consciousness and subsequent recall, with problematic consequences.

The episodes of eating always occur in an involuntary or "out of control" manner after an interval of sleep. Typically, they occur during partial arousals from sleep with subsequent partial recall. On the one hand, some patients cannot be easily brought to full consciousness during an episode of eating, as is the case with sleepwalking, and may have no recall of having eaten during the night. On the other hand, some patients seemingly have considerable alertness during an episode and have substantial recall in the morning. There may be variability of awareness and subsequent recall within one night, and across the evolution of the disorder in individual patients. The recurrent episodes of involuntary eating and drinking during the main sleep period are typically associated with a feeling of lack of control over eating.

Problematic features of the recurrent sleep related eating include the following: consumption of peculiar forms or combinations of food, or of inedible or toxic substances (e.g., frozen pizzas, raw bacon, buttered cigarettes, cat food and salt sandwiches, coffee grounds, ammonia cleaning solutions); sleep related injury (e.g., lacerations from careless manipulation of kitchen utensils; internal or external burns from consuming or spilling hot foods or beverages; or poisoning and internal injuries from ingesting toxic substances); adverse health consequences (e.g., dental caries and tooth chipping from biting frozen foods); weight gain; obesity (including morbid obesity resulting in bariatric surgery); various metabolic problems, such as destabilization or precipitation of diabetes mellitus, hypertriglyceridemia, and hypercholesterolemia; nonrestorative sleep from sleep disruption; morning anorexia and abdominal distention. SRED carries the risk of consuming foods to which one is allergic. Also, overnight fasting prior to next-day surgery or testing can be compromised. Secondary depressive disorders may emerge from longstanding personal dejection and a sense of failure over the inability to control the nocturnal eating. Secondary food restriction, prompted by despair over not being able to stop the nocturnal eating, often occurs at some point during the course of the disorder. Patients may engage in potentially hazardous (and expensive) weight-loss regimens. Insomnia can also be a complication.

Associated Features

Nightly eating, including multiple episodes nightly, is reported by a majority of affected individuals. The episodes of eating occur during any time in the sleep cycle. High-caloric foods are typically preferred. The foods preferentially consumed during sleep related eating are not typically consumed with preference during the daytime. Paradoxically, to the extent that there is recall, hunger and thirst are notably absent during episodes of compulsive eating with SRED. The episodes of eating are sometimes experienced as food-related enactment of a dream. Simple foods or entire hot or cold meals may be prepared and consumed. Careless food handling often occurs. Alcoholic beverages are almost never consumed. The usual response to interference during an eating episode is irritability and agitation.

Clinical or Pathophysiological Subtypes

None known.

Demographics

The following rates of SRED, as determined by self-administered questionnaire, have been reported: 16.7% in an inpatient eating disorders group; 8.7% in an outpatient eating disorders group; and 4.6% in an unselected university student group. This study would indicate a high prevalence of SRED, although confirmatory studies across

different clinical and nonclinical population groups are needed. Females comprise 60% to 83% of patients in reported series. Mean age of onset of SRED is reported to be 22-39 years. In the reported series, the mean duration of SRED prior to clinical presentation ranged from four to 15 years, suggesting that SRED often is a chronic disorder.

Predisposing and Precipitating Factors

SRED can be idiopathic, but it appears to be most commonly associated with a primary sleep disorder, another clinical condition, or use of a sedative-hypnotic medication. Sleepwalking is the most common sleep disorder associated with sleep related eating, although once eating becomes part of the behavioral repertoire, it quickly becomes the predominant, if not the exclusive, nocturnal "sleepwalking" behavior. This would indicate that SRED is most often a "sleepwalking variant disorder." A history of sleepwalking during childhood appears to be a predisposing factor in many cases. A recent retrospective controlled study of SRED patients, sleepwalking patients, and controls found that SRED patients were mainly women with onset of the disturbance in adulthood. They typically experienced nightly episodes and had more frequent eating problems in childhood and higher current anorexia scores than sleepwalking patients or controls. They also shared commonalities with sleepwalking patients, including a high (66%) frequency of past or current sleepwalking, a similar timing of parasomnia episodes (in the first half of the night), and numerous arousals from stage N3. On video-polysomnography, eating episodes occurred mostly within one minute after awakening from stage N2 or N3. The frequencies of RLS, PLMs, and sleep apnea were similar across the three groups.

Other sleep disorders that can be closely associated with SRED include: RLS, PLMD, OSA, and circadian rhythm sleep-wake disorders, particularly irregular sleep/wake pattern. Multiple sleep disorders in the same patient have been reported with SRED, including sexsomnia and a variant of confusional arousals and sleepwalking. Medication-induced SRED has been reported with zolpidem, in particular, but also with a broad range of sedative hypnotics, including benzodiazepines, benzodiazepine receptor agonists, mirtazapine, risperidone, quetiapine, lithium carbonate, anticholinergics, and various other psychotropic agents. Onset of SRED also has been reported with cessation of cigarette smoking, cessation of alcohol and substance abuse, acute stress (usually involving major separation reactions), after daytime dieting, and with onset of narcolepsy, autoimmune hepatitis, encephalitis, and other conditions. SRED can also be associated with daytime eating disorders, and with nocturnal dissociative disorder. In a controlled study of 65 patients with narcolepsy-cataplexy, 32% of patients had SRED vs. 2% of controls. Nocturnal smoking was present in 33% of SRED-narcolepsy-cataplexy patients and in 16% of narcolepsy-cataplexy patients

without SRED. (A link between SRED and nocturnal smoking had previously been identified when nocturnal smoking was first reported in 2008). A study of 88 patients with RLS and 42 patients with insomnia who were systematically questioned for the presence of SRED or other nocturnal eating demonstrated that 36% of patients with RLS versus zero patients with insomnia had SRED, and the very significant difference was not related to arousal frequency. In that study, patients with RLS who were taking hypnotic medications were at additional risk for SRED.

Familial Pattern

A familial basis for SRED is not uncommon, including co-occurrence in fraternal twins, although detailed genetic studies have not been carried out.

Onset, Course, and Complications

The onset of SRED can be insidious and sporadic, or it can be precipitous and fulminant with rapid development of nightly episodes of eating, related or unrelated to the start of hypnotic medication therapy of insomnia. The course is usually unremitting. Fires can occur when the individual with SRED begins to cook foods on the stove or in the oven, and then abandons them. A variety of other complications have been described previously.

Developmental Issues

SRED can emerge in childhood, either associated or unassociated with a family history of SRED.

Pathology and Pathophysiology

The underlying pathophysiology of SRED is unclear. Despite the broad range of predisposing and precipitating factors in SRED, the relatively homogeneous set of clinical features suggests the presence of a "final common pathway" that can be accessed by a variety of factors. Although SRED has prominent features of both a sleep disorder and an eating disorder, its relatively homogeneous presentation supports its classification as a separate diagnostic entity. More than half of patients with SRED have a history of another parasomnia that preceded the onset of nocturnal eating, suggesting that the presence of another parasomnia is a major risk factor for SRED. However, the female predominance in SRED is more consistent with eating disorders, which are female predominant, than with sleepwalking or movement disorders (RLS/PLMD) which have slight to no female bias. Thus it appears that two basic drive states—sleeping and eating—are pathologically intertwined in SRED.

Objective Findings

Although not routinely indicated in the assessment of SRED, vPSG evaluations have often reported positive findings. The most common finding consists of multiple confusional arousals, with or without eating, arising from slow wave sleep. However, abnormal arousals have been documented from all stages of NREM sleep and also occasionally from REM sleep. The level of consciousness has typically spanned the range from virtual unconsciousness to various levels of partial consciousness despite a concurrent EEG pattern that is often predominantly awake, suggesting dissociation between the EEG and the level of consciousness. This dissociation also can be found in adult sleepwalking without associated eating. In contrast, classic sleepwalking in childhood is usually associated with the persistence of high-voltage delta waves or the admixture of delta, theta, and alpha activity. A predominant wake pattern is rare in childhood sleepwalking. PLMs and OSA may be observed in polysomnographic monitoring of SRED patients. In one recent study that addressed the boundaries between SRED and fully conscious abnormal nocturnal eating, 22 of 35 patients had PLMs, 5 of 35 had RLS, and 29 of 35 had recurring chewing and swallowing movements during sleep that were associated with nearly half of the total number of EEG arousals.

Differential Diagnosis

SRED must be distinguished primarily from *night eating syndrome (NES)*, which is characterized by excessive eating between dinner and bedtime and during full awakenings during the sleep period. In contrast to daytime eating disorders (*bulimia nervosa*, *anorexia nervosa*), inappropriate compensatory behavior, such as self-induced vomiting, enemas, misuse of laxatives, diuretics, or other medications, or other purging activity, are not present in SRED, although the two conditions may be comorbid. A person with a daytime eating disorder may also have a coexisting SRED that is associated with confusional arousals but not associated with purging behaviors during the night or upon arising in the morning. Patients with longstanding SRED and excessive weight gain may eventually fast during the daytime and/or engage in excessive exercise to prevent obesity from the SRED. Likewise, patients who otherwise fulfill criteria for SRED may consciously eat during the prebedtime period in a futile attempt to suppress the compulsion to eat after subsequently falling asleep.

SRED appears to be considerably more female predominant that NES (which has < 60% female prevalence), and mood disorders are more common with NES than with SRED. Nevertheless, SRED and NES share a considerable number of overlapping features and may exist along a common spectrum of pathophysiology. SRED should also be distinguished from nocturnal (sleep related) extensions of *bulimia nervosa*, *binge-eating disorder*, and *anorexia nervosa, binge/purge type*.

The *nocturnal eating (drinking) syndrome* described in the original International Classification of Sleep Disorders is primarily a disorder of infancy that is characterized by recurrent awakenings with the inability to resume sleep without eating or drinking. *Kleine-Levin syndrome* (periodic hypersomnia) can present with inappropriate nocturnal eating, but its predominance in adolescent males and its hallmark symptom complex of periodic hypersomnia, hypersexuality, and hyperphagia lasting days to weeks should easily distinguish it from SRED. Medical and neurologic disorders that could be associated with abnormal recurrent eating during the main sleep period (usually with full or almost full alertness) should also be excluded. These include: *hypoglycemic states*, *peptic ulcer disease*, *reflux esophagitis*, and *Kluver-Bucy syndrome*.

Unresolved Issues and Future Directions

The extent of overlap and divergence between SRED and NES needs to be further elucidated.

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REM-Related Parasomnias

REM Sleep Behavior Disorder

ICD-9-CM code: 327.42 ICD-10-CM code: G47.52

Alternate Names

None.

Diagnostic Criteria

Criteria A-D must be met

A. Repeated episodes of sleep related vocalization and/or complex motor behaviors.[1,2]

B. These behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep.

C. Polysomnographic recording demonstrates REM sleep without atonia (RWA)[3]

D. The disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use.

Notes

1. This criterion can be fulfilled by observation of repetitive episodes during a single night of video polysomnography.
2. The observed vocalizations or behaviors often correlate with simultaneously occurring dream mentation, leading to the frequent report of "acting out one's dreams."
3. As defined by the guidelines for scoring PSG features of RBD in the most recent version of the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events.
4. Upon awakening, the individual is typically awake, alert, coherent, and oriented.
5. On occasion, there may be patients with a typical clinical history of RBD with dream-enacting behaviors, who also exhibit typical RBD behaviors during vPSG, but do not demonstrate sufficient RWA, based on the current evidence-based data, to satisfy the PSG criteria for diagnosing RBD. In such patients, RBD may be provisionally diagnosed, based on clinical judgment. The same rule applies when vPSG is not readily available.

6. Medications may unmask latent RBD with preexisting RWA, according to current expert opinion. Therefore, medication-induced RBD can be diagnosed as RBD, using clinical judgment, pending future longitudinal studies.

Essential Features

RBD is characterized by abnormal behaviors emerging during REM sleep that may cause injury or sleep disruption. RBD is also associated with EMG abnormalities during REM sleep. The EMG demonstrates an excess of muscle tone during REM sleep, and/or an excess of phasic EMG twitch activity during REM sleep.

A complaint of sleep related injury is common with RBD, which usually manifests as an attempted enactment of unpleasant, action-filled, and violent dreams in which the individual is being confronted, attacked, or chased by unfamiliar people or animals. Typically, at the end of an episode, the individual awakens quickly, becomes rapidly alert, and reports a dream with a coherent story. The dream action corresponds closely to the observed sleep behaviors.

Sleep and dream-related behaviors reported by history and documented during vPSG include both violent and (less commonly) nonviolent behaviors: talking (including giving speeches), smiling, laughing, singing, whistling, shouting, swearing profanities, crying, chewing, gesturing, reaching, grabbing, arm flailing, clapping, slapping, punching, kicking, sitting up, leaping from bed, crawling, running, or dancing. Walking, however, is quite uncommon with RBD, and leaving the room is especially rare, because the eyes are usually closed, precluding attention to the environment. There can be rare occurrences of smoking a fictive cigarette, masturbation-like behavior, pelvic thrusting, and mimics of eating, drinking, urinating, and defecating. The eyes usually remain closed during an RBD episode, with the person attending to the dream action and not to the actual environment.

Medical attention is usually sought after sleep related injury has occurred to either the person or the bed partner, and rarely because of sleep disruption. Because RBD occurs during REM sleep, it usually appears at least 90 minutes after sleep onset, unless there is coexisting narcolepsy, in which case RBD can emerge shortly after sleep onset during a sleep onset rapid eye movement period (SOREMP). There is an acute form of RBD that emerges during intense REM sleep rebound states, such as during withdrawal from alcohol and sedative-hypnotic agents, or in association with certain medication use, drug intoxication, or relapsing multiple sclerosis.

Associated Features

PLMs during NREM sleep are very common with RBD and may disturb the sleep of the bed partner. Daytime tiredness or sleepiness is uncommon, unless narcolepsy is also present. There is typically no history of irritable, aggressive, or violent behavior during the day. There may be a longstanding prodromal history of sleep talking, yelling, limb twitching, and jerking during sleep that may or may not be dream related.

Clinical or Pathophysiological Subtypes

Parasomnia overlap disorder is a condition in which patients have both RBD and either a disorder of arousal, sleep related eating disorder, sexsomnia, or rhythmic movement disorder. This condition is male predominant, but less so than isolated RBD. Most cases begin during childhood or adolescence. Virtually all age groups can be affected. It can be idiopathic or symptomatic of a broad set of disorders, including narcolepsy, multiple sclerosis, brain tumor (and therapy), rhombencephalitis (right pontine tegmentum/medulla lesion), brain trauma, congenital Moebius syndrome, agrypnia excitata, Machado-Joseph disease, various psychiatric disorders and their pharmacotherapies, and substance abuse disorders and withdrawal states.

Status dissociatus can be classified as a subtype of RBD that manifests as an extreme form of state dissociation without identifiable sleep stages, but with sleep and dream-related behaviors that closely resemble RBD. Status dissociatus represents a major breakdown of the polysomnographic markers for REM sleep, NREM sleep, and wakefulness, with admixtures of these states being present, but with conventional sleep stages not being identifiable during polysomnographic monitoring. There is abnormal behavioral release that can be associated with disturbed dreaming, strongly suggestive of dream-enacting behaviors that closely resemble RBD. Not uncommonly, the individual thinks he is awake when observers presume he is asleep and attempting to act out a dream, or vice versa. An underlying neurologic or medical condition, spanning a broad range of pathology, is virtually always present.

Dream enactment ("oneirism") that is REM sleep related or related to a dissociated REM sleep-wakefulness state can be a core feature of a pathologic condition called agrypnia excitata that is characterized by generalized motor overactivity, impaired ability to initiate and maintain sleep (with "wakeful dreaming"), loss of slow wave sleep, and marked motor and autonomic sympathetic activation. Agrypnia excitata is found with such diverse conditions as delirium tremens, Morvan syndrome, and fatal familial insomnia. Thus, agrypnia excitata manifests as both a severe parasomnia and a severe insomnia.

Demographics

RBD is a male predominant disorder that usually emerges after age 50 years. Cases of RBD from early childhood up to age 88 years have been reported. RBD emerging in adults before age 50 years tends to have different demographics and associated features, including greater sex parity and increased rates of idiopathic RBD and parasomnia overlap disorder (POD), comorbid narcolepsy, antidepressant medication use, and possibly autoimmune diseases. In addition, the clinical presentation of RBD in younger adults differs from that in older adults in being less aggressive and violent, presumably due to greater female representation and higher rates of comorbid narcolepsy (which manifests with milder RBD behaviors).

RBD associated with neurologic disorders and other symptomatic forms of RBD are as male predominant as idiopathic RBD, with the exception of narcolepsy (as described below) and multiple system atrophy. Of note, RBD may not be the presenting complaint to a sleep disorders center. Therefore, systematic questioning for RBD should be included for all newly evaluated patients at a sleep center. RBD in children is virtually never idiopathic and is usually associated with narcolepsy (at times emerging months before the emergence of narcoleptic symptoms), brainstem tumors, antidepressant medications, neurodevelopmental disorders, and various rare conditions.

The prevalence is not known with much certainty, although a prevalence of 0.38% to 0.5% is reported in the elderly and the general population. A 2.1% prevalence of current sleep related violence has been reported; 38% of these events have associated dream enactment, suggesting a prevalence of RBD as high as 0.8%.

Predisposing and Precipitating Factors

The major predisposing factors are male sex, age 50 years or older, and an underlying neurological disorder, particularly Parkinson disease, multiple system atrophy, dementia with Lewy bodies, narcolepsy, or stroke. A recent multicenter case-control study of environmental risk factors of RBD found that smoking, head injury, pesticide exposure, and farming were significant risk factors. Medications, particularly the antidepressants venlafaxine, serotonin-specific reuptake inhibitors (SSRIs), mirtazapine, and other antidepressant agents (but not bupropion) are an increasingly recognized precipitating factor. Beta-blockers (bisoprolol, atenolol), anticholinesterase inhibitors, and selegiline can also trigger RBD. Psychiatric disorders involving depression (that require antidepressant pharmacotherapy) may comprise a predisposing factor, particularly in adults younger than 50 years. RBD may also be associated with posttraumatic stress disorder.

Familial Pattern

A recent multicenter controlled study revealed a significantly increased positive family history of dream enactment, raising the possibility of a genetic contribution to RBD.

Onset, Course, and Complications

Onset of chronic RBD can be gradual or rapid, and the course is often progressive. Complications include sleep related injuries to self and/or bed partner that at times are life threatening, and disruption of the bed partner's sleep that can be severe. Marital discord due to the RBD is uncommon but can be severe when present, due to repeated injury and/or disruption of the bed partner's sleep.

Delayed emergence of a neurodegenerative disorder, often more than a decade after the onset of idiopathic RBD, is very common in men 50 years of age and older. These disorders include Parkinson disease (PD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB). Two recently reported series found 81% and 82% eventual conversion rates from idiopathic RBD to parkinsonism/dementia (and also mild cognitive impairment in the latter study). Conversely, RBD is present in >90% of reported cases of MSA, in approximately 50% of reported cases of DLB, and in up to 46% of reported patients with PD.

Developmental Issues

As stated previously, RBD can emerge in children, usually in association with narcolepsy-cataplexy, brainstem tumors, or antidepressant medications.

Pathology and Pathophysiology

Current evidence suggests a selective association between RBD and *neurodegenerative disorders*. The synucleinopathies comprise a set of neurodegenerative disorders that share a common pathologic lesion composed of aggregates of insoluble α-synuclein protein in selectively vulnerable populations of neurons and glial cells. These pathologic aggregates appear to be closely linked to the onset and progression of clinical symptoms and the degeneration of affected brain regions in neurodegenerative disorders. The major synucleinopathies include PD, DLB, and MSA.

RBD can be strongly linked with *narcolepsy* (almost always narcolepsy type 1), representing another form of REM sleep motor-behavioral dyscontrol. The RBD may be precipitated or worsened by the pharmacologic treatment of cataplexy. RBD associated with narcolepsy is now considered to be a distinct phenotype of RBD, characterized by lack of sex predominance, less complex and more elementary movements in REM sleep, less violent behavior in REM sleep, earlier age of onset, and hypocretin

deficiency (that is characteristic of narcolepsy type 1). The presence of RBD in pediatric patients may be an initial manifestation of narcolepsy type 1.

Other reported etiologic associations of RBD with *neurologic disorders* include ischemic or hemorrhagic cerebrovascular disease, multiple sclerosis, progressive supranuclear palsy, Guillain-Barré syndrome, brainstem neoplasms (including cerebellopontine angle tumors), Machado-Joseph disease (spinocerebellar ataxia type 3), mitochondrial encephalomyopathy, normal pressure hydrocephalus, Tourette syndrome, group A xeroderma, and autism.

The pathophysiology of human RBD is presumed to correspond to the findings from an animal model of RBD with respect to interruption of the REM atonia pathway and/or disinhibition of brainstem motor pattern generators.

Objective Findings

Polysomnography demonstrates an excessive amount of sustained or intermittent loss of REM atonia and/or excessive phasic muscle twitch activity of the submental and/or limb EMGs during REM sleep. Some patients have almost exclusively arm and hand behaviors during REM sleep, indicating the need for both upper and lower extremity EMG monitoring in fully evaluating for RBD. Some patients preserve most of their REM atonia but have excessive EMG twitching during REM sleep. The most current evidence-based data for detecting RWA in the evaluation of RBD indicate that any (tonic/phasic) chin EMG activity combined with bilateral phasic activity of the flexor digitorum superficialis muscles in >27% of REM sleep (scored in 30-second epochs) reliably distinguishes RBD patients from controls. Autonomic nervous system activation (such as tachycardia) is uncommon during REM sleep motor activation in RBD, in contrast to the disorders of arousal. Approximately 75% of patients have PLMs during NREM sleep; a low percentage of these movements is associated with EEG signs of arousal. Increased percentages of slow wave sleep and increased delta power in RBD have been found in controlled and uncontrolled studies, but this can be a highly variable finding in RBD, depending on the clinical population. Sleep architecture and the customary cycling among REM and NREM sleep stages are usually preserved in RBD, although some patients show a shift toward N1 sleep.

Validated RBD screening questionnaires that can assist in the process of diagnosing RBD are currently available.

Differential Diagnosis

RBD is one of several disorders that can manifest as complex, injurious, and violent sleep related and dream-related behaviors in adults. Other disorders that can mimic RBD in adults and/or children include *sleepwalking*, *sleep terrors*, *OSA*, *nocturnal seizures (nocturnal frontal lobe epilepsy; nocturnal complex partial seizures)*; *rhythmic movement disorders*; *sleep related dissociative disorders*, *frightening hypnopompic hallucinations*, and *posttraumatic stress disorder*; a diagnosis of *malingering* also should be considered.

In general, RBD involves attempted enactment of unpleasant, aggressive dreams that usually occurs two or more hours after sleep onset, with rapid awakening from an episode. In contrast, sleepwalking and sleep terror episodes often emerge within two hours after sleep onset, are not usually associated with rapid alertness, and are rarely associated with dreaming in children. Adults can have dreams associated with disorders of arousal, but they are usually more fragmentary and limited than RBD dreams. Sleep related seizures usually present with repetitive, stereotypical behaviors.

Parasomnia overlap disorder can be distinguished from status dissociatus in several ways: if there is an awakening after an episode of RBD, sleepwalking, or sleep terror, there is the realization of having just been asleep; status dissociatus, however, is more likely to manifest with confusion over whether one is asleep, awake, or dreaming. vPSG in overlap conditions shows the typical findings for both RBD and disorders of arousal, whereas with status dissociatus, there is an inability to discern sleep stages. Also, patients with status dissociatus do not walk far during an episode, and their behavioral repertoire more closely resembles that of RBD than that of the disorders of arousal.

Unresolved Issues and Future Directions

Numerous questions related to the vPSG evaluation of RBD remain unresolved. These include issues of defining and quantifying RWA and RBD activity such as: (1) What is the minimum REM sleep percentage of total sleep time (and minimum absolute REM sleep time) needed to diagnose RWA or rule out RWA? (2) What is the minimum number of REM sleep epochs and minimum duration of REM sleep epochs necessary to diagnose RWA or rule out RWA? (3) What guidelines can be developed for diagnosing or ruling out RWA in the setting of disrupted REM sleep continuity associated with conditions such as obstructive sleep apnea and with medications? (4) What are the minimal amounts of true RBD behaviors documented by vPSG needed to identify RBD in patients without sufficient RWA?

It is unclear why there is a male predominance of this disorder in middle-aged and older adults. It is unknown if RBD subgroups other than men age 50 years or older demonstrate increased risk for development of parkinsonism or dementia. One such subgroup comprises patients with antidepressant-triggered RBD for whom the potential risk for future parkinsonism and dementia is unclear. New antidepressant or other psychotropic agents being developed for clinical use should be assessed for their immediate and long-term effects on REM atonia, REM phasic activity, REM sleep behavioral release, and proclivity to precipitate dream-enacting behaviors.

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Recurrent Isolated Sleep Paralysis

ICD-9-CM code: 327.43 ICD-10-CM code: G47.53

Alternate Names

Hypnagogic and hypnopompic paralysis, predormital and postdormital paralysis, kanashibari (Japan).

Diagnostic Criteria

Criteria A-D must be met

A. A recurrent inability to move the trunk and all of the limbs at sleep onset or upon awakening from sleep.
B. Each episode lasts seconds to a few minutes.
C. The episodes cause clinically significant distress including bedtime anxiety or fear of sleep.
D. The disturbance is not better explained by another sleep disorder (especially narcolepsy), mental disorder, medical condition, medication, or substance use.

Essential Features

Recurrent isolated sleep paralysis is characterized by an inability to perform voluntary movements at sleep onset (hypnagogic or predormital form) or on waking from sleep (hypnopompic or postdormital form) in the absence of a diagnosis of narcolepsy. The event consists of an inability to speak or to move the limbs, trunk, and head. Respiration is usually unaffected. Consciousness is preserved, and full recall is present. An episode of sleep paralysis lasts seconds to minutes. It usually resolves spontaneously but can be aborted by sensory stimulation, such as being touched or spoken to, or by the patient making intense efforts to move.

Associated Features

At least during the initial episodes, intense anxiety is usually present. Hallucinatory experiences accompany the paralysis in about 25% to 75% of patients. These may include auditory, visual, or tactile hallucinations, or the sense of a presence in the room. Some patients experience predormital or postdormital hallucinations at separate times from episodes of sleep paralysis.

Clinical or Pathophysiological Subtypes

A familial form of sleep paralysis has been described (see below).

Demographics

Estimates of the prevalence of sleep paralysis vary widely due to differences in the definition used, the age of the population sampled, and possibly cultural and ethnic factors. Most prevalence studies of sleep paralysis (usually of students younger than 30 years) have investigated the occurrence of one or more episodes without requirement of recurrence or distress. These suggest a 15% to 40% prevalence of at least one episode of sleep paralysis. Two notable exceptions are a 1962 study of mostly college students that reported a prevalence of 5%, and a 1999 study of all adult ages that found a prevalence of 6%. No consistent sex differences have emerged from multiple studies. The mean age of onset is 14 to 17 years, although onset earlier and later in life has been reported.

Predisposing and Precipitating Factors

Sleep deprivation and irregular sleep-wake schedules have been identified as predisposing factors to episodes of sleep paralysis. Mental stress has been reported as a precipitating factor in some but not other studies. Sleep paralysis appears to be more common with sleep in the supine position. Personality factors have not been shown to play a major role, although one study found a higher score on the paranoia scale of the Minnesota Multiphasic Personality Inventory in patients with sleep paralysis compared to controls. Other factors that have been noted on regression analysis include an association with bipolar disorder, the use of anxiolytic medication, and sleep related leg cramps.

Familial Pattern

Two families with apparent familial sleep paralysis occurring over three and four generations have been reported. A maternal form of transmission has been postulated.

Onset, Course, and Complications

Onset is usually in adolescence. Most events appear to occur in the second and third decades, but may continue later in life. There are no known complications, apart from anxiety over the episodes.

Developmental Issues

Though sleep paralysis may be present as part of the narcolepsy tetrad in children, there is no information currently available about childhood presentation of recurrent isolated sleep paralysis.

Pathology and Pathophysiology

Episodes of sleep paralysis elicited by awakening patients from nocturnal sleep appear to arise from REM sleep. Sleep paralysis is an example of state dissociation with elements of REM sleep persisting into wakefulness. Early-onset REM sleep after forced awakenings has been shown to predispose an individual to having sleep paralysis. It may be that subjects with less tolerance to sleep disruption are more likely to experience the phenomenon.

Objective Findings

Analysis of sleep paralysis after forced awakenings during PSG studies reveals the event to be a dissociated state with the persistence of REM-related electromyographic atonia into conscious wakefulness. Hallucinatory experiences may be present but are not essential for the diagnosis.

Differential Diagnosis

Cataplexy produces similar generalized paralysis of skeletal muscles but occurs during wakefulness and is precipitated by emotion. *Atonic seizures* occur during wakefulness. *Nocturnal panic attacks* are not usually associated with paralysis. *Familial periodic paralysis syndromes*, especially *hypokalemic periodic paralysis*, may occur at rest and on awakening. However, the episodes usually last hours, may be associated with carbohydrate intake, and are usually accompanied by hypokalemia. There are also *hyperkalemic and normokalemic periodic paralysis syndromes*.

Unresolved Issues and Further Directions

Not applicable or known.

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Nightmare Disorder

ICD-9-CM code: 307.47 ICD-10-CM code: F51.5

Alternate Names

Nightmares, REM nightmares, recurrent nightmares, dream anxiety disorder, anxiety dreams.

Diagnostic Criteria

Criteria A-C must be met

A. Repeated occurrences of extended, extremely dysphoric, and well-remembered dreams that usually involve threats to survival, security, or physical integrity.
B. On awakening from the dysphoric dreams, the person rapidly becomes oriented and alert.
C. The dream experience, or the sleep disturbance produced by awakening from it, causes clinically significant distress or impairment in social, occupational, or other important areas of functioning as indicated by the report of at least one of the following:
    1. Mood disturbance (e.g., persistence of nightmare affect, anxiety, dysphoria).
    2. Sleep resistance (e.g., bedtime anxiety, fear of sleep/subsequent nightmares).
    3. Cognitive impairments (e.g., intrusive nightmare imagery, impaired concentration, or memory).
    4. Negative impact on caregiver or family functioning (e.g., nighttime disruption).
    5. Behavioral problems (e.g., bedtime avoidance, fear of the dark).
    6. Daytime sleepiness.
    7. Fatigue or low energy.
    8. Impaired occupational or educational function.
    9. Impaired interpersonal/social function

Notes

1. Nightmare disorder in children is most likely to occur in those exposed to severe psychosocial stressors. Because childhood nightmares often resolve spontaneously, the diagnosis should be given only if there is persistent distress or impairment.

Essential Features

Nightmare disorder is characterized by recurrent, highly dysphoric dreams, which are disturbing mental experiences that generally occur during REM sleep and that often result in awakening. Given that these experiences are most often associated with REM sleep, the episodes have a greater tendency to occur during the second half of the major sleep episode when the REM pressure is most pronounced. Nightmares involve an internally generated conscious experience or dream sequence that seems vivid and real. They have a tendency to become increasingly more disturbing as they unfold. Emotions are characteristically negative and most frequently involve anxiety, fear, or terror but may also involve anger, rage, embarrassment, and disgust. Nightmare content most often focuses on imminent physical danger to the individual but may also involve other distressing themes. Ability to detail the nightmare's contents upon awakening is common in nightmare disorder. Multiple nightmares within a single sleep episode may occur and may bear similar themes. Because nightmares typically arise during REM sleep, they may occur at any moment that REM pressure is high.

Nightmares are very common in children. They typically occur in the last third of the night and result in a complete awakening, after which the child can often provide a detailed description of the frightening scenario. However, clear distinction from confusional arousals and sleep terrors in young children is often not possible.

Associated Features

Postawakening anxiety and difficulty returning to sleep may be present. Nightmares are more common in those with higher levels of anxiety. Additionally, nightmares are commonly seen in those who have been physically or sexually abused and in those suffering from posttraumatic stress disorder.

Nightmares arising either immediately following a trauma (acute stress disorder [ASD]) or one month or more after a trauma (posttraumatic stress disorder [PTSD]) have been described during NREM sleep, especially N2, as well as during REM sleep and at sleep onset. Posttraumatic nightmares may take the form of a realistic reliving of a traumatic event or may depict only some of its elements or emotional content.

Clinical or Pathophysiological Subtypes

None known.

Demographics

Occasional nightmares are very common in children, occurring in 60% to 75% of children, beginning as young as 2.5 years of age. The occurrence of occasional nightmares

in children does not constitute a nightmare disorder. However, frequent nightmares are uncommon, occurring in 1% to 5% of preadolescent children. It is estimated that 10% to 50% of children aged three to five years have at least occasional nightmares severe enough to disturb their parents. Nightmares appear to be a trait-like characteristic that persists over time during childhood. The best predictor of recurrent nightmares at an older age is recurrent nightmares in childhood. Approximately 2% to 8% of the general population has a current problem with nightmares, and this frequency is higher in clinical populations. Trauma-related nightmares are the most consistent problem reported by patients with PTSD. Nightmares beginning within three months of a trauma are present in up to 80% of patients with PTSD. Although approximately 50% of PTSD cases resolve within three months, posttraumatic nightmares may persist throughout life.

Predisposing and Precipitating Factors

Frequent nightmares are associated with enduring personality characteristics and psychopathologies; they are inversely correlated with measures of well-being. Associations with psychopathology have been identified for adults and adolescents, but research on children is largely absent other than for assessments of PTSD. Measures of nightmare distress are much more robustly associated with psychopathology than are measures of nightmare frequency.

The clinical use of pharmacologic agents affecting the neurotransmitters norepinephrine, serotonin, and dopamine is associated with the complaint of nightmares. A majority of these agents are antidepressants, antihypertensives, and dopamine-receptor agonists. Agents affecting the neurotransmitters gamma-aminobutyric acid (GABA), acetylcholine, and histamine, and the withdrawal of REM sleep suppressive agents also can be associated with the complaint of nightmares. Of note, nightmares are a common reaction in varenicline, which is an agent that blocks α-4-β-2 nicotinic acetylcholine receptors.

Familial Pattern

Twin-based studies have identified persistent genetic predisposition to nightmares in childhood (reported retrospectively by adults) and adulthood as well as genetic influences on the co-occurrence of nightmares and some other parasomnias, such as sleep talking (somniloquy).

Onset, Course, and Complications

Nightmares usually start between ages three years and six years. The proportion of children reporting nightmares reaches a peak between six and ten years of age and decreases thereafter. A subgroup of children continue to have nightmares into

adolescence or adulthood and may become lifelong nightmare sufferers. Nightmares generally diminish in frequency and intensity over the course of decades, but some patients still describe frequent episodes at the age of 60 or 70 years. Nightmare disorder can lead to sleep avoidance and deprivation, and thereby to more intense nightmares, which can produce insomnia.

ASD and PTSD associated nightmares can develop at any age after physical or emotional trauma. Individuals with PTSD are at risk for developing mood disorders and depression, social and employment consequences, self-destructive and impulsive behavior, and substance abuse; it is not known to what extent the nightmares symptomatic of PTSD contribute to these complications.

Developmental Issues

As stated above, nightmares are very common in children but the occurrence of occasional nightmares does not constitute nightmare disorder. Population studies have revealed that the prevalence and frequency of nightmares increases through childhood into adolescence. For example, preschoolers seldom report "bad dreams." Furthermore, in regard to the prevalence of nightmares, children appear to exhibit a sex divergence over time, with girls demonstrating higher prevalence by late adolescence.

Pathology and Pathophysiology

Not applicable or known.

Objective Findings

PSG recordings during actual nightmares are few in number and, in some instances, have shown abrupt awakenings from REM sleep preceded by accelerated heart and respiratory rates. Highly disturbing dream content frequently contrasts strikingly with relatively minor autonomic changes. Distinctive anomalies in nightly sleep architecture have not been demonstrated; brainstem and auditory-evoked potentials appear normal. Recordings during posttraumatic nightmares are few but have been recorded from both REM and NREM sleep. PSG recordings of sleep in patients with PTSD have provided widely variable results.

PSG evaluation is not routinely performed but may be indicated in some circumstances to exclude other parasomnias such as disorders of arousal and sleep-associated seizures. A PSG is particularly appropriate if patients report nightmares in conjunction with sleep behaviors that are repetitive or stereotyped or are injurious to self or others.

Differential Diagnosis

Nightmare disorder must be distinguished from dream disturbances associated with certain other neurological and sleep disorders. Rare cases of *seizures* presenting only as "nightmares" have been reported and should be considered in the differential diagnosis, particularly in those patients who present with a history of central nervous system disease. PSG or continuous video EEG may be necessary to identify nightmares associated with nocturnal seizures. Nightmares differ from *sleep terrors* in having detailed recollection of dreaming in contrast to fragments of dreams or no dream recall, presenting no or minimal overt movement or autonomic activity, occurring late in the night, being followed by rapid awakening and difficulty returning to sleep, and most often arising from REM sleep. *RBD* occurs more often in late middle-aged men and is more often associated with violent explosive movements and a history of nocturnal injuries. The dream disturbance of RBD usually involves being threatened or attacked by unfamiliar people or animals and is controlled in tandem with the sleep behavioral disturbance by appropriate medication. Nightmares occur at any age and are not typically associated with movements, overt behaviors, or injuries. Anxiety may accompany episodes of *sleep paralysis* occurring either at sleep onset (hypnagogic) or offset (hypnopompic), when the individual feels conscious but unable to move, speak, and, at times, breathe properly. Anxiety may be further worsened if disturbing *hypnagogic hallucinations* or dream sequences accompany the paralysis. Nightmares, although they may involve some degree of movement inhibition or some degree of apparent wakefulness, are usually not accompanied by feelings of either total paralysis or complete waking consciousness.

Patients with *narcolepsy* often report nightmares; these may occur at sleep onset. However, narcolepsy and nightmare disorder are clearly distinguishable by other clinical symptoms. *Nocturnal panic attacks* occur either during or immediately after nocturnal awakenings from NREM sleep, usually in the first four hours of the sleep episode. Although frequency of panic attacks is correlated with frequency of nightmares and many patients report that dysphoric dreams precede their attacks, there may be no dream recall reported on awakening with a panic attack.

Sleep related dissociative disorders comprise a sleep related variant of the dissociative disorders as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V). These include dissociative identity disorder (formerly called multiple personality disorder) and dissociative fugue, in which individuals meeting waking criteria for these diagnoses may at times experience the recall of actual physical or emotional trauma as a "dream" during periods of EEG-documented nocturnal waking.

Nightmares that occur intermittently during the course of *ASD* or *PTSD* are an expected symptom of those mental disorders and do not always require independent coding as nightmare disorder. However, as is often the case, when the frequency and/or severity of posttraumatic nightmares is such that they require independent clinical attention, then a diagnosis of nightmare disorder should be applied. In some cases, other symptoms of PTSD may have largely resolved while the nightmares persist. Nightmare disorder should be coded in these cases as well. It is clinically important to establish whether nightmares are associated with PTSD or ASD because the evaluation, course, complications, and treatment differ significantly for these groups.

Unresolved Issues and Further Directions

Basic pathophysiologic studies are still needed, especially studies contrasting "idiopathic" nightmare disorder and nightmares associated with PTSD. In particular, determining whether posttraumatic nightmares arise from sleep or primarily from wakefulness would be an important distinguishing feature particularly when determining effective clinical interventions. The PSG correlates of nightmare disorder and posttraumatic nightmares as well as the variables affecting dream mentation and recall require further definition and delineation.

The distinction between nightmares and sleep terrors is difficult when assessed only by questionnaires. It still remains unclear to what degree and level of complexity sleep mentation is associated with sleep terrors. The topic of NREM sleep dream disturbances (other than disturbed mentation that may occur with sleep terrors) also needs formal investigation, including whether or not the term NREM sleep nightmare should be utilized.

The optimal methods for assessing nightmare frequency and nightmare distress are still unclear. Standardized scales assessing nightmare distress should be developed and utilized. Retrospective questionnaire-based evaluations of nightmares are problematic inasmuch as they underestimate nightmare frequencies relative to home logs, whereas home logs may selectively increase recall of nightmares.

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Other Parasomnias

Exploding Head Syndrome

ICD-9-CM code: 327.49 ICD-10-CM code: G47.59

Alternate Names

Sensory sleep starts, sensory sleep shocks.

Diagnostic Criteria

Criteria A-C must be met

A. There is a complaint of a sudden loud noise or sense of explosion in the head either at the wake-sleep transition or upon waking during the night.
B. The individual experiences abrupt arousal following the event, often with a sense of fright.
C. The experience is not associated with significant complaints of pain.

Essential Features

Exploding head syndrome is characterized by a sudden, loud imagined noise or sense of a violent explosion in the head occurring as the patient is falling asleep or waking during the night.

The event is variously described as a painless loud bang, an explosion, a clash of cymbals, or a bomb exploding, but occasionally may be a less alarming sound. It is usually associated with a sense of fright, and many patients believe they are having a stroke. In a minority of cases a flash of light or myoclonic jerk may accompany the event. The abnormal sensation lasts a few seconds and may recur during further attempts at sleeping. The number of attacks varies—from many on a single night to infrequent—with some patients reporting clustering of attacks over several nights followed by a gap of weeks to months. A high level of clinical distress can be associated with recurrent attacks, with concern about their underlying cause.

Associated Features

A flash of light may accompany the sound, and a myoclonic jerk may sometimes occur. Although the event is typically painless, a simultaneous stab of pain in the head has occasionally been reported. An insomnia complaint may develop as a result of the recurring arousals and anxiety regarding the events.

Clinical or Pathophysiological Subtypes

None known.

Demographics

The prevalence is unknown. Exploding head syndrome is reported to be more common in women than in men. The median age of onset is 58 years, but onset at all ages has been reported, including the first and eighth decades.

Predisposing and Precipitating Factors

Most patients do not detect precipitating factors, but some report increased numbers of attacks when under personal stress or overtired.

Familial Pattern

Occasional cases of exploding head syndrome occurring in the same family have been reported, although it is not clear whether this represents a true familial pattern.

Onset, Course, and Complication

The course is benign with no reported neurologic sequelae. Frequent events on a single night can result in insomnia. Clinical levels of anxiety may result from patient concern about a serious medical basis for the exploding head syndrome. The condition may also exacerbate a comorbid migraine disorder. In many patients, the symptoms appear to remit spontaneously over some years.

Developmental Issues

Not known or applicable.

Pathology and Pathophysiology

The events occur most frequently during a period of drowsiness preceding sleep. Some events are reported to occur upon waking during the night, but may actually be occurring during reinitiating sleep. The condition appears to be a sensory variant of the better-known transient motor phenomenon of sleep starts or hypnic jerks occurring at wake-sleep transition. The neurophysiologic mechanisms underlying these hypnagogic phenomena are unknown.

Objective Findings

VPSG in a small sample of patients found that events arose from early drowsiness with predominant alpha rhythm interspersed with some theta activity. In one patient, events arose during transition from N1 sleep, in another patient from N1 sleep to wakefulness, and in a third patient from N2 sleep to wakefulness. Events occurring in the N1/

N2 to wake transition have been recorded during both nocturnal vPSG and MSLTs. Slow eye movements were present in the only tracing reproduced in the report of a patient with exploding head syndrome emerging during wake to N1 sleep transition. Arousals occurred immediately following the episodes. No epileptiform discharges accompany the event.

Differential Diagnosis

Exploding head syndrome should be distinguished from *sudden onset-headache syndromes*. *"Idiopathic stabbing headache" (ice-pick headache)* is a benign syndrome of brief stabs of pain on the side of the head. Although they can occur at sleep onset, they are more common during wakefulness. *"Thunderclap headache"* is a very severe sudden onset headache characteristic of subarachnoid hemorrhage but also resulting from other causes and occasionally occurring as a benign symptom. It does not usually occur at sleep onset. *"Hypnic headache syndrome"* affects older people who regularly awaken 4-6 hours after sleep onset, with a diffuse headache that lasts 30-60 minutes and is often associated with nausea but no autonomic symptoms. Other conditions to be considered include *sleep related migraines*, *cluster headaches*, and *nocturnal paroxysmal hemicrania*. In contrast to headache syndromes, exploding head syndrome is usually painless. *Simple partial seizures* can present with sensory phenomena but do not usually occur predominantly at sleep onset. *Nocturnal panic attacks* can waken a person from sleep, but are not usually associated with a sense of noise or explosion. *Recurrent nightmares* are characterized by recall of more complex and longer-lasting visual imagery. *Sleep starts* occur at wake-sleep transition but are predominantly a motor phenomenon with sudden myoclonic jerks rather than an emphasis on sensory symptoms.

Unresolved Issues and Future Directions

The neurophysiologic basis of these events requires further study.

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Sleep Related Hallucinations

ICD-9-CM code: 368.16 ICD-10-CM code: H53.16

Alternate Names

Hypnagogic hallucinations, hypnopompic hallucinations, complex nocturnal visual hallucinations.

Diagnostic Criteria

Criteria A-C must be met

A. There is a complaint of recurrent hallucinations that are experienced just prior to sleep onset or upon awakening during the night or in the morning.
B. The hallucinations are predominantly visual.
C. The disturbance is not better explained by another sleep disorder (especially narcolepsy), mental disorder, medical disorder, medication, or substance use.

Essential Features

Sleep related hallucinations are hallucinatory experiences that occur at sleep onset or on awakening from sleep. Sleep related hallucinations are predominantly visual but may include auditory, tactile, or kinetic phenomena. Hallucinations at sleep onset (hypnagogic hallucinations) may be difficult to differentiate from sleep onset dreaming. Hallucinations on waking in the morning (hypnopompic hallucinations) may arise out of a period of REM sleep, and patients also may be uncertain whether they represent waking or dream-related experiences. Complex nocturnal visual hallucinations may represent a distinct form of sleep related hallucinations. They typically occur following a sudden awakening, without recall of a preceding dream. They usually take the form of complex, vivid, relatively immobile images of people or animals, sometimes distorted in shape or size. These hallucinations may remain present for many minutes but usually disappear if ambient illumination is increased. Patients are clearly awake but often initially perceive the hallucinations as real and frightening.

Associated Features

Sleep related hallucinations may be associated with episodes of sleep paralysis, either at the same time or on different nights. Patients with complex nocturnal visual hallucinations may jump out of the bed in terror, sometimes injuring themselves. Some patients may experience other parasomnias, such as sleep talking or sleepwalking, separate from the hallucinations; some patients may also experience similar complex hallucinations during the day, unassociated with sleep.

Clinical and Pathophysiological Subtypes

Dream-like hypnagogic and hypnopompic hallucinations appear to differ in clinical features and pathogenesis from complex nocturnal visual hallucinations arising in wakefulness after sudden arousals during the night. Sleep related hallucinations are common in narcolepsy and also occur as occasional phenomena in a high percentage of the general population. In contrast, complex nocturnal visual hallucinations appear to be rare and occur in the setting of a range of neurologic and visual disorders (see Differential Diagnosis) as well as in an idiopathic form. However, further work is needed to establish whether or not these forms of hallucinations represent different entities.

Demographics

In large European population studies, sleep related hallucinations have been reported to occur with a prevalence of 25% to 37% for hypnagogic hallucinations, whereas the equivalent reported prevalence for hypnopompic hallucinations is 7% to 13%. Both hypnagogic and hypnopompic hallucinations are more common in younger persons and occur slightly more frequently in women than in men.

Predisposing and Precipitating Factors

Multivariate analyses in large population studies have suggested that sleep related hallucinations are associated with younger age, current drug use, past alcohol use, anxiety, mood disorder, sleep onset insomnia, and perceived insufficient sleep.

Familial Pattern

Not applicable or known.

Onset, Course, and Complications

Sleep related hallucinations appear to be more common in adolescence and early adulthood. In many patients, the frequency appears to decrease with age. The natural history of complex nocturnal visual hallucinations depends on the underlying cause.

Developmental Issues

Not known or applicable.

Pathology and Pathophysiology

It is presumed that most sleep related hallucinations are due to dream ideation of REM sleep intruding into wakefulness, but this has not been firmly established. Infrequent hallucinations of this type may be within the limits of normal sleep-wake transition. Complex nocturnal visual hallucinations may in some cases be release phenomena in

which loss of visual input or decreased reticular activating system activity results in the visual cortex generating aberrant images.

Objective Findings

Hypnagogic hallucinations appear to arise predominantly from sleep onset REM periods. However, the very few reports of polysomnography in complex nocturnal visual hallucinations suggest an onset from NREM sleep. MRI scans of the brain, PSG, EEG, and neuropsychological testing may help in the differential diagnosis and in identifying underlying disorders.

Differential Diagnosis

Nightmares are frightening dreams awakening the patient from sleep. They are clearly recognized as dreams and do not persist into wakefulness. *Exploding head syndrome* consists of a sudden sensation of an explosion in the head, usually at sleep onset and sometimes accompanied by a noise or flash of light. It does not involve complex visual imagery and lasts only seconds. In *RBD*, the patient acts out dreams during REM sleep. If not awakened by an observer, the person usually has little recollection of dream content. *Sleepwalking* may occasionally be associated with dream ideation, but the patient recognizes that the dream occurred during sleep. Visual hallucinations can be due to *epileptic seizures* but are usually brief, stereotyped, and fragmentary in such cases. Occasionally, complex visual hallucinations may be associated with *migraine* but are usually followed by a headache.

Complex nocturnal visual hallucinations may be seen in patients with *narcolepsy*, *PD*, *DLB*, *visual loss (Charles Bonnet hallucinations)*, and *midbrain and diencephalic pathology (peduncular hallucinosis)*, as well as with the use of β-adrenergic receptor-blocking medications. *Anxiety disorders* have been noted in some patients.

Unresolved Issues and Further Directions

In contrast to the extensive study of sleep paralysis, little work has been reported on sleep related hallucinations. It is uncertain whether they represent normal variants or pathologic entities. It is unclear whether they are always associated with REM sleep intruding into wakefulness. It is uncertain how frequently complex nocturnal visual hallucinations are an independent entity, as opposed to representing a final common pathway of a range of other disorders. Further work is needed to determine from which stages of sleep they arise.

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Sleep Enuresis

ICD-9-CM code: 788.36 ICD-10-CM code: N39.44

Alternate Names

Enuresis nocturna; nocturnal bedwetting; primary, familial, functional, idiopathic, monosymptomatic, or essential enuresis; night wetting; sleep related enuresis.

Diagnostic Criteria

Primary Sleep Enuresis – Criteria A-D must be met

A. The patient is older than five years.
B. The patient exhibits recurrent involuntary voiding during sleep, occurring at least twice a week.
C. The condition has been present for at least three months.
D. The patient has never been consistently dry during sleep.

Secondary Sleep Enuresis – Criteria A-D must be met

A. The patient is older than five years.
B. The patient exhibits recurrent involuntary voiding during sleep, occurring at least twice a week.
C. The condition has been present for at least three months.
D. The patient has previously been consistently dry during sleep for at least six months.

Essential Features

Sleep enuresis (SE) is characterized by recurrent involuntary voiding that occurs during sleep. In primary SE, recurrent involuntary voiding occurs at least twice a week during sleep after five years of age in a patient who has never been consistently dry during sleep for six consecutive months. SE is considered secondary in a child or adult who had previously been dry for six consecutive months and then began wetting at least twice a week. Both primary and secondary enuresis must be present for a period of at least three months. Though primary and secondary enuresis share the common symptom of voiding during sleep, they are understood as distinct phenomena with different etiologies.

SE is associated with difficulty arousing from sleep in response to an urge to urinate and may occur during any sleep stage. Sleep disorders that fragment sleep such as sleep apnea are associated with SE, and treatment of these disorders may cure or reduce their incidence.

Associated Features

Involuntary voiding during wakefulness may be associated with SE and, if present, generally points toward a physiological etiology. Psychosocial problems are considered a relatively rare cause in primary SE, though it does occur more commonly in children with attention deficit hyperactivity disorder and in children living in disorganized families. Secondary SE is seen more commonly in children who have recently experienced a significant psychosocial stress, such as parental divorce, physical or sexual abuse, or neglect. Chronic constipation and encopresis (fecal soiling) often occur in children with secondary SE.

SE can occur in association with diabetes and urinary tract infection. It may occur in individuals with nocturnal epilepsy. Among older adults, SE may be associated with symptoms of congestive heart failure, OSA, depression, and dementia.

SRBD is reported in 8% to 47% of children with enuresis, compared to an overall prevalence of 1% to 2%. PLMS have been reported in patients with refractory SE. A large epidemiology study of children aged 6-10 years found that a current complaint of SE was significantly associated with increased ORs (2.7-3.4) for subjectively high arousal threshold, night terrors, nocturia, and confusion when awakened from sleep. Other studies have found mouth breathing, nasal congestion, snoring, and restless sleep to be highly related to enuresis in children.

Clinical and Pathophysiological Subtypes

The most important distinction is between primary and secondary SE.

Demographics

SE occurs in 15% to 20% of 5-year-olds. It is three times more common in boys than in girls. SE is reported by 2.1% of community-dwelling older adults and is more common among women than men.

Predisposing and Precipitating Factors

The etiology of SE is complex. The factors that precipitate SE on a particular night and at a particular time remain unknown. One popular model hypothesizes that SE consists of three interrelated factors: large nocturnal urine volume production, nocturnal bladder overactivity, and difficulty arousing from sleep. Several studies suggest difficulty arousing from sleep is most important in primary enuresis, whereas bladder instability/overactivity is more important in secondary enuresis.

Children with enuresis are often described by their families as "deep sleepers" and very difficult to arouse. A high arousal threshold has been objectively confirmed in these children.

It has been reported that fragmentation of sleep by disorders such as sleep apnea is highly correlated with SE. Sleep fragmenting disorders such as sleep apnea and PLMS have been previously reported to be proximal triggers for the occurrence of disorders of arousal—sleepwalking, confusional arousals, and night terrors. Successful treatment of sleep apnea in these disorders has been reported to result in reduction or elimination of disorders of arousal. Similarly, surgical treatment of sleep apneas by adenotonsillectomy has been reported to cure nocturnal enuresis in 60% or more of patients, although this is not a consistent result. Several studies have noted the presence of sleep related breathing disorder in > 40% of enuresis patients studied. However, not all sleep studies have noted SRBD in patients with enuresis. Those without SRBD were still found to have high arousal threshold from sleep.

Primary SE is a disorder that occurs when an individual fails to arouse from sleep in response to bladder sensations or fails to inhibit a bladder contraction. These are developmentally acquired skills, and, as such, there is a range in the ages of their acquisition. A small proportion of children with primary SE lack the normal increase in vasopressin release during sleep, leading to a high urinary volume that exceeds the bladder capacity. If these children do not arouse to the sensation of a full bladder, primary SE is the result. Secondary SE can be caused by, or be associated with, any one of the following

identifiable problems: (1) an inability to concentrate urine due to diabetes mellitus, diabetes insipidus, nephrogenic diabetes insipidus (idiopathic or pharmacologic [e.g., secondary to the use of lithium carbonate]), or sickle cell disease; (2) increased urine production secondary to the ingestion of caffeine, diuretics, or other agents; (3) urinary tract pathology, such as urinary tract infections, irritable bladder, malformations of the genitourinary tract (e.g., ectopic ureter); (4) chronic constipation and encopresis; (5) neurologic pathology, such as seizures or neurogenic bladder; or (6) psychosocial stressors, such as parental divorce, neglect, physical or sexual abuse, and institutionalization. The mechanisms by which secondary SE is associated with these problems are often not understood.

Familial Patterns

Hereditary factors are suspected in children with primary enuresis. There is often a high prevalence of enuresis among the parents, siblings, and other relatives of the child with primary enuresis. The reported prevalence is 77% when both parents were enuretic as children and 44% when one parent has a history of enuresis. Recent linkage studies support the hypothesis of genetic and phenotypic heterogeneity of SE. A putative linkage of SE to a region on chromosomes 22q, 13q, and 12q across different families has been reported.

Onset, Course, and Complications

Voiding is a spinal reflex during wakefulness and sleep during infancy, until about 18 months of age. Between 18 months and three years of age, the child is able to delay voiding with a full bladder, first during wakefulness and at a later age during sleep. The primary determinant of the age at which this skill is acquired is developmental maturation. Somewhat arbitrarily, primary SE is defined as a problem if it persists beyond five years of age. The spontaneous cure rate is 15% per year. The primary complication of SE is to the child's self-esteem. How well the child's family deals with the symptom is an important determinant of whether complications develop. Secondary SE can occur at any age. Complications of secondary SE are determined by the problem leading to the enuresis.

Developmental Issues

The developmental pattern of enuresis is similar to NREM parasomnias, although its first occurrence in adulthood is uncommon.

Pathology and Pathophysiology

SE is a heterogeneous disorder with various underlying pathophysiological mechanisms, resulting in a mismatch between nocturnal bladder capacity and the amount of

urine produced during sleep, in association with a simultaneous failure of arousal from sleep in response to the sensation of bladder fullness. SE can be seen in association with sleep fragmentation disorders including SRBD, which in children is most often secondary to adenotonsillar hypertrophy.

Objective Findings

In primary and secondary SE, enuretic episodes can occur in all sleep stages, during nocturnal wakefulness, and in association with transient arousals. Sleep stages have not been found to be different on nights when enuresis occurs versus nights on which it does not occur. The results of polysomnographic studies of children with enuresis compared to normal controls have been inconsistent. A computerized power analysis of sleep data suggested an increase in delta power, whereas the majority of other studies have reported no differences. However, a recent study found those age 6-14 years had elevated light stage N1 sleep and reduced N3 sleep and REM sleep compared to normal controls. The population with enuresis had a significantly elevated arousal index.

SRBD has been reported in 8% to 47% of children with SE. SE and sleep apnea are highly correlated with an increasing prevalence of enuresis as the respiratory disturbance index (RDI) increases. In addition to SRBD, PLMS (range of 3.9 to 38.6 per hour of sleep) have been reported in a group of children with treatment-resistant SE.

Recent studies have demonstrated that patients with enuresis are subjectively sleepier than normal controls. This has been hypothesized to result from fragmented nocturnal sleep and is consistent with a large body of sleep research in other areas.

Differential Diagnosis

Enuresis may be caused by a variety of medical or neurological disorders such as *diabetes mellitus, diabetes insipidus, epilepsy, sickle cell disease, bowel or bladder dysfunction, anatomical abnormalities or infection of the urinary tract, neurological/developmental disorders or other sleep disorders, especially OSA*. Organic pathology of the urinary tract is more prevalent in children who, in addition to sleep enuresis, also exhibit daytime enuresis, abnormalities in the initiation of micturition, or abnormal urinary flow.

Evaluation of sleep enuresis should include complete enuresis history, sleep history, physical examination and laboratory studies (as indicated) to exclude these etiologies. When signs and symptoms of *sleep apnea* are present—mouth breathing, snoring, adenotonsillar hypertrophy, daytime sleepiness, hyperactivity—a sleep study should be conducted.

Unresolved Issues and Further Directions

Recent advances suggest that the terms primary and secondary enuresis may be overly simplistic. Further work is necessary to understand the genetic and clinical aspects of SE.

Other sleep disorders are common in children with SE. Though it may be possible that the apneas, hypopneas, and snoring-related arousals in children with SRBD could be the trigger of SE, many children with SE do not have a sleep disorder. In such cases, the underlying bladder overactivity may be the stimulus for arousal.

Studies of the relationship of sleep, sleep disorders, and sleep fragmentation to SE performed to date have been inconsistent. This is likely due to differing definitions of enuresis and varying research methodologies. Further sophisticated sleep laboratory studies are necessary to elucidate the relationship. In particular, the proximal trigger for episodes of SE has not been determined. Some studies suggest enuresis is spontaneous, whereas others suggest a relationship to sleep disorders that result in arousals—similar to findings in disorders of arousal.

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Parasomnia Due to a Medical Disorder

ICD-9-CM code: 327.44 ICD-10-CM code: G47.54

The essential feature of this diagnosis is the presence of a parasomnia that is attributable to an underlying neurological or medical condition. RBD is the parasomnia most commonly associated with an underlying neurological condition ("symptomatic RBD"). However, when diagnostic criteria for RBD are met, the more specific diagnosis of REM sleep behavior disorder should be made.

Complex nocturnal sleep related (hypnagogic and hypnopompic) visual hallucinations can occur with neurological disorders such as *narcolepsy*, *PD*, *DLB*, *visual loss (Charles Bonnet hallucinations)*, and *midbrain and diencephalic pathology (peduncular hallucinosis)*. Dreaming and sleep paralysis may or may not be associated with these hallucinations.

Parasomnia Due to a Medication or Substance

ICD-9-CM code: 292.85 (drug-induced); 291.82 (alcohol-induced)
ICD-10-CM code: F11-F19 (see table in Appendix B for detailed coding instructions)

The essential feature of this diagnosis is the close temporal relationship between exposure to a drug, medication, or biological substance and the onset of the signs and symptoms of that disorder. A likely causal relationship can be inferred if signs and symptoms of the parasomnia disappear when the drug or substance is withdrawn.

The emergent parasomnia can be a de novo parasomnia, the aggravation of a chronic intermittent parasomnia, or the reactivation of a previous parasomnia. As discussed previously, a variety of medications and biological substances, including

selective serotonin reuptake inhibitors, venlafaxine, tricyclic antidepressants, monoamine oxidase inhibitors, mirtazapine, bisoprolol, selegiline, or cholinergic treatment for Alzheimer disease, have been reported to be associated with acute or chronic RBD. Acute RBD can also be seen during states of withdrawal from cocaine, amphetamine, alcohol, barbiturate, and meprobamate abuse. Caffeine and chocolate abuse have been implicated in causing or unmasking RBD. However, when diagnostic criteria for RBD are met, the more specific diagnosis of REM sleep behavior disorder should be made.

The use of medications such as β-adrenergic receptor-blocking agents can be associated with sleep related hallucinations. When the clinical presentation suggests a direct relationship between a drug or substance and sleep related hallucinations, a diagnosis of parasomnia due to a medication or substance should be employed.

Sedative-hypnotics such as zolpidem and zopiclone have been associated with apparent NREM parasomnias including SRED and sleep driving. It has been suggested that sleep driving is an overlap behavior in which the sedative-hypnotic increases the arousal threshold during sleep at the beginning of the behavior, while later behavior is due to the CNS depressing effects of the drug while awake. It has not been determined if drug-related NREM parasomnias are associated with the same genetic predisposition, priming factors, and triggers observed in disorders of arousal. When clinical presentation suggests a direct relationship between disorders of arousal and use of a drug or substance, a diagnosis of parasomnia due to a medication or substance should be employed.

Alcohol has often appeared on lists of potential sleepwalking triggers without a basis in reliable empirical scientific research. Recent evidence-based reviews have found no relationship between alcohol and sleepwalking. The behavior of the alcohol-intoxicated individual may superficially resemble that of the sleepwalker. However, the sleepwalker is typically severely cognitively impaired, but with only limited motor impairment. The alcohol-intoxicated individual's level of cognitive functioning may be reduced, but not absent, whereas motor behavior is severely impaired.

Proponents of the theory of alcohol related sleepwalking suggest that the effects of alcohol are similar to that of sleep deprivation—that is, alcohol increases deep sleep. However, this claim in not substantiated by sleep laboratory-based studies in normal controls, and no empirical sleep studies of alcohol and sleepwalking have ever been conducted.

There is no scientific evidence that complex behaviors occurring during the sleep period following alcohol ingestion are anything other than the nocturnal wandering of

an alcohol-intoxicated individual. Unconsciousness, intoxication, and sleep are very different states of consciousness. Parasomnias should be easily distinguished from alcohol intoxication by the presence of significant alcohol ingestion prior to bedtime.

The association of therapeutic doses of sedative hypnotic drugs and apparent parasomnias should be carefully distinguished from the expected effects of drug abuse or misuse that result in CNS depression. Investigations of drivers who had accidents attributed to drug-related sleep driving are reported to show that (1) blood levels of prescribed sedative hypnotics exceeded therapeutic ranges; (2) the individuals failed to take the medication at the correct time or remain in bed for sufficient time following ingestion; and/or (3) the individuals combined sedative-hypnotics with other CNS depressants and/or alcohol. Driving with a high blood level of a sedative-hypnotic can result in significant cognitive and motor impairment. Serious accidents can result. Sleep driving and other complex behaviors in this population are more likely to have resulted from drug misuse and abuse rather than true parasomnias.

Parasomnia, Unspecified

ICD-9-CM code: 327.40 ICD-10-CM code: G47.50

This diagnosis is intended for parasomnias that cannot be classified elsewhere or for cases in which the physician has a clinical suspicion of a parasomnia but is unable to establish a specific diagnosis. In many cases, "parasomnia, unspecified" will be a temporary diagnosis. However, in other patients, an underlying condition may not ever be established, and in those patients, "parasomnia, unspecified" should remain an ongoing diagnosis.

Isolated Symptoms and Normal Variants

Sleep Talking

Alternate Names

Somniloquy.

The essential feature is talking, with varying degrees of comprehensibility, during sleep. Sleep talking may occur during REM or NREM sleep. Sleep talking can be idiopathic or associated with parasomnias such as RBD or disorders of arousal such as confusional arousal. Sleep talking may follow arousals from sleep or more rarely cause them. Sleep talking is highly prevalent. A recent cross-sectional epidemiologic study found the lifetime prevalence of sleep talking to be 66% and current prevalence—in the past three months—to be 17%. There is no apparent sex difference. Onset and course are unknown.

Complications usually arise when sleep talking is very frequent or loud or if the content is objectionable to others. Sleep talking is usually reported by the bed partner or someone sleeping in the same room or sleeping area as the affected individual. Sleep talking can disrupt the sleep of a bed partner, roommate, or others in a group-sleeping situation (such as college dormitories, military barracks, fire stations, or a tent while camping). The content of sleep talking has not been shown to reflect actual prior waking behavior or memories. The sleep talker is rarely aware of his or her sleep talking.

Nocturnal vocalization, including frank sleep talking, is often seen in patients with RBD and subclinical RBD. A recent report notes that sleep talking may be a useful diagnostic marker for differentiating DLB from Alzheimer disease and other types of dementia. The vocalizations of RBD may be loud, emotional, profane, and associated with behaviors that correlate with remembered dream mentation. Nocturnal seizures may be associated with vocalization that tends to be stereotypic. The vocalizations associated with sleep terrors are emotionally laden and associated with behaviors of intense arousal and agitation. In PTSD, increased vocalizations during sleep have been described.

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Sleep Related Movement Disorders

Isolated Symptoms and Normal Variants

Sleep related movement disorders are primarily characterized by relatively simple, usually stereotyped, movements that disturb sleep or its onset. Restless legs syndrome (RLS) is an exception in that patients typically engage in walking or nonstereotypic limb movement to reduce leg discomfort. However, RLS is closely associated with periodic limb movements (PLMs), which are usually simple and stereotyped within a series. Nocturnal sleep disturbance or complaints of daytime sleepiness or fatigue are a prerequisite for a diagnosis of a sleep related movement disorder. For example, many normal sleepers exhibit episodes of periodic limb movements of sleep (PLMS) but have no complaint of a sleep disturbance, nor do they show a significant objective disturbance of their sleep as a result of the movements. Such persons should not be classified as having periodic limb movement disorder (PLMD), but instead, the presence of PLMS should simply be noted. Similar considerations relate to the distinction between rhythmic movement disorder and the presence of rhythmic movements.

Body movements that disturb sleep also are seen in many other sleep disorder categories (e.g., in parasomnias such as sleepwalking, sleep terrors, and rapid eye movement (REM) sleep behavior disorder (RBD)). However, these parasomnias differ from the simple stereotyped movements categorized as sleep related movement disorders in that they involve complex behaviors during the sleep period. Parasomnia-related movements may appear

purposeful and goal directed, but are outside the conscious awareness of the individual. Parasomnias are listed in a separate section from the sleep related movement disorders.

Although the history may be diagnostic, polysomnography is sometimes necessary to make a firm diagnosis of sleep related movement disorders and distinguish them from parasomnias. In these cases, it is necessary to add all-night video recording to the polysomnographic recording and to correlate the documented movements with the technician's description of the patient's behavior and level of consciousness in order to establish a diagnosis. There are some movement disorders that may occur during both sleep and wakefulness. If the presentation during sleep is significantly different from that during wakefulness, or if the movement is entirely confined to sleep, then the movement disorder is classified here (e.g., the occurrence of bruxism exclusively in sleep).

Restless Legs Syndrome

ICD-9-CM code: 333.94 ICD-10-CM code: G25.81

Alternate Names

Willis-Ekbom disease.

Diagnostic Criteria

Criteria A-C must be met

A. An urge to move the legs, usually accompanied by or thought to be caused by uncomfortable and unpleasant sensations in the legs.[1,2] These symptoms must:
   1. Begin or worsen during periods of rest or inactivity such as lying down or sitting;
   2. Be partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues;[3] and
   3. Occur exclusively or predominantly in the evening or night rather than during the day.[4]

B. The above features are not solely accounted for as symptoms of another medical or a behavioral condition (e.g., leg cramps, positional discomfort, myalgia, venous stasis, leg edema, arthritis, habitual foot tapping).

C. The symptoms of RLS cause concern, distress, sleep disturbance, or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning.[5]

Notes

1. Sometimes the urge to move the legs is present without the uncomfortable sensations, and sometimes the arms or other parts of the body are involved in addition to the legs.
2. For children, the description of these symptoms should be in the child's own words.
3. When symptoms are very severe, relief by activity may not be noticeable but must have been previously present.
4. As a result of severity, treatment intervention, or treatment-induced augmentation, the worsening in the evening or night may not be noticeable but must have been previously present.
5. For certain research applications, such as genetic or epidemiological studies, it may be appropriate to omit criterion C. If so, this should be clearly stated in the research report.

Essential Features

RLS is a sensorimotor disorder characterized by a complaint of a strong, nearly irresistible urge to move the limbs. This urge to move is often but not always accompanied by other uncomfortable sensations felt deep inside the limbs or by a feeling that is simply difficult or impossible to describe. Although the legs are most prominently affected, "restless legs" is a misnomer, in that 21% to 57% of individuals with RLS describe some arm sensations. The most common adult RLS descriptors in English are "restless," "uncomfortable," "twitchy," "need to stretch," "urge to move," and "legs want to move on their own." About half express their RLS sensations as painful. "Numb" and "cold" are very uncommon descriptors for RLS.

Criteria A1-3 specify the necessary characteristics of the RLS sensations: worse at rest, better with movement, and predominant occurrence in the evening or night. The separation of worsening at rest (criterion A1) from worsening in the evening/night (criterion A3) is based on circadian rhythm studies that show an increase at night, independent of activity level. RLS must be differentiated from other conditions that can mimic RLS (criterion B). Clinically significant RLS is defined by RLS symptoms causing substantial distress, sleep disturbance, or impairment of function (criterion C).

Associated Features

Disturbed sleep is a common, prominent, and distressing aspect of RLS. Sleep onset and maintenance complaints in individuals with RLS are notably higher than in controls, with odds ratios (OR) between 1.7 and 3.5. In clinical populations, disturbed

sleep is reported in 60% to 90% of individuals with RLS, is typically the most troubling symptom, and is often the primary reason for seeking medical care. The Medical Outcomes Study Sleep Questionnaire scores for sleep quantity, sleep disturbance, sleep adequacy, and sleep problems are significantly worse for RLS patients than controls. Daytime fatigue and daytime sleepiness are also common complaints; however, the sleepiness is not as severe as expected for the degree of sleep disruption, implying hyperarousal in RLS. In contrast to obstructive sleep apnea, Epworth Sleepiness Scale scores in RLS are typically in the normal range, and either no different or marginally elevated when compared to normal controls. Clinical sleep disturbance correlates with both severity of RLS and health impact of RLS. Some individuals with RLS may choose to work at night, thereby shifting quiet activities and their sleep schedule away from the circadian peak of their RLS symptoms.

PLMs, a family history of RLS, and response to dopaminergic therapy are supportive of the diagnosis. Periodic limb movements can occur in sleep (PLMS) or wakefulness (PLMW). PLMW occur during quiet rest and frequently at the transition between waking and sleep, disrupting sleep onset or the return to sleep. PLMS are frequently associated with arousal from sleep. RLS sensory and motor features respond initially to treatment with dopaminergic therapy in almost all cases.

Multiple clinic-based and population-based studies have shown an increased prevalence of mood and anxiety disorders in individuals with RLS. Most controlled studies using validated assessments have shown significantly increased ORs for moderately or highly elevated depressive symptoms (OR 1.95 and 3.67), major depression (OR 2.6), major depressive disorder (OR 2.57 and 4.7), generalized anxiety disorder (OR 3.5), panic disorder (OR 4.7, 12.9, and 18.9), and posttraumatic stress disorder (OR 3.76). In addition, a positive correlation has been found between the severity of RLS and depression/anxiety symptoms. Relevant to the RLS-depression relationship is the emerging evidence that treatment of RLS improves depressive symptoms.

Similarly, increased rates of attention deficit hyperactivity disorder (ADHD) have been found in RLS, both in pediatric and adult studies. Emerging data indicate that about one fourth of individuals with RLS have ADHD symptoms, and conversely, that 12% to 35% of those with ADHD meet criteria for RLS. Other medical conditions for which there is some evidence for greater-than-chance association include narcolepsy, migraine, chronic obstructive pulmonary disease, Parkinson disease, multiple sclerosis, peripheral neuropathy, obstructive sleep apnea, diabetes mellitus, fibromyalgia, rheumatoid arthritis, nocturnal eating, obesity, thyroid disease, and heart disease.

Clinical and Pathophysiological Subtypes

Evidence in the literature is not sufficient to support well-defined subtypes of RLS. Early-onset RLS (prior to age 45 years) is more familial and associated with slower progression than late-onset RLS. In addition, the classification of "secondary" RLS has been suggested when the condition occurs in association with iron deficiency, pregnancy, and chronic renal failure, but this construct has been challenged based on pathophysiological, family history, genetic, and clinical course data.

Demographics

The overall prevalence of RLS has been estimated at 5% to 10% in European and North American population-based studies. However, in Asian countries, studies thus far indicate a lower prevalence. Prevalence is about twice as high in women than in men. In most studies, prevalence increases with age up to 60-70 years, except in Asian populations where an age-related increase has not been found. Various measures of clinical significance such as frequency (1-2 times/week), severity (moderate to severe distress), differential diagnosis, and impact have been applied to population-based studies. These analyses indicate the prevalence of clinically significant RLS to be 2% to 3% in Europe and North America, but lower in Asia. Annual incidence rates have been reported as 0.8% to 2.2%.

Pediatric prevalence rates are 2% to 4% in UK/US and Turkish studies, with moderate to severe RLS in about 0.5% to 1%. Adolescents are more likely to have moderate to severe RLS symptoms than younger children—one half of 12- to 17-year-olds compared to one fourth of 8- to 11-year-olds with RLS. Boys are affected as often as girls, with the sex difference not emerging until the late teens or twenties.

Predisposing and Precipitating Factors

A positive family history of RLS, the genetic variants noted below, and female sex confer increased risk for RLS. The best characterized precipitating factors are iron deficiency, certain medications, pregnancy, chronic renal failure, and prolonged immobility. Mild iron deficiency, characterized by serum ferritin below 50 µg/L, has been associated with increased severity of RLS, and repletion of iron stores from below 50-75 µg/L has been found to diminish RLS symptoms. Medications that may precipitate or aggravate RLS and/or PLMS include sedating antihistamines, some centrally active dopamine receptor antagonists, and most antidepressants. An exception is the antidepressant bupropion, with its dopamine-promoting activity.

The prevalence of RLS during pregnancy is two to three times greater than in the general population. There is a peak in the number of women affected by RLS in the

third trimester, with resolution of symptoms for most, but not all, by one month after delivery. Independent predictors of RLS during pregnancy are a family history of RLS (OR 8.43), a history of RLS in prior pregnancy (OR 53.74), a history of RLS in the past (OR 12.91), and hemoglobin ≤11 g/dL (OR 2.05). Parity, the number of previous pregnancies, appears to account for the 2:1 sex difference between women and men in the general population prevalence of RLS.

In chronic renal failure patients, the prevalence of RLS is two to five times greater than in the general population. This represents prevalence rates of 11% to 58% in US and European chronic renal failure clinics. Compared to patients with chronic renal failure without RLS, those with RLS have greater sleep disturbance, report poorer quality of life, and more frequently discontinue dialysis prematurely. Typically, RLS symptoms improve dramatically within one month after kidney transplantation but become severe again with transplant failure.

There is limited or contradictory evidence for sleep deprivation, peripheral neuropathy, radiculopathy, pain, caffeine, tobacco, or alcohol as exacerbating factors for RLS.

Familial Patterns

Early-onset RLS is highly familial, with 40% to 92% of cases reporting affected family members. High concordance rates are observed in monozygotic twins. The risk of RLS is two to six times greater for first-degree relatives of patients with RLS than for those from the general population. Although an autosomal dominant model of RLS is suggested by many family studies, recent genomewide linkage and association studies suggest a more complex gene-environment pattern. Linkage analyses have reported several different gene loci associated with RLS but, to date, no single causative gene. However, genomewide association studies have identified single nucleotide polymorphisms in RLS, four of which have been replicated: *BTBD9*, *MEIS1*, *MAP2K5/LBXCOR*, and *PTPRD*. Nonetheless, the relationship between familial RLS and these findings remains to be determined.

Onset, Course, and Complications

Onset of RLS symptoms occurs at all ages, from childhood to late adult life. Mean age of onset for familial RLS is in the third or fourth decade, with onset prior to age 21 years in about one third of cases. The clinical course of RLS differs based on age of onset. In early-onset RLS (before age 45 years), slow progression of symptoms is found in about two thirds of cases. Most of the remaining one third report stable symptoms over time, although remission has been described. In late-onset RLS, rapid progression is typical and aggravating factors are common.

Significant impairment of health-related quality of life (HRQoL) has been found in moderate to severe RLS. Both physical health and mental health scores have consistently been found to be lower for individuals with RLS, using standard QoL assessment tools. The HRQoL impairments are strongly associated with severity of RLS and remain after controlling for age, sex, and disease comorbidity. In addition, patients with cancer, type 2 diabetes, or renal failure who also have RLS have been shown to have poorer quality of life than those without RLS. Overall, RLS accounts for a major disease burden on those who suffer from it, demonstrated to be similar to or worse than that associated with osteoarthritis, congestive heart failure, depression, Parkinson disease, or stroke.

Large population-based studies have found positive associations between RLS and cardiovascular disease, including coronary heart disease and stroke. Repetitive surges in heart rate and blood pressure associated with PLMS are a potential mediator in the physiology of these relationships. Only limited mortality data are available, suggesting increased risk of mortality in women and in chronic renal failure patients with RLS.

Developmental Issues

The accurate diagnosis of RLS in children and adolescents requires understanding of developmental language and cognitive skills. Adequate verbal skills are needed for children to communicate the sensory component of RLS and description must be in "the child's own words," rather than by a parent or caretaker. For criterion A, children rarely use or understand the word "urge." Instead they describe that their legs "need to" "have to" or "got to" move. Descriptors for the discomfort include: bugs, ants, weird/funny feelings, tingle, wiggly, and shaky. Younger children often use the word "kick" rather than "move," e.g., "my legs want to kick." Similar to adults, children report arm involvement in almost half of cases. Sitting in class, lying in bed, reading a book, and riding in a car are situations where children report onset or worsening of their symptoms. Relief is typically achieved by moving around, walking, rubbing, kicking, or distraction. Perhaps as a result of prolonged periods of sitting in class, two thirds of children and adolescents with RLS report daytime leg sensations. Because of this, for diagnostic criterion A3 (worse in the evening/night), it is important to compare equal duration of sitting or lying down in the day to sitting or lying down in the evening/night. However, even with such comparisons, a significant subset of children do not report worsening at evening/night, yet meet all other diagnostic criteria and have supportive features for RLS, including a positive family history. Children who are age six years or older and developmentally normal have been shown to report detailed, adequate descriptors for RLS symptoms. For children who are too young to adequately describe RLS sensations or are developmentally delayed, a PLMD diagnosis may be

the initial diagnosis, with full RLS symptomatology evident over time. Diagnosis by observational techniques has been suggested but not yet validated.

The differential diagnosis of pediatric RLS includes positional discomfort, sore leg muscles, joint/tendon injury, and bruises, all of which are common mimics. In childhood, RLS is frequently misdiagnosed as "growing pains." Four specific domains that are affected in pediatric RLS are sleep, daily activities, mood, and energy/vitality. Difficulties with sleep onset, sleep maintenance, and sleep quality are common. Negative influence of RLS on waking activities includes academic impact due to disruption of schoolwork, homework, and ability to concentrate. Severity assessment of pediatric RLS has thus far been limited to simple measures of self-reported frequency and intensity.

Because pediatric RLS is highly familial, the presence of RLS in a first-degree relative helps to increase diagnostic certainty in childhood RLS. Similarly, the presence of PLMS or a history of PLMD is quite helpful in supporting an RLS diagnosis in children. As in adults, approximately 70% of children with RLS demonstrate PLMS $\geq$ 5/hour on a single night and nearly 90% when multiple nights are sampled. PLMS $\geq$ 5/hour are uncommon in pediatric normative samples. As noted above, pediatric RLS is comorbid with ADHD in about one fourth of cases, and, as in adults, higher rates of anxiety and depressive symptoms are found. RLS is common in pediatric chronic kidney disease.

Prevalence rates of RLS increase with age until late adulthood then stabilize or decrease slightly in the elderly. However, strong associations with anxiety, mood disorders, and decreased QoL measures remain in the elderly. Diagnostic criteria for RLS in the cognitive-impaired elderly have been suggested but not validated.

Pathology and Pathophysiology

Brain iron deficiency, central nervous system dopamine regulation, and genetics appear to be primary factors in the pathophysiology of RLS. Iron is important in brain dopamine production and synaptic density, as well as in myelin synthesis and energy production. A connection between RLS and low brain iron is supported by autopsy data, MRI, brain sonography, and cerebrospinal fluid analysis. Evidence for central nervous system dopaminergic system involvement comes mainly from multiple randomized clinical trials that have clearly demonstrated the effect of dopaminergic drugs for RLS and PLMS. In addition, an altered dopaminergic profile in RLS is supported by functional MRI, positron emission tomography, and autopsy data. Association of gene variants *BTBD9*, *MEIS1*, *MAP2K5/LBXCOR*, and *PTPRD* with RLS has been replicated,

indicating a genetic substrate upon which environmental factors might act. *BTBD9* is estimated to confer a population attributable risk (PAR) of 50% for RLS. Together, *BTBD9*, *MEIS1*, and *MAP2K5/LBXCOR* account for 70% of the PAR for RLS in individuals with European ancestry. Thus far, two of the variants, *BTBD9* and *MEIS1*, appear to influence expression of PLMS, as well as iron homeostasis. However, the full role of RLS gene variants has not been adequately defined.

Objective Findings

Although polysomnography is not routinely indicated in the evaluation of RLS, polysomnographic studies demonstrate significant objective sleep abnormalities in RLS, with increased latency to persistent sleep and higher arousal index as the most consistent differences in sleep architecture. PLMS ≥5/hour occur in 70% to 80% of adults with RLS on single-night testing but in >90% when multiple nights are sampled. In adult RLS, PLMS are more prominent during the first half of the night and vary in frequency from night to night. About one third of PLMS are associated with cortical arousals, and most have associated autonomic arousals. PLMS are not influenced by placebo effect. PLMS arousals contribute to the primary RLS morbidity of sleep disturbance. Furthermore, RLS sensory symptoms impair return to sleep, and thereby result in more prolonged awakening.

The Suggested Immobilization Test (SIT) evaluates PLMW and related sensory components of RLS during resting wakefulness. A standard polysomnogram recording without respiratory measures is used for one hour before the usual bedtime while the subject sits comfortably awake and upright in bed with the legs outstretched. RLS diagnosis is supported by a finding of more than 40 PLMW/hour.

Activity monitors with high-frequency sampling and body-position monitoring may be attached to the ankle or foot to provide an alternate measure of PLMs. Recordings assess the frequency and variability of PLMs from night to night, typically over three to five nights.

Differential Diagnosis

The differentiation of RLS from other conditions that may have characteristics of RLS is essential, because approximately 40% of individuals without RLS will report some urge or need to move the legs while at rest. Fulfilling diagnostic criteria A2 (better with movement) and A3 (worse in the evening/night) improves specificity for an RLS diagnosis to only about 70%, based on studies that have used structured diagnostic interviews. However, differentiating RLS from *leg cramps* and *positional discomfort* improves specificity to 94%, emphasizing the importance of differential diagnosis. The

most important "mimics" of RLS are *leg cramps*, *positional discomfort*, *arthralgias/arthritis*, *myalgias*, *leg edema*, *peripheral neuropathy*, *radiculopathy*, and *habitual foot tapping*. Not characteristic of RLS are: "knotting" of the muscle (cramps), relief with a single postural shift (positional discomfort), limitation to joints (arthritis), soreness to palpation (myalgias), and other abnormalities on physical examination. Less common conditions to be differentiated from RLS include *neuroleptic-induced akathisia*, *myelopathy*, *symptomatic venous insufficiency*, *peripheral artery disease*, *eczema*, *orthopedic problems*, *painful legs and moving toes*, and *anxiety-induced restlessness*. Neuroleptic-induced akathisia differs from RLS in that akathisia is associated with the need to move the entire body and occurs in association with use of dopamine-receptor antagonists. Painful legs and moving toes have neither a clear circadian pattern nor the sense of an urge to move.

Pain involving the legs occurs with numerous conditions, including arthritis, vascular problems, sports/orthopedic injuries, and neuropathy. These pains can have a nocturnal presentation and may be worse at rest, but improvement with movement either does not occur or entails more exercise than simple movement of the leg. The urge to move, if present at all, usually stems from awareness that movement produces relief rather than the strong primary urgency of movement felt with RLS. The presence of pain, however, does not exclude a diagnosis of RLS, because about 50% of patients with RLS report their RLS symptoms as painful.

Although it is important that RLS symptoms not be attributable solely to another medical or behavioral condition, it should also be appreciated that any of these mimics can occur in an individual who also has RLS. For example, some subjects may have both RLS and leg cramps. When the diagnosis of RLS is not certain, evaluation for the supportive features such as the presence of PLMS or a family history of RLS may be helpful. Diagnostic interviews that include differential diagnosis have been validated for RLS. These demonstrate sensitivity and specificity of > 90%.

Unresolved Issues and Further Directions

The diagnosis of RLS relies on the subjective report of sensory symptoms that lie outside the range of common sensory experience. Many patients have difficulty describing the sensations. Further studies of the biological bases for RLS may lead to better classification of RLS and possibly to objective tests for diagnosis. Iron, dopamine, and genetic research hold particular promise. Additional epidemiological and genetic studies outside the US and Europe are needed to explore apparent population differences. The diagnostic standards and severity assessment for children and cognitively impaired adults require further development. Clarification of the natural course

and potential exacerbating factors is needed. Better understanding of RLS with comorbidities such as mood disorders and attention deficit hyperactivity disorder might lead to improved outcomes in those disorders. Further evaluation of long-term complications is important, including clarification of associations with hypertension, cardiovascular disease, and stroke.

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Periodic Limb Movement Disorder

ICD-9-CM code: 327.51 ICD-10-CM code: G47.61

Alternate Names

Periodic movement disorder of sleep, sleep myoclonus syndrome, nocturnal myoclonus syndrome.

Diagnostic Criteria

Criteria A-D must be met

A. Polysomnography demonstrates PLMS, as defined in the most recent version of the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events.
B. The frequency is > 5/hour in children or > 15/hour in adults.[1]
C. The PLMS cause clinically significant sleep disturbance or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning.[2,3]
D. The PLMS and the symptoms are not better explained by another current sleep disorder, medical or neurological disorder, or mental disorder (e.g., PLMS occurring with apneas or hypopneas should not be scored).[4,5]

Notes

1. The PLMS Index must be interpreted in the context of a patient's sleep related complaint. In adults, normative values greater than five per hour have been found in studies that did not exclude respiratory event-related arousals (using sensitive respiratory monitoring) and other causes for PLMS. Data suggest a partial overlap of PLMS Index values between symptomatic and asymptomatic individuals, emphasizing the importance of clinical context over an absolute cutoff value.
2. If PLMS are present without clinical sleep disturbance or daytime impairment, the PLMS can be noted as a polysomnographic finding, but criteria are not met for a diagnosis of PLMD.
3. The presence of insomnia or hypersomnia with PLMS is not sufficient to establish the diagnosis of PLMD. Studies have shown that in most cases the cause of the accompanying insomnia or hypersomnia is something other than the PLMS. To establish the diagnosis of PLMD, it is essential to establish a reasonable cause-and-effect relationship between the insomnia or hypersomnia and the PLMS. This requires

that other causes of insomnia such as anxiety or other causes of hypersomnia such as obstructive sleep apnea or narcolepsy are ruled out. PLMS are common, but PLMD is thought to be rare in adults.

4. PLMD cannot be diagnosed in the context of RLS, narcolepsy, untreated obstructive sleep apnea, or REM sleep behavior disorder; PLMS occur commonly in these conditions but the sleep complaint is more readily ascribed to the accompanying disorder. The diagnosis of RLS takes precedence over that of PLMD when potentially sleep-disrupting PLMS occur in the context of RLS. In such cases, the diagnosis of RLS is made and the PLMS are noted.
5. When it is reasonably certain that the PLMS have been induced by medication, and full criteria for PLMD are met, it is preferred that the more specific diagnosis of PLMD be used, rather than "Sleep related movement disorder due to a medication or substance."

Essential Features

PLMD is characterized by periodic episodes of repetitive, highly stereotyped limb movements that occur during sleep (PLMS), in conjunction with clinical sleep disturbance or fatigue that cannot be accounted for by another primary sleep disorder or other etiology.

PLMS occur most frequently in the lower extremities. They typically involve extension of the big toe, often in combination with partial flexion of the ankle, the knee, and sometimes, the hip. Similar movements can occur in the upper limbs. Individual movements may be associated with an autonomic arousal, a cortical arousal, or an awakening. Typically, the patient is unaware of the limb movements or the frequent sleep disruption. An arousal may precede, coincide with, or follow the limb movement, suggesting that a central generator may give rise to both the periodic movements and the related sleep disturbance.

A clinical history of sleep onset problems, sleep maintenance problems, or unrefreshing sleep attributable to the PLMS is needed for a diagnosis of PLMD. These symptoms have most consistently been associated with PLMS, and the presence of these clinical symptoms differentiates PLMD from asymptomatic PLMS. Although excessive daytime sleepiness has been reported with PLMD in the past, newer data do not find significantly elevated Epworth Sleepiness Scale scores or Multiple Sleep Latency Test (MSLT) values in subjects with PLMS. If the only complaint is sleep disruption for the bed partner, then PLMD should not be diagnosed but the sleep disturbance of the bed partner can be noted.

The PLMS index should exceed five per hour in children and 15 per hour in adult cases for a diagnosis of PLMD. This is based on substantial normative data in children. In adults, there is a significant increase in sleep disturbance symptoms with PLMS >15/hour.

The PLMS and the symptoms of sleep disturbance or nonrestorative sleep should not be better explained by another etiology. Most important in the differential diagnosis are RLS, REM sleep behavior disorder (RBD), and narcolepsy. Research studies indicate that five or more PLMS per hour occur in 80% to 90% of patients with RLS, in about 70% with RBD, and in 45% to 65% with narcolepsy. In RBD, PLMS are often present without arousals during nonrapid eye movement sleep (NREM) sleep but can also continue into REM sleep, which is unusual in all other settings. If significant daytime sleepiness and PLMS are present, a diagnosis of narcolepsy should be considered. PLMD should not be diagnosed when criteria for one of these three disorders is met. However, the primary disorder "with PLMS" can be specified (e.g., "RLS with PLMS").

A sensitive technique, such as pressure transducer airflow monitoring or esophageal manometry, should be used to monitor breathing during polysomnography to reasonably exclude sleep related breathing disorders (SRBDs) as the direct cause of the PLMS. When independent PLMS are present in patients with SRBDs, a separate diagnosis of PLMD may be considered if the PLMS persist despite adequate treatment of the SRBD and otherwise unexplained sleep disturbance remains. Ideally, polysomnography for the diagnosis of PLMD should be performed after the biologic effect of a medication or substance, such as an antidepressant known to induce or aggravate PLMS, has ended.

Associated Features

Higher rates of mood disorders, anxiety, attention deficits, oppositional behaviors, and parasomnias have been reported in some studies of patients with PLMD. In children with PLMD, a family history of RLS is common. A sustained clinical response to dopaminergic therapy is supportive of the diagnosis of PLMD. Although PLMD symptoms may be responsive to benzodiazepines, benzodiazepine responsiveness is not supportive of the diagnosis due to the nonspecific effect of benzodiazepines on sleep.

Clinical and Pathophysiological Subtypes

Not applicable or known.

Demographics

Although PLMD is thought to be rare, the exact prevalence is not known. PLMD has been reported in both children and adults. PLMS >5/hour are very uncommon in

children and adults younger than the age of 40 years, but then increase markedly with advancing age, occurring in over 45% of the elderly. The population prevalence of PLMS >15/hour has been estimated at 7.6% of 18- to 65-year-olds, with 4.5% of the total population also reporting sleep disturbance or excessive sleepiness. However, RLS and medication-induced PLMS were not exclusionary criteria in this population, suggesting much lower rates for PLMD. The increase in PLMS with age may occur as a partial expression of familial or genetic factors associated with RLS, based on data that show very little increase in PLMS with age when individuals who have RLS or first-degree relatives with RLS are excluded. PLMS are less common in black adults and children than in whites. No sex difference has been described for PLMS or PLMD.

Predisposing and Precipitating Factors

A positive family history of RLS confers increased risk for PLMS and PLMD. The genetic variants noted below may be a mediator of this risk. Precipitation or aggravation of PLMS has been reported with the use of several medications. Selective serotonin reuptake inhibitor antidepressants, tricyclic antidepressants, lithium, and dopamine receptor antagonists have most often been associated with this effect.

Low brain iron, as reflected by serum ferritin level, may worsen PLMS via the role of iron in dopamine function. Less evidence is available for obstructive sleep apnea (OSA), alcohol, pain, and sleep deprivation as factors that worsen PLMS.

Familial Patterns

The familial pattern of PLMD has not been studied in detail. Families with RLS have been found to include first-degree relatives without RLS but with increased rates of PLMS or PLMD, raising the possibility that PLMD is an attenuated manifestation or a precursor to RLS. The gene variants *BTBD9* and *MEIS1*, which were found in genome-wide studies of RLS, appear to influence the expression of PLMS.

Onset, Course, and Complications

Although the typical age of onset is not known, PLMD occurs in both children and adults, with onset as early as infancy. The natural history has not been described in detail, but some pediatric cases of PLMD progress to RLS. Incidence and remission rates are unknown. Impaired performance in a simulated driving task has been found in patients with PLMD. Increased PLMS have been associated with a higher risk of cardiovascular disease, stroke, and mortality in some studies. PLMS-related overactivity of the sympathetic nervous system is postulated to be a potential mechanism for these associations.

Developmental Issues

Given the low background rates of PLMS in children, PLMD has emerged as a useful diagnostic category in pediatric sleep medicine. Pediatric PLMD has important clinical and polysomnographic correlates that are comparable in severity to pediatric OSA. However, PLMS and PLMD normative data remain sparse for children younger than two years.

In the elderly, frequent occurrence of other conditions that can account for sleep disturbance and fatigue makes application of PLMD criteria difficult, even though PLMS are common.

Pathology and Pathophysiology

Dopaminergic impairment has been implicated in the pathophysiology of PLMS and PLMD. The study of PLMS in RLS and in children also suggests genetic diathesis and iron status as factors. Cyclic alternating pattern, a marker of nonrestorative sleep, is increased in individuals with PLMS and may influence the periodicity of PLMS. Cortical arousals can precede, coincide with, or follow PLMS, indicating that PLMS do not cause the arousals. In addition, PLMS can be dissociated from arousals pharmacologically, suggesting an indirect relation, possibly mediated by a central generator. The autonomic arousals associated with PLMS are characterized by significant heart rate and blood pressure surges, a mechanism for possible increased cardiovascular and cerebrovascular disease risk.

Objective Findings

PLMS can appear immediately with the onset of stage N1 sleep, are frequent during stage N2 sleep, decrease in frequency in stage N3, and are usually absent during stage R sleep. PLMS typically occur in discrete episodes that last from a few minutes to an hour. Both lower limbs should be monitored for the presence of limb movements. Movements of the upper limbs may be sampled if clinically indicated. The anterior tibialis electromyogram (EMG) shows repetitive contractions, each lasting 0.5 to 10 seconds. The movements may affect one or, more typically, both of the lower limbs, but not necessarily in a symmetric or simultaneous pattern. Specific scoring criteria for PLMS are described in the AASM Manual for the Scoring of Sleep and Associated Events.

Self-reports, bed partner observations, or parental reports for children have not been found to have sufficient specificity or sensitivity to replace objective testing for PLMS.

Care must be taken to discriminate PLMS from other movements such as a simple change in body position, stretching of a limb, or a muscle cramp. PLMS are longer in

duration than myoclonic jerks, which, by definition, are typically 50 to 150 milliseconds long. Movements associated with respiratory events, hypnagogic foot tremor, or alternating leg muscle activation during sleep (ALMA) should not be included in the PLMS index.

PLMS may be associated with electroencephalographic (cortical) arousals or with awakenings. Autonomic arousals—measured by a change in heart rate, blood pressure, or pulse transit time—have been shown to be more frequent than cortical arousals. In some cases, periodic arousals may persist even though the PLMS have subsided. The arousals are typically more difficult to measure than are the PLMS, and their clinical significance is a topic of ongoing debate. As with obstructive sleep apnea, the associated cortical arousal index has not proven more useful than the PLMS index in making clinical decisions. Although a subjective report of excessive daytime sleepiness is present in some patients with PLMD, mean sleep latency measured by MSLT has not been found to be consistently abnormal or to correlate with the PLMS cortical arousal index.

The movements should be reported as an index of total sleep time, called the PLMS index. The PLMS index is the number of periodic limb movements per hour of total sleep time, as determined by polysomnography. The PLMS arousal index is the number of PLMS associated with a cortical arousal, expressed per hour of total sleep time. Other parameters for the description of PLMS include periodicity index, intermovement interval distribution, and time of night distribution. These features have been shown to help differentiate PLMS patterns in different conditions (e.g., a finding of the highest periodicity indices in adult RLS and PLMD).

Leg actigraphy has been validated against PSG for the measurement of PLMS and provides a methodology to assess PLMS in large populations, as well as night-to-night variability.

Differential Diagnosis

As described in the essential features section, PLMD is a diagnosis of exclusion and it is important to differentiate it from other conditions in which PLMS occur, particularly *RLS*, *RBD*, *narcolepsy*, and *SRBDs*. Increased rates of PLMS have also been reported in *multiple system atrophy*, *dopa-responsive dystonia*, *sleep related eating disorder*, *spinal cord injury*, *end-stage renal disease*, *congestive heart failure*, *Parkinson disease*, *sickle cell disease*, *posttraumatic stress disorder*, *Asperger syndrome*, *Williams syndrome*, and *multiple sclerosis*. Dopaminergic impairment and/or diminished inhibition of the central pattern generator for PLMS have been proposed as common factors linking various disorders and PLMS.

Sleep starts (hypnic jerks) need to be differentiated from PLMS. Sleep starts typically are limited to the transition from wakefulness to sleep, are not periodic, and are briefer (20 to 100 milliseconds) than PLMS. Normal *phasic REM activity* is limited to REM sleep, typically occurs in 5- to 15-second clusters, and is usually associated with bursts of REMs. Phasic REM EMG twitches are more variable in duration and do not have the periodicity of PLMS. *Fragmentary myoclonus* is characterized by EMG activity that is briefer (75 to 150 milliseconds), more variable in duration, less periodic than PLMS, and has little or no associated visible movement. Also, PLMS must be differentiated from movements associated with *nocturnal epileptic seizures* and *myoclonic epilepsy* and from a number of forms of myoclonus seen while awake, such as in *Alzheimer disease*, *Creutzfeldt-Jakob disease*, and *other neuropathologic conditions*. However, in these disorders, the involuntary movements are prominent during the daytime, often do not disappear with activity, are prominent in the arms and other body parts in addition to the legs, and do not display the periodicity seen with PLMS.

Unresolved Issues and Further Directions

There has been controversy over the clinical significance of PLMS. To date, the interpretation of most studies has been confounded by multiple factors that include: imprecise diagnostic criteria; confusion between PLMS and PLMD; inadequate monitoring for subtle SRBDs; a lack of consideration of medications known to induce, worsen, or suppress PLMS; and inadequate measurement of the known night-to-night variability of PLMS. Newer respiratory monitoring techniques for polysomnography and the use of actigraphy monitors over several nights should help address a number of these issues. The role of associated arousals in relation to clinical symptoms is yet to be determined, but the appreciation of autonomic arousals as well as cortical arousals might be critical. It is possible that PLMS are a measurable marker of unstable sleep, related to genetic diathesis and dopaminergic impairment.

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Sleep Related Leg Cramps

ICD-9-CM code: 327.52 ICD-10-CM code: G47.62

Alternate names

Leg cramps, "charley horse," nocturnal leg cramps.

Diagnostic Criteria

Criteria A-C must be met

A. A painful sensation in the leg or foot associated with sudden, involuntary muscle hardness or tightness, indicating a strong muscle contraction.
B. The painful muscle contractions occur during the time in bed, although they may arise from either wakefulness or sleep.
C. The pain is relieved by forceful stretching of the affected muscles, thus releasing the contraction.

Essential Features

Sleep related leg cramps are painful sensations caused by sudden and intense involuntary contractions of muscles or muscle groups during which there is muscle spasm and hardness for several seconds. These painful sensations are usually in the calf or small muscle of the foot. Occurring during the time in bed, sleep related leg cramps may arise from either wakefulness or sleep.

Sleep related leg cramps usually start abruptly but may in some cases be preceded by a less painful warning sensation. The muscle contractions last for a few seconds up to several minutes and then remit spontaneously. The frequency of sleep related leg cramps varies considerably from less than yearly to multiple episodes every night.

The cramps can be relieved by strongly stretching the affected muscle and sometimes also by local massage, application of heat, or movement of the affected limb. Leg cramps can be present primarily during the daytime.

Associated Features

The muscle cramp affects sleep. The pain from the cramp itself and from the activities used to relieve it commonly disturb sleep onset or cause an awakening from sleep. Often the presenting complaint is insomnia, at times severe.

Tenderness and discomfort in the muscle may persist for several hours after the cramping. Persisting discomfort after the cramping episode often delays subsequent return to sleep.

Clinical and Pathophysiological Subtypes

Sleep related leg cramps are known to be either idiopathic or secondary to other medical conditions, but there have been no indications of significant differences in the clinical features of the disorder related to the cause.

Demographics

Sleep related leg cramps are common. It has been suggested that nearly every adult older than 50 years has experienced sleep related leg cramps at least once. Both the prevalence and the frequency of the events increase with age. Sleep related leg cramps have been reported to occur at least occasionally in about 7% of children and adolescents, 33% in adults older than 60 years, and 50% in adults older than 80 years, with both older groups reporting a symptom frequency of at least once every two months. Nightly leg cramps have been reported in 6% of adults older than 60 years. No definitive sex information has been reported, though a single study reported a higher prevalence in women.

Predisposing and Precipitating Factors

Predisposing factors include diabetes mellitus, amyotrophic lateral sclerosis, cramp fasciculation syndrome, peripheral vascular disease, hypokalemia, hypocalcemia, hypomagnesemia, and metabolic disorders. The disorder can be associated with prior vigorous exercise, prolonged standing at work, dehydration, fluid and electrolyte disturbances, endocrine disorders, neuromuscular disorders, disorders of reduced mobility, vascular disease, cirrhosis, and hemodialysis. Medications that have been associated with sleep related leg cramps include oral contraceptives, intravenous iron sucrose, teriparatide, raloxifene, diuretics, long-acting β-agonists, and statins. Sleep related leg cramps occur in about 40% of pregnant women and generally resolve after delivery.

Familial Pattern

Not known.

Onset, Course and Complications

Sleep related leg cramps have not been reported in infancy, nor in children younger than eight years. The peak onset is usually in adulthood, but the condition may be seen for the first time in old age. The natural history of leg cramps is not well understood. Many patients describe a waxing and waning course of many years' duration. Complications include muscle tenderness, insomnia, and occasional daytime fatigue due to interrupted sleep. No marked mental or social dysfunction has been described due to sleep related leg cramps alone.

Pathology and Pathophysiology

Many sleep related leg cramps appear to be idiopathic. Although leg cramps involve abnormal muscle tone, they are generally considered not to involve agonist-antagonist co-contractions and, thus, are not classified as dystonias. Some nocturnal leg cramps, particularly those in the feet, may resemble dystonias but, unlike classic dystonias, sleep related leg and foot cramps are relieved by stretching the affected muscle or muscles.

Electrophysiologic recordings show that the cramps typically start with spontaneous firing of anterior horn cells followed by motor unit discharges for contractions at rates up to 300 Hz (considerably more than with voluntary muscle contractions). The pain may result from local metabolite accumulations or from local ischemia.

Muscle and tendon shortening due to age or lack of stretching exercise is thought to contribute to the development of sleep related leg cramps. Exercise involving stretching the affected muscles is thought to help prevent or reduce the occurrence of sleep related leg cramps.

Objective Findings

Polysomnographic studies of patients with chronic sleep related leg cramps reveal nonperiodic bursts of gastrocnemius EMG activity. Episodes arise from sleep without any specific preceding physiologic changes during sleep.

Differential Diagnosis

Sleep related leg cramps are common in *chronic myelopathy*, *peripheral neuropathy*, *muscular pain fasciculation syndrome*, and *disorders of calcium metabolism*. These causes should be differentiated by clinical history and physical examination. *RLS* is

sometimes confused with sleep related leg cramps because both can present with leg discomfort during the sleep period and RLS patients sometimes complain of a cramping sensation. However, if patients meet the diagnostic criteria for RLS and do not describe an actual cramp or hardening of the muscle, the diagnosis should be RLS. Because leg cramps can mimic RLS and meet all the criteria for RLS, the description of an actual spasm or hardening of the muscle is a critical differentiating factor. A leg cramp is also a much briefer event than the typical symptoms of RLS, which can persist for hours. However, RLS and leg cramps may sometimes be seen in the same individual.

Dystonia is ongoing daily spasm of muscles and is distinguished electrophysiologically from leg cramps by ongoing co-contraction of agonist and antagonist muscles. Dystonia can be focal, as in the case of muscles of the neck (torticollis) or hand (writer's cramp), or generalized as in the case of torsion dystonia.

Unresolved Issues and Further Directions

Sleep related leg cramps are common and can affect sleep. Their association with other disorders and different medications hinder accurate epidemiological data and underestimate their effect on sleep and on quality of life. Instruments to quantify the severity of the disorder and its impact are needed to adequately address clinical relevance, treatment, and the potential occupational hazards. Effective treatments for sleep related leg cramps have yet to be developed. The prophylactic benefits of stretching exercises remain to be adequately validated.

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Sleep Related Bruxism

ICD-9-CM code: 327.53 ICD-10-CM code: G47.63

Alternate Names

Nocturnal bruxism, nocturnal tooth grinding, tooth clenching.

Diagnostic Criteria

Criteria A and B must be met

A. The presence of regular or frequent tooth grinding sounds occurring during sleep.

B. The presence of one or more of the following clinical signs:
   1. Abnormal tooth wear consistent with above reports of tooth grinding during sleep.
   2. Transient morning jaw muscle pain or fatigue; and/or temporal headache; and/or jaw locking upon awakening consistent with above reports of tooth grinding during sleep.

Notes

1. Although polysomnography is not required for the diagnosis, sleep bruxism, as described in the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events, is ideally recorded with masseter muscle activity with audio-video signal to increase diagnostic reliability.

Essential Features

Bruxism is defined as a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible. Bruxism

has been divided into its two distinct circadian manifestations: sleep bruxism and awake bruxism.

In sleep, jaw muscle contractions are frequently repeated over time and are termed rhythmic masticatory muscle activity (RMMA). These contractions can take two forms on electromyographic traces: a series of repetitive activity (phasic muscle contractions) or isolated sustained jaw clenching (tonic contractions). These contractions during sleep produce tooth-grinding sounds and are referred to as sleep related bruxism.

Sleep related bruxism can lead to abnormal tooth wear, tooth pain, jaw muscle pain, and temporal headache. Severe sleep related bruxism may also result in sleep disruption. This may involve not only the individual affected, but also the bed partner, because the sounds made by the friction of the teeth are usually perceived as being unpleasant and can be quite loud and disturbing to those nearby.

The disorder is typically brought to dental or medical attention because of the tooth damage, pain, or disturbing sounds. Less commonly, it may present as a cause of disturbed sleep. Young and otherwise healthy individuals with sleep related bruxism appear to have normal sleep structure and homeostasis. The majority of RMMA episodes during sleep occur in association with sleep arousal.

Jaw muscle pain, tenderness in the masseter and temporalis muscle regions, morning headache, or fatigue can arise due to sleep related bruxism.

Associated Features

Additional symptoms include a variety of unpleasant muscle and tooth sensations, limitation of jaw movements, orofacial pain, and temporal/tension headaches. Tooth wear, fractured teeth, and buccal lacerations also can occur. These symptoms may be induced by sleep related bruxism, but the connection may not be apparent to the affected individual and diagnostic discrimination is weak.

Headaches are frequently reported by both adults and children with sleep related bruxism. The headache usually involves the temporal regions and it has the characteristics of a tension headache. It is reported either in the morning (more frequently) or during the day (with wake bruxism). The estimated OR for headache in individuals with sleep related bruxism is > 4 compared to controls.

There is high individual variability in the intensity and duration of sleep related bruxism, but in the most severe cases, hundreds of events can occur during a night

of sleep. However, no direct relationship has been observed between the severity of sleep related bruxism and the appearance of clinical signs and symptoms. Indeed, individuals with a mild to moderate index of sleep bruxism (2 to 4 RMMA episodes/hour of sleep) have a higher risk of reporting painful jaw upon awakening (OR 3.9), and masticatory muscle fatigue (OR 5.1) compared to individuals with severe sleep related bruxism (> 4 RMMA episodes/hour of sleep).

Psychosocial components may also be linked to sleep related bruxism. The psychological assessment of otherwise healthy adults with sleep related bruxism suggests a correlation (not yet proven as a causality) between bruxism and stress/anxiety. Moreover, both children and adults with sleep related bruxism seem to have higher scores in stress, anxiety, and psychiatric scales compared to control individuals.

Clinical and Pathophysiological Subtypes

Sleep related bruxism without clear cause is termed ***primary*** *or* ***idiopathic***.

Forms of sleep related bruxism associated with the use of psychoactive medications, recreational drugs, or a variety of medical disorders (e.g., Parkinson disease, RBD, Down syndrome) are defined as ***secondary sleep related bruxism***. Treatment-induced sleep related bruxism is also termed ***iatrogenic***.

Although the primary form of sleep related bruxism is most often reported in healthy children and adults, secondary sleep related bruxism is observed in children with cerebral palsy and mental retardation and in adult patients with abnormal movements such as in oromandibular myoclonus/facio-mandibular myoclonus or with sleep related breathing disorders. OSA and sleep related bruxism commonly co-occur.

Tooth grinding and clenching also can occur during wakefulness, as an oral parafunctional activity known as awake bruxism. ***Awake bruxism*** is considered a different disorder, probably with different diagnostic criteria and pathophysiology; its association with sleep bruxism is still under debate. However, the two oral activities may coexist in the same individual.

Demographics

The prevalence of sleep related bruxism, based on reports from parents or sleep partner, is highest in childhood (approximately 14% to 17%) and then decreases over the life span. In teenagers to young adults, prevalence is in the 12% range. In young to middle-aged adults, it is approximately 8% but as little as 3% in older persons. The reported reduction in tooth grinding in the elderly probably overestimates the actual

reduction, because edentulism, use of dentures, and changes in sleeping behaviors (i.e., in isolation) may influence reporting. There is no reported sex difference for the prevalence of sleep related bruxism.

Predisposing and Precipitating Factors

Predisposing factors include personality types; for example, individuals who are highly motivated or characteristically maintain high vigilance may have an increased prevalence of sleep related bruxism.

Genetic predisposition is plausible but still under investigation. As described below, there is some familial predisposition due to environmental or shared genetic factors. Recently, a serotonin gene was described in bruxism patients but the absence of distinction between the wake and sleep forms in this report preclude firm conclusions.

Precipitating factors can include anxiety related to current life events, tasks requiring high levels of performance, and repetitive tasks with short deadlines. The use of cigarettes or caffeine in the hours before sleep also can contribute to the occurrence of sleep related bruxism (probably due to the increased arousals and sleep instability).

The role of dental morphologic "defects" (occlusal interferences) remains controversial in the etiology of sleep related bruxism. Tooth contacts do not usually set in motion a bruxism episode; they are usually late in the series of events occurring during sleep related bruxism/tooth grinding. Hence, the causality link between tooth contact and sleep related bruxism is not supported by the temporal sequence.

Familial Patterns

Sleep related bruxism tends to occur in families; approximately 20% to 50% of affected individuals have at least one direct family member with a history of tooth grinding, and childhood sleep related bruxism appears to persist into adulthood in two thirds of reported cases. However, no genetic variants or genetic inheritance patterns so far have been associated with sleep related bruxism.

Onset, Course, and Complications

The onset of sleep related bruxism may occur during childhood, adolescence, or adulthood. It is difficult to establish the time of onset with precision because it is mainly based on the awareness of the individual or his/her family members who report the disorder.

Sleep related bruxism in childhood has been reported by parents to begin as soon as both upper and lower teeth have erupted. Secondary sleep related bruxism may occur at any age, but is more common in younger and middle-aged adults.

Even without a tooth grinding history or complaints, RMMA may be observed in most normal sleepers (on average, one episode per hour of sleep) across the life span. However, in individuals with sleep related bruxism, jaw-muscle contractions are more frequent and more intense. This may explain the secondary tooth damage and the occurrence of pain and other symptoms.

The night-to-night variability in episodes of audible tooth grinding sounds is large (greater than 50% coefficient of variation). In-laboratory polysomnographic recordings indicate that the corresponding variability in frequency of RMMA is smaller (approximately 25%), although ambulatory recording has suggested somewhat higher RMMA variability. First-night effect on RMMA index is minimal.

Dental damage and abnormal tooth wear are the most frequent signs of the disorder. However, they are not a direct proof of current sleep related bruxism and many contributing factors have to be ruled out (e.g., type of diet in the occurrence of abnormal tooth wear). Diagnostic discriminative strength of these dental findings is weak; severity of wear cannot account for the index (i.e., frequency of RMMA). Sleep related bruxism could lead to temporomandibular joint disorders (e.g., pain, joint sound [click], or jaw movement limitations), although recent evidence does not support this association. Transient morning orofacial pain, including temporal headaches, is not uncommon, as described above. Hypertrophy of the masseter and temporalis muscles can occur, but the diagnostic specificity of this finding for sleep related bruxism is also weak.

The natural course of this sleep disorder is usually benign. Many individuals with sleep related bruxism remain asymptomatic for most of their lives. Others can experience associated symptoms (i.e., pain) that may interfere with their quality of life and/or sleep and may require treatments. Further diagnostic investigations and assessment are recommended if sleep related bruxism is associated with other more severe sleep or medical disorders (e.g., SRBD, RBD, epilepsy).

Developmental Issues

Sleep related bruxism is frequently reported in childhood but decreases with age. However, some individuals may experience it every night for most of their lives.

Conceptualizations of sleep related bruxism in children vary. Some consider this a physiological oral parafunction while teeth are erupting or exfoliating, whereas others view this as a sleep disorder with many associated signs and symptoms. Sleep related bruxism, especially in children, has been associated with attention deficit hyperactivity disorder, parasomnias, SRBD, snoring, and many psychological and medical conditions.

In the elderly, sleep related bruxism has been observed in association with movement disorders (e.g., Parkinson disease or oral tardive dyskinesia persisting during sleep), RBD, and dementia.

Pathology and Pathophysiology

The majority of RMMA episodes during sleep (up to 80%) occur in association with sleep arousals. Sleep related bruxism episodes typically follow a clear arousal sequence, starting with increased sympathetic-cardiac activity and fast electroencephalographic (EEG) waves in the minutes to seconds preceding the onset of an RMMA episode. The jaw muscle contractions are then followed by, or are concomitant with, an increase in blood pressure and ventilation. RMMA episodes sometimes conclude with swallowing. Other causes of sleep bruxism onset are unknown, although potential candidates include airway resistance and oropharyngeal dryness.

In the majority of individuals with sleep related bruxism, the frequency of sleep arousals is within the normal range. However, they may have an exaggerated responsiveness to ongoing sleep arousals or an increased magnitude of arousal. Individuals with sleep related bruxism show more CAP phase A3 (as described by the scoring and analysis of cyclic alternating pattern (CAP) during sleep) than controls, an expression of increased arousal pressure and increased sleep instability. This increased sleep instability seems to be the "permissive window" for occurrence of RMMA during sleep.

Objective Findings

Polysomnographic (PSG) monitoring of individuals with sleep related bruxism demonstrates increased masseter and temporalis muscle activity during sleep, along with grinding sounds. RMMA episodes can occur during all sleep stages, but are most common in sleep stages N1 and N2 (more than 80% of episodes), whereas fewer than 10% of RMMA episodes occur during REM sleep. However, in some individuals, sleep related bruxism occurs predominantly in REM sleep.

As described above, the majority of sleep related bruxism episodes are temporally associated with sleep arousal and are preceded by signs of autonomic/cardiac activation (e.g., increased heart rate and blood pressure).

Three subtypes of the EMG pattern of sleep related bruxism have been described: phasic activity at 1 Hz frequency with EMG bursts lasting 0.25 to 2 seconds; sustained tonic activity lasting longer than 2 seconds; or a mixed pattern. An episode begins after at least a three-second interval with no muscle activity.

Polysomnography is not usually performed in otherwise healthy individuals with sleep related bruxism in routine clinical settings. However, PSG may be indicated to demonstrate the disorder and to rule out associated respiratory disturbances, gastroesophageal reflux, RBD, night terrors, faciomandibular myoclonus, or epilepsy. The sensitivity of polysomnographic study in detecting sleep related bruxism in severe cases is moderate to high; in milder cases, however, it may be low due to the night-to-night variability in RMMA and tooth grinding.

Ambulatory home monitoring may be used for screening, diagnosis, and treatment outcome assessment by studying the individual in his/her usual environment, but it is characterized by lower diagnostic specificity due to the absence of audiovisual recordings (i.e., 20% overestimation in RMMA frequency is expected due to poor capacity to exclude concomitant nonspecific activities).

To record and score sleep related bruxism activity (i.e., RMMA), there must be a minimum of one masseter muscle monitor, ideally with audiovisual recording, to associate muscular activity with grinding sound production. Video monitoring helps distinguish bruxism from other orofacial and masticatory movements that normally occur during sleep (e.g., swallowing, coughing) and from specific movement disorders (RBD, epilepsy and tooth tapping, oromandibular myoclonus).

For the best level of diagnostic specificity and sensitivity, bilateral masseter and temporalis muscle EMG recordings, referenced to ear, mastoid, or zygomatic bone, are advisable.

Differential Diagnosis

The disorder seldom poses diagnostic problems. Evaluation for temporomandibular disorders and damage to dentition is indicated.

Sleep related bruxism needs to be differentiated from other faciomandibular activities occurring during sleep, such as *faciomandibular myoclonus*, *SRBD, RBD*, *abnormal swallowing*, *gastro-esophageal reflux*, *night terrors*, *confusional arousals*, *dyskinetic jaw movements persisting in sleep (dystonia, tremor, chorea, dyskinesia)*, and, rarely, *sleep related epilepsy*.

Oromandibular or faciomandibular myoclonus has been observed in approximately 10% of individuals with severe sleep related bruxism, but it can also occur in individuals without abnormally increased RMMA events. As opposed to sleep related bruxism, faciomandibular myoclonus consists of EMG bursts of brief duration (less than 250 milliseconds in length) in the facial muscles; these can occur either as isolated bursts or as a cluster of regularly or irregularly occurring brief bursts. A high index of oromandibular myoclonus in sleep has been observed in idiopathic RBD patients.

Rhythmic jaw movements also have been observed in association with *partial complex or generalized seizure disorders*. Epilepsy needs to be considered in the differential diagnosis, although the presentation of epilepsy as relatively isolated sleep related bruxism is very rare.

Unresolved Issues and Further Directions

An expert bruxism international group has proposed a diagnostic grading system of "possible," "probable," and "definite" for both sleep and awake bruxism. Such a clinical tool will help to discriminate sleep bruxism from awake bruxism, although further validation is required for clinical and research purposes in all relevant dental and medical domains. In summary, this group suggests that a rating of: (1) "possible" is given if based on self-report, by means of questionnaires, and/or the anamnestic part of a clinical examination; (2) "probable" sleep or awake bruxism is given if based on self-report and supportive physical findings; (3) "definite" sleep bruxism if based on self-report, physical findings, and a polysomnographic recording, preferably with audiovisual recordings.

The clinical relevance of sleep related bruxism in cases of comorbidity with other medical problems such as snoring, sleep related breathing disorder, RBD, attention deficit hyperactivity disorder, headache, and orofacial pain needs to be assessed in order to distinguish primary benign forms of sleep related bruxism from those that represent an epiphenomenon of other more severe sleep and medical disorders.

Sleep related bruxism may be concomitant to breathing disorders, including any level of severity of OSA; further research is in progress to assess the specificity and validity of this association.

There is currently no evidence supporting the possibility that patients with sleep related bruxism, in its primary form, are at increased risk of neurological disorders; such a risk factor assessment needs long- term study before any conclusion can be drawn.

Investigation of genetic associations to sleep related bruxism require large sample sizes, using valid tools to assess the specificity of RMMA versus other oromandibular activities and to discriminate gene candidates specific for bruxism from those related to its comorbidities such as stress or other related triggers of RMMA.

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Sleep Related Rhythmic Movement Disorder

ICD-9-CM code: 327.59 ICD-10-CM code: G47.69

Alternate Names

Body rocking, head banging, head rolling, body rolling, jactatio capitis nocturna, jactatio corporis nocturna, rhythmie du sommeil.

Diagnostic Criteria

Criteria A-D must be met

A. The patient exhibits repetitive, stereotyped, and rhythmic motor behaviors involving large muscle groups.
B. The movements are predominantly sleep related, occurring near nap or bedtime, or when the individual appears drowsy or asleep.
C. The behaviors result in a significant complaint as manifest by at least one of the following:[1]
    1. Interference with normal sleep.
    2. Significant impairment in daytime function.
    3. Self-inflicted bodily injury or likelihood of injury if preventive measures are not used.
D. The rhythmic movements are not better explained by another movement disorder or epilepsy.

Notes

1. When there are no clinical consequences of the rhythmic movements, the rhythmic movements are simply noted but the term rhythmic movement disorder is not employed.

Essential Features

Sleep related rhythmic movement disorder (RMD) is characterized by repetitive, stereotyped, and rhythmic motor behaviors (not tremors) that occur predominantly during drowsiness or sleep and involve large muscle groups. The occurrence of significant clinical consequences differentiates RMD from developmentally normal sleep related movements.

Typically seen in infants and children, but also in adults, RMD comprises several subtypes. Body rocking may involve the entire body, with the individual on hands and knees, or it may be limited to the torso, with the individual sitting. Head banging often occurs with the person prone, repeatedly lifting the head or entire upper torso, and forcibly banging the head back down into the pillow or mattress. Alternately, the individual

may sit with the back of the head against the headboard or wall, repeatedly banging the occiput. Combining head banging and body rocking, they may rock on hands and knees, banging the vertex or frontal region of the head into the headboard or wall. Head rolling consists of side-to-side head movements, usually with the child (or adult) in the supine position. Less common rhythmic movement forms include body rolling, leg banging, or leg rolling. Rhythmic humming or inarticulate sounds often accompany the body, head, or limb movements and may be quite loud.

Episodes often occur near sleep onset, although they also may occur at any time during the night and even during quiet wakeful activities, such as listening to music or traveling in vehicles. The movement frequency can vary, but the rate is usually between 0.5 per second and two per second. Duration of the individual movement clusters also varies but generally is less than 15 minutes. Cessation of movements may occur following environmental disturbance or being spoken to. Children who have sufficient language development to be asked about event recall in the morning are typically amnestic for the episodes. Rarely, adults will report a volitional component.

Sleep related rhythmic movements are common in normal infants and children. Without evidence for significant consequences, the movements alone should not be considered a disorder. Sleep related rhythmic movements should be considered a disorder only if the behaviors significantly interfere with normal sleep, cause significant impairment in daytime function, or result in self-inflicted bodily injury (or would result in injury if preventive measures are not used).

Associated Features

The vast majority of infants and children with sleep related rhythmic movements are otherwise developmentally and intellectually normal, as are most adolescents and adults.

Clinical and Pathophysiological Subtypes

Body Rocking: The whole body is rocked while on the hands and knees.

Head Banging: The head is forcibly moved, striking an object.

Head Rolling: The head is moved laterally, typically while in a supine position.

Other: Includes body rolling, leg rolling, and leg banging.

Combined: Involves two or more of the individual types.

Demographics

At nine months of age, 59% of all infants have been reported to exhibit one or more of the following sleep related rhythmic movements: body rocking (43%), head banging (22%), or head rolling (24%). At 18 months, the overall prevalence has been reported to decline to 33%, and by five years, to only 5%. Most pediatric studies have found no sex difference.

Over 50 cases of RMD have been reported in adolescents and adults, with a male preponderance found in adults.

Predisposing and Precipitating Factors

The soothing effect of vestibular stimulation has been proposed as the initiating factor in infants and toddlers. Environmental stress and lack of environmental stimulation have also been proposed as factors. One study found higher anxiety scores in children with body rocking than in controls. Self-stimulation has been suggested as a factor, particularly in intellectually disabled, autistic, and emotionally disturbed children. Rhythmic movements have been postulated to be a calming technique employed by children to combat insomnia.

Rhythmic movements have been reported in association with RLS, OSA, narcolepsy, RBD, and ADHD. Rhythmic movements may be used as a conscious strategy to relieve the urge to move or the uncomfortable sensations associated with RLS. OSA-associated RMD often improves with positive airway pressure. Individuals with narcolepsy may initiate rhythmic movements to terminate episodes of sleep paralysis.

In older children or adults, stereotypic movements may be associated with intellectual disability or autism spectrum disorder. However, in most of these cases, the movements are not predominantly sleep related, and an additional diagnosis of RMD is not indicated.

Familial Patterns

A familial pattern has been reported rarely, as has occurrence in identical twins.

Onset, Course, and Complications

The onset of sleep related rhythmic movements is typically in early childhood. Body rocking has a mean age of onset of six months, head banging of nine months, and head rolling of ten months. The condition may rarely present at an older age following central nervous system trauma. Sleep related rhythmic movements commonly resolve in the second or third year of life. Persistence at five years of age occurs in about 5% of children. Sleep related movements rarely continue into adolescence and adulthood.

Worsening or spontaneous onset in adults is very rare. In some adult cases the chief concern is disturbance of the bed partner's sleep. Most adolescents and adults have one form of RMD, although some have two or more.

Head banging is the most disturbing form of the problem. Typical cases in infants and toddlers pose little risk of serious injury. Vigorous rhythmic movements can produce loud noises when the patient hits the bed frame or when the bed bangs against the wall or floor. The noises can be very disturbing to other family members. Parental concern is common, and psychosocial consequences in the older individual can be distressing. It is important to discuss appropriate safety precautions with the patient's caretakers. Under extraordinary circumstances, particularly in the developmentally disabled, injury to soft tissues or bone has been reported.

Developmental Issues

Because age-related factors are a critical dimension for RMD, developmental issues are discussed under Essential Features and other sections.

Pathology and Pathophysiology

In infants and young children, rhythmic movements have been hypothesized to promote motor development by stimulation of the vestibular system. More recently, the role of inhibitory control on the central motor pattern generator has been suggested as a physiologic mechanism to explain both pediatric and adult forms of sleep related rhythmic movements.

Objective Findings

Polysomnographic scoring rules for RMD are defined in the AASM Manual for the Scoring of Sleep and Associated Events. Video-polysomnographic studies have shown rhythmic movements to occur most often in association with stages N1 and N2 sleep; 46% occur while falling asleep or during NREM sleep; 30% during both NREM and REM sleep; and 24% only during REM sleep. The exclusively REM-related rhythmic movements occur more frequently in adults. Although an epileptic etiology has been reported in one individual, most EEG studies have shown normal activity between episodes of rhythmic behavior.

Differential Diagnosis

RMD must be distinguished from other repetitive movements involving restricted small muscle groups, such as *sleep related bruxism*, *thumb sucking*, and *rhythmic sucking* of a pacifier or the lips, as well as other specifically defined rhythmic movements of sleep, such as *hypnagogic foot tremor*.

In adults, RMD can be misdiagnosed as *RBD* or be comorbid with RBD. Video polysomnography is particularly helpful in these cases. Rhythmic movements may occur as a conscious or unconscious strategy to relieve *RLS* symptoms. If the rhythmic movements are clearly in response to RLS sensations, then a separate diagnosis of RMD is not needed. However, RMD may be diagnosed if RMD criteria are met and RLS does not adequately explain the presence or extent of rhythmic movements.

Children with autism spectrum disorder often exhibit repetitive behaviors, but these movements typically occur during wakefulness and are not predominantly sleep related. *Stereotypic movement disorder* is a Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnosis that is typically seen with intellectual disability and is not predominantly sleep related. In children with autism spectrum disorder or intellectual disability, an additional diagnosis of RMD should be made only if the movements are predominantly sleep related. *Akathisia* is seen as a complication of neuroleptic medication and is not predominantly sleep related.

Autoerotic or masturbatory behaviors may involve body rocking or other repetitive body movements, but the primary focus is genital stimulation as is evident by direct genital contact. Rarely, RMD needs to be differentiated from *epilepsy*, *tic disorders*, or *involuntary movements* associated with other neurological conditions.

Unresolved Issues and Further Directions

There is controversy about the classification of hypnagogic foot tremor as a separate entity or as a subtype of sleep related rhythmic movements. Many aspects of sleep related rhythmic movements deserve further study, including the relationship of the typical form seen in otherwise normal infants and young children to the rhythmic movements seen in children with intellectual disability and autism spectrum disorder. The pathophysiology of persistent RMD is poorly understood, as is the association with other sleep disorders in adults.

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Benign Sleep Myoclonus of Infancy

ICD-9-CM code: 327.59 ICD-10-CM code: G47.69

Alternate Names

Benign neonatal sleep myoclonus.

Diagnostic Criteria

Criteria A-E must be met

A. Observation of repetitive myoclonic jerks that involve the limbs, trunk, or whole body.
B. The movements occur in early infancy, typically from birth to six months of age.
C. The movements occur only during sleep.
D. The movements stop abruptly and consistently when the infant is aroused.
E. The disorder is not better explained by another sleep disorder, medical or neurological disorder, or medication use.

Essential Features

Benign sleep myoclonus of infancy (BSMI) is characterized by repetitive myoclonic jerks that occur during sleep in neonates and infants. Although BSMI is benign and relatively rare, it is included in the sleep related movement disorders section because it is commonly confused with epilepsy. However, unlike the jerks of myoclonic seizures and myoclonic encephalopathy, the jerks of BSMI occur exclusively during sleep. The jerks are often bilateral and massive, typically involving large muscle groups. The movements can occur in the whole body or exclusively in the limbs, the trunk, or rarely, the face.

Associated Features

Not applicable or known.

Clinical and Pathophysiological Subtypes

Most infants with BSMI are neurologically normal, born to mothers with no history of illicit drug use. However, BSMI has been described in more than half of infants with neonatal opioid withdrawal syndrome, suggesting a subtype with this specific etiology. It must be stressed, however, that some cases of neonatal abstinence syndrome do not follow a benign clinical course. Whether such cases should be included with those of BSMI is an unresolved matter.

Demographics

The prevalence is unknown. The incidence has been estimated at 3.7 per 10,000 live births. More than 200 cases have been described in the literature. Males are affected more than females by a ratio of about 2:1. The typical age range is birth to six months of age.

Predisposing and Precipitating Factors

Predisposing factors have not been delineated. Rocking or repetitive noises may precipitate individual episodes of BSMI.

Familial Patterns

Familial occurrence has been described.

Onset, Course, and Complications

Onset is usually noted between birth and one month of age in a neurologically normal infant. The course is self-limited and benign. The disorder may be present for only a few days or may last for several months. Maximum expression is typically between 15 and 35 days of age. BSMI resolves by three months of age in 64% of affected infants, by six months in 95%, and by 12 months in 97% with persistence rarely into the second year of life or later. There are no known complications. Long-term follow-up in a limited number of children has shown normal psychomotor development and normal cognitive function at five to 10 years of age. There is no evidence for an increased risk of seizures.

Developmental Issues

Because age-related factors are a critical dimension for BSMI, developmental issues are discussed throughout this section.

Pathology and Pathophysiology

The presence of a generator in the cervical spinal cord that is not adequately inhibited due to immature myelination of descending pathways has been hypothesized.

Objective Findings

Video-polysomnographic EEG and EMG monitoring has demonstrated paroxysmal muscle activity, without ictal or interictal EEG abnormalities. BSMI occurs predominantly during quiet sleep but also may be present during active sleep. The muscle jerks are usually seen in clusters of four or five jerks per second, each jerk lasting 40 to 300 milliseconds. BSMI clusters typically repeat in irregular series for one to 15 minutes, but, in some cases, the clusters may recur for up to 60 minutes or longer and

be mistaken for status epilepticus. One study showed 30% of the jerks to involve the whole body, 20% to involve the abdominal or proximal muscles, and 50% to involve only the arms or the legs. The arms are usually more involved than the legs. Activity is symmetrical in over 90% of cases but can be lateralized. The myoclonus is not associated with arousals, awakenings, or sleep stage transitions.

Spontaneous or provoked awakening of the infant leads to prompt, abrupt, and consistent cessation of the movements. Gentle rocking of the infant or the infant's crib has been shown to provoke the myoclonus. This may be a useful maneuver during EEG monitoring when differentiation from seizures is of concern. In contrast to jitteriness and other nonepileptic etiologies, BSMI will often increase rather than be suppressed by gentle restraint. Neuroimaging studies are normal.

Differential Diagnosis

BSMI should be distinguished from *myoclonic seizures*; misdiagnosis may lead to unnecessary diagnostic testing or medication use. The absence of episodes while awake in infants with BSMI is the single most helpful clinical feature. In addition, BSMI will stop abruptly and consistently when the infant is aroused. Neonatal seizures are often seen in the context of perinatal disorders such as hypoxic-ischemic encephalopathy, infection, or metabolic abnormalities, whereas BSMI is typically present in neurologically normal infants. *Infantile spasms (West syndrome)* are most often seen after the first month of life but sometimes occur earlier. Infantile spasms are usually manifest by sudden head flexion with arm extension and lower extremity flexion. They are usually associated with a hypsarrhythmic EEG pattern. *Pyridoxine-dependency seizures* are responsive to treatment with vitamin B_6. In cases that are difficult to differentiate, an EEG obtained during sleep will show normal patterns when BSMI is elicited by gentle rocking. Anticonvulsant medications are ineffective and unnecessary in BSMI.

BSMI also should be distinguished from other disorders that occur during wakefulness, including *myoclonic encephalopathies*, *hyperekplexia (startle disease)*, *drug withdrawal*, and *jitteriness*. Benign myoclonus of early infancy usually occurs after the third month of life and only occurs during wakefulness.

PLMD can occur in infants but typically has a distinctly different duration and frequency. The muscle activity is of longer duration (0.5 to 10 seconds) and recurs at a more regular and longer interval (typically 20 to 40 seconds). PLMD can be associated with EEG arousals, whereas BSMI is not. BSMI is more often seen in the arms than the legs, whereas PLMD predominantly occurs in the lower limbs.

Phasic-REM muscle activity typically involves smaller muscle groups and can be linked to observable eye movements. *Sleep starts* occur at the wake-sleep transition and typically are not repetitive. *Propriospinal myoclonus at sleep onset* is a rare disorder that has not been reported in children and is characterized by jerks involving the abdominal and truncal muscles at the transition from wakefulness to sleep. *Fragmentary myoclonus* has been described in adults and is primarily a nonspecific EMG finding with little or no visible movement.

Unresolved Issues and Further Directions

The prevalence, incidence, and pathophysiology of BSMI warrant further study.

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Propriospinal Myoclonus at Sleep Onset

ICD-9-CM code: 327.59 ICD-10-CM code: G47.69

Alternate Names

Spinal myoclonus, plurisegmental myoclonus, intersegmental myoclonus, axial myoclonus.

Diagnostic Criteria

Criteria A-E must be met

A. The patient complains of sudden jerks, mainly of the abdomen, trunk, and neck.
B. The jerks appear during relaxed wakefulness and drowsiness, as the patient attempts to fall asleep.
C. The jerks disappear upon mental activation and with onset of a stable sleep stage.
D. The jerks result in difficulty initiating sleep.
E. The disorder is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

Notes

1. Although there is no current definitive evidence that propriospinal myoclonus confined to sleep onset is associated with significant structural lesions of the spinal cord, propriospinal myoclonus that is persistent during the day has been linked to structural spinal cord pathology in 16% to 20% of cases.

Essential Features

Propriospinal myoclonus at sleep onset (PSM) consists of sudden myoclonic jerks occurring in the transition from wakefulness to sleep and, rarely, during intrasleep wakefulness and upon awakening in the morning. The jerks arise mainly in the axial muscles and spread rostrally and caudally according to propriospinal propagation. The jerks may be of variable intensity; they are isolated, recurring in quasi-periodic fashion for variable durations, or may be repeated in brief clusters of a few movements, separated by longer intervals. Jerks involve the abdominal and truncal muscles first and are then propagated to proximal muscles of the limbs and the neck. The pattern of movement is usually flexor but may be an extension of the trunk. Vocalization rarely occurs. The jerks are most often spontaneous but, in some cases, can be evoked by external stimulations. The jerks appear to be related to the recumbent position and a state of

relaxed wakefulness, particularly when the patient tries to fall asleep. Any mental activation makes the jerks disappear. The jerks eventually disappear at sleep onset and remain absent throughout all stages of sleep, even though they sometimes reappear during intrasleep wakefulness.

Associated Features

PSM often is associated with severe sleep-onset insomnia due to the inability of the patient to fall asleep because of the recurrent disturbing muscular activity.

Clinical and Pathophysiological Subtypes

PSM may be considered a variant of the more generally described propriospinal myoclonus seen during the daytime. In daytime PSM, myoclonic jerks involve the thoracoabdominal/paraspinal or cervical muscles and spread caudally or rostrally to the other myotomes. The jerks are provoked or worsened by the recumbent position and cannot be voluntarily suppressed. They are often preceded by premonitory sensations, are stable over time, and respond unpredictably to drug treatment. The frequent presleep worsening of daytime PSM (around 50% of the cases) suggests that patients with PSM may have a milder or variant form of a single clinical and neurophysiologic entity.

Demographics

Epidemiologic data are lacking. PSM is probably a rare condition. A higher prevalence in men is reported. The disorder affects adults and has not been reported in children.

Predisposing and Precipitating Factors

Not applicable or known.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

PSM arises in adulthood and is usually a chronic, unremitting condition. Patients may develop a fear of falling asleep, anxiety, and depression. Intense myoclonic jerks may cause injury to the patient or the bed partner.

Pathology and Pathophysiology

The pathophysiology of PSM is unknown. PSM is thought to originate from a focal spinal pattern generator, set into motion by supraspinal dysfacilitatory influences typical of the state of relaxed wakefulness and drowsiness. PSM is presumed to propagate up and down the spinal cord via slowly conducting, long propriospinal

(intersegmental) pathways. A focal spinal generator thus is able to recruit muscles from multiple segments.

Objective Findings

Polysomnography demonstrates brief myoclonic EMG bursts recurring nonperiodically with alpha activity present on the EEG and, in particular, when alpha activity spreads from the posterior to the anterior brain regions. Epileptic EEG discharges are not observed in PSM. Jerks disappear either with EEG desynchronization, due to mental activation, or with appearance of sleep spindles and K-complexes. Jerks remain absent throughout sleep but may occasionally reappear upon awakening and during intrasleep wakefulness. Polysomnography with extended EMG recording demonstrates that the jerks arise first in spinal innervated muscles and then propagate to more caudal and rostral muscles according to a propriospinal pattern of propagation. Detailed analysis of the jerks shows that the EMG activity originates in muscles innervated by thoracic or cervical spinal segments (sternocleidomastoid, paraspinalis, rectus abdominis) and then spreads to more rostrally and caudally innervated muscles at a slow velocity (2 to 16 milliseconds; around 5 milliseconds on average). Back-averaging of the EEG does not show any jerk-locked cortical activity. MRI of the brain is normal. In a recent review of PSM, only one patient with exacerbation at sleep onset had a hypersignal at T10-T11 and a nonspecific medullary cone lesion. The remaining patients had no signs on spinal cord MRI at sleep onset.

MRI of the spine is usually normal but demonstrates a focal lesion in around 20% of the cases. The causal relationship of PSM with these spinal lesions is unclear, although magnetic resonance diffusion tensor imaging with fiber tracking may demonstrate spinal tract disorganization.

Differential Diagnosis

PSM shows features similar to those of the syndrome of *intensified sleep starts*. However, sleep starts (hypnic jerks) usually appear during the transition between wakefulness and sleep and during light NREM sleep, whereas PSM may sometimes be present during relaxed wakefulness. Unlike PSM, sleep starts (hypnic jerks) sometimes affect only one or a few body segments; propriospinal propagation is not present in neurophysiological studies of sleep starts. *Phasic REM twitches*, which are a normal phenomenon during REM sleep, involve the distal muscles of the hands and face, often without displacement of the body segment. *Fragmentary myoclonus* resembles physiological hypnic myoclonus, but in an enhanced form, and persists throughout all stages of NREM and REM sleep. Both physiological hypnic myoclonus and fragmentary myoclonus are EMG findings not associated with overt muscular activity and

do not involve muscles acting across large joints. *Epileptic myoclonus* is not confined to relaxed wakefulness and may be associated with epileptic discharges on the EEG. *PLMS* are longer in duration, involve mainly the lower limbs, and usually spare truncal and abdominal muscles. PLMs may begin during presleep wakefulness but generally occur during NREM sleep. Some patients with *RLS* may have prominent PLMs in wakefulness while sitting or lying down. However, prominent leg discomfort is usually present in these patients. Occasionally PSM may be present in RLS/PLMS patients in wake before sleep, but the EMG morphology is different. In addition, when myoclonic jerks involving leg muscles appear, the PSM disappears. *Psychogenic myoclonus* may simulate PSM but the muscle recruitment pattern, the spread velocity, and the recording of cortical premovement activity observed before voluntary movements may be useful to differentiate the two types of jerks.

Unresolved Issues and Further Directions

Future studies are needed to better define the distinctions between PSM and related conditions such as sleep starts (hypnic jerks) and, in particular, the syndrome of intensified sleep starts. Also, neuroimaging and possibly postmortem studies may detect the neural structures responsible for the initiation of the myoclonic jerks.

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Sleep Related Movement Disorder Due to a Medical Disorder

ICD-9-CM code: 327.59 ICD-10-CM code: G47.69

Diagnostic Criteria

Criteria A-C must be met

A. The patient manifests sleep related movements that disturb sleep or its onset.
B. The movement disorder occurs as a consequence of a significant underlying medical or neurological condition.
C. The symptoms are not better explained by another sleep related movement disorder, other untreated sleep disorder, substance use, or mental disorder.

This diagnosis is intended for sleep related movement disorders due to an underlying medical or neurologic condition that do not meet criteria for another specific movement disorder. Many neurological conditions may be associated with movement abnormalities that are evident in wake and sleep. In some cases, the nocturnal manifestations of the movement abnormalities may be apparent before establishment of a firm neurological diagnosis. Thus, in some cases, "sleep related movement disorder due to a medical disorder" is a temporary diagnosis, given when a sleep diagnosis is required before the underlying medical or neurological condition can be fully diagnosed. Once the presence of a medical or neurological condition is clearly established, that becomes the sole diagnosis unless the sleep complaint is the focus of independent clinical attention.

When a movement disorder that is listed elsewhere in the sleep related movement disorder section of the International Classification of Sleep Disorders, 3rd Edition is caused or exacerbated by a medical or neurological condition (e.g., restless legs syndrome), it is preferred that the more specific diagnosis (e.g., RLS) be used rather than "sleep related movement due to a medical disorder," with annotation of the relationship to the medical or neurological disorder.

Sleep Related Movement Disorder Due to a Medication or Substance

ICD-9-CM code: 292.85 (drug-induced); 291.82 (alcohol-induced)
ICD-10-CM code: F11-F19 (see table in Appendix B for detailed coding instructions)

Diagnostic Criteria

Criteria A-C must be met

A. The patient manifests sleep related movements that disturb sleep or its onset.
B. The movement disorder occurs as a consequence of current medication or substance use or withdrawal from a wake-promoting medication or substance.
C. The symptoms are not better explained by another sleep related movement disorder, other untreated sleep disorder, or medical, neurological, or mental disorder.

This diagnosis is intended for sleep related movement disorders due to a medication or substance (toxin or other bioactive substance) that do not meet criteria for another specific movement disorder. Many substances may be associated with movement abnormalities that are evident in wake and sleep. To the extent that the movement abnormality is an expected complication of the substance(s) involved (e.g., tardive dyskinesia or akathisia associated with neuroleptic usage), this diagnosis is unnecessary unless the sleep related aspects of the movement abnormality or its sequelae, are the focus of independent clinical attention.

When a movement disorder that is listed elsewhere in the sleep related movement disorder section of the International Classification of Sleep Disorders, 3rd Edition is caused or exacerbated by drugs or substances (e.g., restless legs syndrome), it is preferred that the more specific diagnosis (e.g., RLS) be used rather than "Sleep related movement disorder due to a medication or substance," with annotation of the relationship to drug or substance.

Sleep Related Movement Disorder, Unspecified

ICD-9-CM code: 327.59 ICD-10-CM code: G47.69

This diagnosis is assigned when patients have a sleep related movement disorder that cannot be classified elsewhere or is suspected to be associated with an underlying psychiatric condition. In some cases, "sleep related movement disorder, unspecified" is a temporary diagnosis prior to establishment of an underlying psychiatric condition that may explain the sleep related movement (e.g., movements associated with posttraumatic stress disorder nightmares prior to firm establishment of the psychiatric diagnosis). Once the psychiatric diagnosis is established, that becomes the sole diagnosis unless the sleep complaint is the focus of independent clinical attention.

Isolated Symptoms and Normal Variants

Excessive Fragmentary Myoclonus

Excessive fragmentary myoclonus (EFM) is a largely incidental polysomnographic finding on EMG, characterized by small movements of the corners of the mouth, fingers, or toes, or by no visible movement at all. The finding is associated with no known clinical consequence. Large limb movements across large joint spaces are not characteristic of EFM and, if present, should exclude the diagnosis of EFM. Scoring of EFM is described in the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events. The condition is a NREM phenomenon and the movements resemble the phasic twitches seen in normal REM sleep except that they are more universally dispersed throughout a sleep epoch than phasic REM twitches, which are generally clustered within small groups in a sleep epoch. Its importance lies in that it is within the differential diagnosis of other sleep related movement disorders.

Patients usually are not aware of the twitch-like movements. Patients may have other coexistent sleep disorders, but EFM does not appear to contribute to the symptoms of these sleep disorders.

EFM, a NREM phenomenon, is less common than phasic REM twitches, which occur in REM sleep in normal individuals without sleep complaints. Most cases have been reported in adults. EFM is predominantly found in males. A recent study found EFM in 100% of 62 patients with a variety of sleep disorders, bringing into question the specificity of EFM.

Numerous causes of chronic sleep fragmentation may be associated with EFM. The condition has been described with obstructive sleep apnea and primary central sleep apnea, sleep related hypoxemic/hypoventilation syndromes, narcolepsy, PLMD, and various causes of insomnia. In apneic patients, the twitching intensifies during periods of increased hypoxemia. One report has found excessive fragmentary myoclonus to be very common in children with Niemann-Pick disease, type C. No specific precipitating factors have been reported. The contribution of EFM to the symptomatology of any of these disorders is unknown.

The course is not well studied but appears to be benign and non-progressive. The disorder may be the sole abnormality in some cases of excessive daytime sleepiness, but causality is questionable. No other serious consequences of the disorder have been described when it occurs in isolation.

In some cases, EFM is present in normal individuals. Its relatively benign course suggests that it is not associated with a neurodegenerative process. In most reported cases, there have been associated sleep abnormalities and sleep disruption, suggesting that EFM may be due to disruptions of normal motor-control mechanisms during sleep. Whether there is a genetic or other basis predisposing individuals to develop the condition is unknown. In any case, it would appear to result from intensification of an otherwise normal motor phenomenon. The predominant topographic distribution of EFM in distal and facial muscles suggests that cortical motor centers participate in its generation.

EFM is detected as isolated, very brief (usually 75 to 150 milliseconds), asymmetrical, asynchronous EMG potentials in various muscles of the face, trunk, arms, and legs. The amplitude varies from approximately 50 to several hundred microvolts; the taller amplitudes are often associated with visible movement of the fingers, toes, or corners of the mouth, whereas the smaller ones may resemble fasciculation potentials and be without overt movement. Large movements across large joint spaces preclude a diagnosis of EFM. Small twitch-like movements may be observed on video recording. Episodes of these myoclonic potentials typically last from 10 minutes to several hours. They often appear at sleep onset and continue through the NREM sleep stages, including slow wave sleep. The presence of EFM in REM is difficult to determine because it is superimposed on the normal phasic clusters of physiological phasic REM twitches. EFM is electromyographically similar to the latter. Occasionally, the EMG activity also persists during EEG periods of wakefulness within the sleep period or is present in drowsiness prior to sleep onset. The EEG usually shows no changes at the time of the movements, although high-amplitude EMG potentials may be associated with a K complex or even with transient EEG arousal. There are no ocular or autonomic accompaniments. It seems possible that, depending on the digitalization rates, digital systems may record less fragmentary myoclonus than earlier paper records. No laboratory tests other than polysomnography (optimally with multiple EMG leads) have been reported to be helpful in assessing EFM.

EFM generally has a maximum burst duration of only 150 milliseconds and does not recur periodically. It can be distinguished from PLMS because PLMS are characterized by a longer burst duration (typically 0.5 to 10 seconds) and a long period between bursts (5-90 seconds). EFM, which occurs in NREM, must also be differentiated from normal physiological *phasic REM twitches*, which have a similar burst duration but are limited to the REM state and tend to occur in clusters within an epoch, as opposed to EFM in which bursts tend not to cluster within a particular epoch. Larger body movements across the large joints are not a feature of excessive fragmentary myoclonus. The presence of such movements suggests other disorders.

Further investigation is necessary to determine whether EFM occurs as a consequence of sleep disruption or whether it is an independent cause of sleep disruption and daytime symptoms in its own right. It must also be determined whether there are any physiological differences that distinguish fragmentary myoclonus seen in many normal individuals from EFM. It is not known whether some additional pathophysiological element is required to increase fragmentary myoclonus into an abnormal range. The current threshold for the diagnosis of EFM should be further investigated because the scoring criteria lack specificity. The apparent strong predominance in males also remains unexplained.

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Hypnagogic Foot Tremor and Alternating Leg Muscle Activation

Hypnagogic foot tremor (HFT) is rhythmic movement of the feet or toes that occurs at the transition between wake and sleep or during light NREM sleep (stages N1 and N2). Alternating leg muscle activation (ALMA) consists of brief activation of the anterior tibialis in one leg in alternation with similar activation in the other leg during sleep or arousals from sleep. HFT may be a relatively common and normal finding. Affected individuals move the feet or the toes rhythmically for seconds to minutes during drowsy wakefulness or lighter stages of sleep. It can be pathologically exaggerated in some patients. ALMA is defined by a polysomnographic pattern with unknown

clinical manifestations, but frequency of muscle activations, length of activations, and occurrence primarily with arousals suggest that ALMA may be similar to HFT or represent an EMG manifestation of some episodes of HFT. The original case series that described ALMA did not link it with movement of the lower extremity, but a subsequent report did. HFT and ALMA are considered together because the relationship between them remains to be clarified, and the similarity in a number of their features suggests they may not be fully independent entities.

Associated features of HFT and ALMA are similar. Most cases of HFT have been reported in persons with other sleep disorders, such as RLS or SRBDs. ALMA has been identified mainly in patients with SRBD or PLMs. Seventy-five percent of patients with ALMA in the original series used antidepressant medication. In that study, patients with ALMA complained of sleepiness, insomnia, or restless of the legs, but only one reported patient had more specific complaints of sudden nocturnal muscle contractions in his legs and a sensation that his legs were vibrating. A separately reported case of a patient with ALMA documented absence of any SRBD, PLMs, or use of antidepressant medication. This patient complained of frequent and easily provoked awakenings, as well as excessive daytime sleepiness. The ALMA and symptoms responded to treatment with pramipexole.

The single series in which HFT was studied found that it occurs in 7.5% of patients in whom a polysomnogram was performed for other reasons. Affected individuals range in age from 14 to 72 years, with a majority in the middle-age range (40 to 65 years). Men and women are equally affected. It is possible that the frequency of these movements may be increased in individuals with disorders such as RLS or SRBD, but it can occur in individuals with otherwise normal sleep. The prevalence of the condition in the general population and its frequency in affected individuals remains uncertain. The initial series reporting ALMA found that it occurs in 1.1% of unselected studies from a sleep disorder center. Patients with ALMA were mostly male (11:5) and ranged in age from 12 to 70 years, with most aged 35 to 55 years (mean age 41 years). Therefore, the age ranges of both conditions are similar, with both males and females affected. These distributions may be due to the incidental discovery of both entities during routine sleep studies for other sleep complaints.

No predisposing factors are known for HFT. The use of antidepressant medication may increase risk for ALMA.

No longitudinal studies have been performed for either entity. In some individuals, HFT is an occasional finding, but others appear to manifest the rhythmic movements

on many nights and over a span of at least months. ALMA showed some tendency to persist between two different recordings in the originally reported series. Because most individuals are unaware of the presence of the HFT movements, and patients with ALMA may have no associated complaint or awareness of the phenomenon, the evolution of HFT and ALMA may be difficult to follow except in the sleep laboratory or with home monitoring. Although usually an incidental and benign finding, HFT may cause sleep disruption and sleep-onset insomnia if sufficiently prolonged or severe.

In HFT, the patient typically reports foot movements (directly experienced or observed by others) that occur at the transition between wake and sleep or during light sleep. On occasion, movement has not been observed but HFT is seen as an incidental finding on sleep study conducted for other indications. Polysomnography demonstrates a pattern of brief, repeated activation of the anterior tibialis in one leg. The minimum frequency is 0.3 Hz; the maximum 4.0 Hz. Multiple leg activations in a single leg occur in a train of at least four movements. EMG recordings of the foot or leg muscles or video recordings of movement may show trains of recurrent 1-Hz to 2-Hz EMG potentials or movements. Typical associated EMG bursts are 300 to 700 milliseconds in duration, and the typical duration of trains is 10 to 15 seconds, although longer bursts and trains have been reported. In morbid conditions, trains may persist much longer. Events are recorded at the transition into sleep and during stages N1 and N2 sleep. Distribution over the night has not been fully investigated. Persistent HFT has been found in about half of the individuals who have had multiple studies. Alternation between legs has not been described, but its potential occurrence is suggested in two published studies of HFT.

In ALMA, polysomnography demonstrates a pattern of brief, repeated activation of the anterior tibialis in one leg alternating with similar activation in the other leg. At a minimum, a single leg muscle activation in one leg is followed sequentially by a similar single activation in the other leg, reactivation in the original leg, and then reactivation in the alternate leg, with some continued alternation beyond this minimal sequence in most instances. The minimum frequency of alternating EMG bursts is 0.5 Hz, and the maximum frequency is 3.0 Hz. The patient may report foot movements (directly experienced or observed by others) that occur at the transition between wake and sleep or during light sleep. As noted above, there is frequently no observation of movement reported but alternating leg muscle activation is recorded as an incidental finding on polysomnography.

ALMA can be demonstrated by polysomnography if the surface EMG is recorded independently from both right and left anterior tibialis muscles. A sequence of ALMA may begin with one to several lengthy activations (one to two seconds) in one or both legs. Some patients show unilateral activity at times. ALMA usually closely precedes or

follows an arousal or awakening and gradually diminishes as sleep returns. However, ALMA can also emerge without arousals from any sleep stage. Proclivity for any specific portion of the nocturnal sleep cycle has not been identified. Leg muscle activations during REM sleep, in comparison to NREM sleep, are often briefer and somewhat less regular. Sequences of ALMA sometimes recur at intervals similar to those of PLMs. Extensor forearm EMG study may suggest alternating muscle activity in the upper extremities, though it is less prominent than activation in the legs. ALMA shows some night-to-night consistency. Repeat studies are likely to show persistent ALMA. The number of sequences recorded, on average, and the timing of ALMA with respect to arousals tends to remain constant.

The specific polysomnographic criteria for HFT during sleep and ALMA are defined in the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events.

Presentation of HFT or ALMA with other concurrent sleep disorders is common.

Because of the similar frequency, duration, and body part involvement of the movements, HFT and ALMA may represent variants of the same disorder. Insufficient scientific evidence has accumulated to make this a certainty. Thus, these entities are listed sequentially but separately.

Of note, some have questioned whether HFT and ALMA might represent a variant of rhythmic movement disorder in which movements are confined to the legs and an older population is affected.

HFT and ALMA should be distinguished from other sleep-onset movements: *PLMD* (especially the polyclonic form), *PSM*, and *sleep related RMD*. Movement disorders that should be distinguished from HFT and ALMA include *dyskinetic movements* of the foot, such as *painful legs and moving toes*; *tremors or rhythmic movements* of other cause (Parkinson disease, clonus); and *neuroleptic-induced akathisia*. None of these conditions involves regular alternation between sides, as seen in ALMA, or an association with the use of antidepressant medication.

Whether HFT should be distinguished from ALMA is not known. Potential differences based on existing reports include the presence of clear movement in HFT as opposed to some uncertainty whether ALMA must involve movement. ALMA, in contrast to HFT, alternates between sides, occurs in any sleep stage, can occur without arousal, and is associated with the use of antidepressants.

High-frequency leg movements (HFLM) also have been described as a repetitive anterior tibialis, polysomnographic activation phenomenon, possibly showing some association with RLS, and with potential overlap with HFT and ALMA. In contrast to HFT, however, HFLM occur in all sleep stages, and are mostly unilateral rather than bilateral. In contrast to ALMA, HFLM are mostly unilateral rather than alternating, and often show sequences that last longer than those reported for ALMA. The reported HFLM may be more common than ALMA, and the possibility exists that ALMA represents a subtype of HFLM in which leg alternation occurs.

The degree to which these movements are quasi-voluntary remains to be determined because some are suppressible. Whether HFT and ALMA are merely alternate forms of the same underlying motor mechanism is also unclear. As reports of these movements have arisen from reviews of sleep center records, nothing is known about their manifestation in the general population. The associations noted may be due to biased sampling caused by a skewing of the population toward those with sleep disorders, especially respiratory disorders. The degree to which HFT and ALMA have clinical significance remains uncertain.

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Sleep Starts (Hypnic Jerks)

Sleep starts, also known as hypnic jerks, are sudden, brief, simultaneous contractions of the body or one or more body segments occurring at sleep onset. Sleep starts (or hypnic jerks) usually consist of a single contraction that often affects the body asymmetrically. The jerks may be either spontaneous or induced by stimuli. The motor activity is often associated with a sensory component, which may be somesthetic, often an impression of falling or less commonly pain or tingling; auditory, such as banging, snapping or crackling noises; or visual, including flashing lights, hypnagogic dreams, or hallucinations. A sharp cry may occur. The patient may not recall a jerk that was noted by a bed partner if the sleep start does not cause awakening. Multiple jerks occasionally occur in succession, usually early in the sleep period. When sleep starts or hypnic jerks are frequent, intense, or repetitive, they may lead to sleep-onset insomnia.

Purely sensory sleep starts are subjective, localized, sensory impressions that occur at sleep onset and are not associated with motor activity. The term "Intensified sleep starts" has been applied to both the motor and purely sensory forms when a complaint of difficulty falling asleep as a result of the starts is present.

A prevalence of 60% to 70% has been reported, but with a highly sporadic occurrence. Sleep starts affect all ages and both sexes.

Excessive caffeine or other stimulant intake, prior intense physical work or exercise, sleep deprivation, and emotional stress can increase the frequency and severity of sleep starts.

Sleep starts are an essentially universal component of the sleep-onset process, although they are often not recalled. Hypnic jerks may occur at any age, as a subjective complaint; however, they are usually encountered in adulthood. The course is usually benign. Intensified sleep starts may lead to avoidance/delay of sleep, a fear of falling asleep and chronic anxiety. As a result, acute and chronic sleep deprivation may occur. Sleep-onset insomnia may result either from repeated awakenings induced by the starts or from anxiety about falling asleep. Injury, such as bruising a foot against a bedstead or kicking a sleeping companion, may occasionally occur.

The physiological mechanisms underlying sleep starts are uncertain. No pathologic finding has been described except for a single case of auditory sleep starts associated with a brainstem lesion. Hypnic jerks are hypothetically caused by sudden descending volleys originating in the brainstem reticular formation activated by the system instability at the transition between wake and sleep. However, the similarity between sleep starts and the startle response has led some to postulate that abnormalities of sensory

processing are primary, with secondary motor manifestations involving the reticulospinal tract. Sleep starts are a prominent symptom in hereditary hyperekplexia, some cases of which are caused by mutations in the glycine receptor. It has also been postulated that sleep starts are a response to hypnagogic imagery.

Polysomnographic monitoring shows that hypnic jerks occur during transitions from wakefulness to sleep, mainly at the beginning of the sleep episode. Superficial EMG recordings of the involved muscles show brief (generally 75-millisecond to 250-millisecond) high-amplitude potentials, either singly or in succession. The EEG typically shows drowsiness or stage N1 sleep patterns, sometimes with a negative-vertex sharp wave occurring at the time of the jerk. Autonomic activation, including tachycardia, tachypnea or irregular breathing, and sudomotor activation may follow an intense jerk. After the jerk, a brief arousal or a return to sustained wakefulness may occur. Physical and neurological examinations and routine laboratory tests are otherwise normal. Although polysomnography is not necessary for diagnosis in most individuals, it may be indicated in occasional cases with complaints of insomnia and frequent movements.

Hypnic jerks must be differentiated from a number of physiological or pathologic movements that occur at sleep onset or during sleep. Physiological *partial hypnic myoclonus* consists of small, isolated contractions of a muscle or part thereof, occurring sporadically in distal muscles and resembling fasciculation potentials. The contractions are particularly evident during stage N1 and REM sleep.

Fragmentary myoclonus consists of profuse, brief, small-amplitude muscle twitches that occur in an asynchronous, symmetrical, and bilateral manner, especially in distal muscles. Fragmentary myoclonus occurs at sleep onset as well as within all sleep stages. Contrary to the massive jerks of the sleep starts or hypnic jerks, the small muscle twitches of physiological partial hypnic myoclonus and of fragmentary myoclonus often represent only an EMG finding and are not associated with overt movements at the joints. *Normal body movements* are complex, with body postural shifts usually at the transition between one sleep stage and another. *Benign sleep myoclonus of infancy* consists of myoclonic jerks at the elbow, fingers, toes, and face during sleep in infants.

PSM is characterized by jerks, usually spontaneous, but sometimes also evoked, arising first in spinal innervated axial muscles of the trunk, neck, or abdomen and then propagated at slow velocity to more rostral and caudal muscles. PSM is present during relaxed wakefulness, characterized by diffuse EEG alpha activity, and disappears with sleep onset or mental activation. PSM is usually a chronic condition associated with sleep-onset insomnia.

Excessive startling and hypnic jerks may occur as part of the *hyperekplexia syndrome*, in which generalized myoclonus is readily elicited by stimuli during either wakefulness or sleep. The major form of this condition is also characterized by stiffness and falls. Brief *epileptic myoclonus* can be differentiated by coexistent EEG discharge, the presence of other features of epileptic seizures, and the occurrence of the myoclonus in both wakefulness and during sleep rather than only at sleep onset.

The muscle contractions of *PLMD* are much longer in duration, involve mainly the feet and lower legs, show periodicity, and occur within sleep. *RLS* consists of slower and repetitive semivoluntary movements at sleep onset that are associated with deep, unpleasant, and sometimes unbearable sensations, which are temporarily relieved by getting up and exercising.

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Other Sleep Disorder

ICD-9-CM code: 327.8 ICD-10-CM code: G47.8

Sleep disorders that cannot be classified elsewhere in the International Classification of Sleep Disorders, 3rd Edition are listed here. This may be due to the fact that the sleep disorder overlaps more than one category or, more often, when insufficient data have been collected to firmly establish another diagnosis. It is also possible that new sleep disorders that do not fall within any of the current major categories will be discovered during the lifetime of the International Classification of Sleep Disorders, 3rd Edition. When a specific diagnosis cannot yet be determined but the presenting problem clearly falls into a specific category (e.g., a circadian rhythm sleep-wake disorder), the "unspecified" diagnosis within that category (e.g., circadian rhythm sleep-wake disorder, unspecified) is preferred.

The International Classification of Sleep Disorders, 2nd Edition included a specific diagnosis of environmental sleep disorder within this section. This diagnosis is infrequently employed in the clinical setting and significant controversy exists regarding whether environmentally induced sleep disturbance represents a clinical disorder per se. The condition is typically characterized by complaints of sleep initiation and/or maintenance that are the direct result of an environmental factor. Associated daytime symptoms such as sleepiness, fatigue, or cognitive or emotional disturbance may be present. The environmental disturbance may be a physical stimulus such as noise (e.g., vehicular traffic, aircraft, bed partner snoring), light, temperature, movement (e.g., bed partner movement disorder or parasomnia), an emotional stimulus such as environmental danger (e.g., combat setting or disaster area), or an environmental requirement (such as caring for an infant or elderly family member). Hospitalization is often cited as a precipitant of environmental sleep disturbance although many additional factors (e.g., anxiety or pain) may also contribute to sleep disturbance in this setting. If the clinician determines that an environmental factor is the primary cause of a sleep disturbance, a diagnosis of Other Sleep Disorder may be employed.

It is the physical aspects of the environment, rather than their psychological meaning, which account for the sleep complaint. Unlike insomnia disorder, the sleep disturbance is dependent on the presence of the environmental factor. In the absence of the stimulus, sleep is normal.

The prevalence of environmentally induced sleep disturbances is not known although, as noted, the diagnosis is not commonly reported in sleep centers. Some individuals

may be more susceptible to environmental disturbances but little is known about specific characteristics that might predispose to this condition.

Although environmental factors may play a contributing role in some cases of chronic insomnia disorder, multiple other factors account for that condition, which is typically evident even in the absence of the offending environmental stimulus. Distinguishing an insomnia disorder from an environmentally induced sleep disturbance may pose a challenge in certain clinical encounters and providers must use clinical judgment in establishing the diagnosis.

In behavioral insomnia of childhood, the child may require certain environmental circumstances in order to sleep (e.g., a pacifier, music, lights, television, or a parent). It is the absence of these circumstances that results in sleep initiation or maintenance problems. In such cases, a diagnosis of chronic insomnia disorder (behavioral insomnia of childhood – sleep-onset association type) is indicated.

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Appendix A: Sleep Related Medical and Neurological Disorders

The disorders presented in this section may have a unique presentation during the sleep period or may present exclusively in association with sleep. 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. Sleep related epilepsy must be considered in the differential diagnosis of certain movement disorders and parasomnias. Sleep related headaches may be a clue to 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 for the early morning hours during the latter phase of the sleep period and may be precipitated by episodes of sleep apnea. It is important to be aware of sleep related laryngospasm as a potentially life-threatening consequence of neurodegenerative diseases such as multiple system atrophy. Fatal familial insomnia, although rare, presents with severe insomnia and has a 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 characterized by initial difficulties in falling asleep and maintaining sleep, spontaneous lapses from quiet wakefulness into a sleep state with enacted dreams (oneiric stupor), and loss of slow wave sleep features. In later stages of the disease, it may not be possible to identify any distinct sleep stages.

Although loss of temporal and spatial orientation develops, cognitive function is retained until impaired alertness makes testing impossible. The disorder progresses to 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 rhythms. Autonomic hyperactivity (e.g., pyrexia, salivation, hyperhidrosis, tachycardia, tachypnea, and dyspnea) is present. The disorder includes somatomotor disturbances, with dysarthria, dysphagia, tremor, spontaneous and reflex myoclonus, dystonic posturing, ataxia, and a positive Babinski sign. Hallucinations may be present.

Clinical and Pathologic Subtypes

None.

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, cosegregating 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 do patients who are methionine-valine heterozygous at codon 129.

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 in comparison to other prion diseases. Complications include infections (in particular of the lungs and bladder) that develop during the course of the disease, especially in the late stages, and represent the usual cause of death. Other frequent complications include skin ulcers when patients become bedridden and aspiration of food due to the severe dysphagia; the latter may require nasogastric or gastrostomy feeding.

Pathology and Pathophysiology

Severe bilateral loss of neurons, with reactive gliosis of the anterior and dorsomedial thalamic nuclei and severe neuronal loss and reactive astrogliosis in the inferior olives, are found. Spongiform changes in cortical layers in cases with a prolonged course have been described. Deposition of proteinase K-resistant prion protein type 2 in the grey matter but not the white matter occurs in both 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 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 and tremor-like limb-muscle activities associated with vivid dreams (oneiric stupor). Sleep spindles and features of slow wave sleep are absent or progressively lost throughout the course of the illness. In the final stages of the disorder, the EEG becomes unreactive and progressively flattens until death occurs; it may display periodic spike discharges.

Positron emission tomography (PET) with (18F)-2-fluorodeoxy-D-glucose shows thalamic hypometabolism. Magnetic resonance spectroscopy with multisequences can detect prion-induced gliosis in vivo. Circadian rhythms of body temperature, systemic blood pressure, and heart and respiratory rate and endocrine rhythms of growth hormone, prolactin, luteinizing hormone, follicle-stimulating hormone, and adrenocorticotropic

hormone may be lost. Serum catecholamine and cortisol values are elevated, with low or undetectable adrenocorticotropic hormone levels. Pathologic examination demonstrates degeneration of the anterior and dorsomedial thalamic nuclei and atrophy of the inferior olivary nucleus. Deposition of proteinase K-resistant prion protein type 2 is found in the brain.

Differential Diagnosis

This disorder must be differentiated from *REM sleep behavior disorder (RBD)*, which is not associated with autonomic hyperactivity or a familial pattern. The differential diagnosis includes *dementia*, *familial Creutzfeldt-Jakob disease* with the 178 codon mutation in the PRNP cosegregating with the valine polymorphism at codon 129 on the mutated allele, *Morvan fibrillary chorea*, *delirium tremens*, or even *schizophrenia*. A sporadic form of fatal insomnia has also been reported.

Unresolved Issues and Future Directions

Not applicable or known.

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Sleep Related Epilepsy

Alternate Names

Sleep epilepsy, nocturnal seizure, sleep related seizures.

Essential Features

A seizure is a paroxysmal event resulting from a sudden excessive discharge of the neurons of the cerebral cortex, whereas epilepsy is a condition of recurrent unprovoked seizures. Sleep facilitates epileptic activity and seizures. The characteristics of specific subtypes of sleep related epilepsy are discussed in the Clinical and Pathologic Subtypes section below.

Associated Features

The different types of nocturnal frontal lobe epilepsy (NFLE) may cause severe sleep disruption, affecting both macrostructure and microstructure of sleep, resulting in poor sleep quality, daytime fatigue, and sleepiness in some patients. The movements also may be so severe that injuries can occur. From one third to one half of patients with sleep related epilepsy also have occasional attacks during the day, although these are not necessarily of the same type as those occurring at night.

Neurocognitive impairment is typically diagnosed in almost all cases of continuous spike waves during NREM sleep (CSWS). Motor impairment in the form of a unilateral deficit is sometimes seen as an associated feature of CSWS.

Clinical and Pathologic Subtypes

Clinical and EEG criteria are used to define a variety of sleep related epilepsy subtypes.

Several types of epileptic syndromes have a marked tendency to manifest only or predominantly during sleep, or after arousal from sleep. These include NFLE, benign epilepsy of childhood with centrotemporal spikes (BECT), benign epilepsy with occipital paroxysms (BEOP), early-onset or late-onset childhood occipital epilepsy, juvenile myoclonic epilepsy (JME), generalized tonic-clonic seizures on awakening, certain forms of temporal lobe epilepsy, tonic seizure (as a component of Lennox-Gastaut syndrome), Landau-Kleffner syndrome, and continuous spike waves during NREM sleep (CSWS).

NFLE may present in three distinct ways: (1) nocturnal paroxysmal arousal, (2) nocturnal paroxysmal dystonia, or (3) episodic nocturnal wanderings.

BECT can present with focal clonic facial twitching that is often preceded by perioral numbness. These seizures are more often seen in drowsiness and sleep than wakefulness. The clinical course is often benign with disappearance of the seizures in adulthood.

BEOP 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 secondary generalized attacks. The clinical evolution of the early-onset type is benign, whereas in the late-onset type with visual seizures, the prognosis is uncertain.

JME is characterized by massive bilaterally synchronous myoclonic jerks, which are most frequently noted on awakening.

CSWS (formerly known as electrical status epilepticus of sleep [ESES]) is characterized 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.

Demographics

There is no significant sex predominance.

Predisposing and Participating Factors

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

Familial Patterns

The idiopathic generalized epilepsies form the largest category of epilepsies that appear to be heritable but show no clear mendelian mode of transmission. Juvenile myoclonic epilepsy and idiopathic generalized epilepsy with adolescent onset appear to be genetically heterogeneous. Among the partial epilepsies, BECT shows a familial pattern. A form of autosomal dominant NFLE with 70% to 80% penetrance has been reported in many countries, and a genetic heterogeneity also has been reported. Genetic factors have not been established in CSWS and seem to play a minor role. Familial antecedents of epilepsy (including febrile convulsions) have been found in 15% of cases.

Onset, Course, and Complications

Idiopathic generalized epilepsies and partial epilepsy may start at any age. The onset of benign epilepsies of childhood with centrotemporal or occipital spikes is between 4 and 12 years of age. The onset of NFLE is generally from age 10 to 16 years, mostly before the age of 20 years. The average age of recognition of CSWS is between 4 and 14 years, but the appearance of the first seizure is early, 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. For focal epilepsies (excluding BECT and the early-onset type of BEOP), the prognosis is less favorable compared to generalized epilepsies. At least 35% of the focal seizures confined to sleep are resistant to antiepileptic drugs.

Definitive data on the natural history of NFLE are not available, although a high prevalence of parasomnias has been documented in NFLE patients.

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. Interictal paroxysmal activity may induce prolonged cognitive and motor impairment. Hyperkinesias, aggressiveness, and psychotic states may appear. OSA may exacerbate sleep related seizures and complicate their treatment.

Pathology and Pathophysiology

In idiopathic generalized epilepsy, genetic factors are contributory. Pathogenic markers, associated neurologic deficits, or characteristic brain imaging findings have not been identified. However, microdysgenesis has been described in some forms of idiopathic generalized epilepsy. EEG recordings with sphenoidal or zygomatic leads may show epileptic activity over the mesiotemporal regions in partial complex seizures.

Video-polysomnographic (vPSG) analysis confirms that the motor pattern of NFLE resembles that noted in orbital and mesial frontal seizures. Nocturnal frontal lobe seizures involve a large neuronal network, and some of their clinical expressions are possible consequences of disinhibition of innate motor patterns produced by the central pattern generator. Recent reports derived from stereo-EEG studies seem to show that in some cases, the seizures (in particular 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 parasomnias.

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 (an acquired epileptic aphasia) is probably secondary to an alteration of function over the temporal area.

Objective Findings

Patients with suspected sleep related epilepsy often need to be evaluated in the sleep laboratory with video and full-head EEG monitoring in order to obtain the correct diagnosis. The characteristic interictal epileptiform activity in idiopathic generalized epilepsies usually increases during NREM sleep, whereas it decreases during REM sleep and wakefulness. Interictal epileptiform activity may be associated with phasic arousals.

In partial 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. Most of the seizures are activated in stage N2 sleep. Monitoring may also detect transient autonomic alterations in cardiac rhythm, blood pressure, and respiration during seizures. If epilepsy is suspected, a standard daytime 16-channel to 20-channel EEG (with partial or total sleep deprivation the night before, as indicated) should be performed. Ambulatory 24-hour EEG recordings may be useful to detect distribution of interictal epileptiform activity during the sleep-wake cycle.

Nocturnal vPSG is the gold standard test for NFLE. Most of the seizures appear during NREM sleep, with preponderance in NREM stages N1 and N2 (greater than 60%). Rarely do they emerge from REM sleep. In some cases, particularly in paroxysmal arousals, the motor attacks may show a periodicity (every 20 seconds to two minutes). Due to the fact that the discharges originate deep in the frontal lobe and are not visible using scalp EEG, the EEG during the attacks is uninformative in almost half of the cases. In a few cases, recording using intracranial or depth electrodes confirms the paroxysms during or preceding the motor components. The interictal sleep EEG is generally normal, but in 30% to 40% of subjects, focal epileptic abnormalities are seen, predominantly in the anterior regions. The video recording of the different types of attacks in NFLE permits categorization of the seizures and characterization of the main features.

During CSWS, diffuse spike waves at two to 2.5 Hz occur in bursts, with or without clinical manifestations. The discharges are continuous and occupy from 85% to 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 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 sleep structure is normal, but 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.

Differential Diagnosis

NFLE may be mistaken for a disorder of arousal from NREM such as *sleepwalking*, *confusional arousal*, or *sleep terror*. Ictal and interictal EEGs are often normal because the focus for the epileptic discharge may be deep in the brain. Disorders of arousal show a different pattern of episodes in that they occur out of stage N3 sleep, are not stereotyped, often have a sustained autonomic component, and are frequently seen during the first part of the night. Partial arousal disorders tend to disappear or decrease in frequency after adolescence. VPSG is often useful. *Sleep talking*, *bruxism*, 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. In the elderly (older than 60 years), the main differentiation from *RBD* is by vPSG recording. *PLMD*, *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 arousal 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

Not applicable or known.

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Sleep Related Headaches

Alternate Names

Various (see Clinical and Pathologic Subtypes).

Essential Features

Sleep related headaches are a group of unilateral or bilateral cephalalgias of varying severity and duration that occur during sleep or upon awakening from sleep. It is a heterogenous group of different headache entities with the common feature of occurrence during sleep or upon awakening. The characteristics of specific subtypes of sleep related headache are discussed in the *Clinical and Pathologic Subtypes* section below.

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 the primary headaches such as migraine, cluster headache, and chronic paroxysmal hemicrania. There are other primary headaches that occur solely with sleep; for example, hypnic headaches. In addition, secondary headaches related to medical, neurological, psychiatric, and sleep disorders can cause sleep related headaches.

Migraines are common recurrent headaches of moderate to severe intensity that last between four and 72 hours. Pain is typically unilateral and pulsating, aggravated by routine physical activity and associated with nausea, and/or photophobia

or phonophobia. They occur during the day or during sleep; approximately 50% of migraine attacks occur between 4:00 a.m. and 9:00 a.m. Migraine headaches do not have a fixed association with a particular sleep stage. The patient may awaken with a migraine out of REM sleep, or the headaches may occur in relationship to stage N3 sleep. A "classic migraine" headache is preceded by an aura (if the patient is awake), which usually lasts four to 60 minutes and typically consists of homonymous visual field defects and scintillating scotomas. In some patients, the aura may continue or even begin during the headache phase. In contrast, "common migraine" does not start with an aura. Other signs of neurological dysfunction may include unilateral paresthesias, weakness, and aphasia. Features of brainstem involvement may include vertigo, tinnitus, dysarthria, decreased hearing, diplopia, ataxia, bilateral paresthesias, and impaired level of consciousness. A familial syndrome with hemiplegia is well described. The hemiplegia is ipsilateral or contralateral to the side of the headache.

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, usually lasting 15 minutes to three hours (mean, 60 minutes). The headaches occur daily during cluster periods—usually one to three attacks per day over a period of one to two months. Most patients have one cluster period per year, though this can vary from patient to patient. The 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. One or more cranial autonomic features (e.g., ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, or eyelid edema) invariably accompany attacks of cluster headaches. A strong predilection for attacks to occur during sleep is well recognized, and these attacks are strongly related to REM sleep.

Chronic paroxysmal hemicrania closely resembles cluster headaches and consists of severe unilateral orbital, supraorbital, or temporal pain associated with one or more cranial autonomic features. However, the attacks are usually of shorter duration (lasting two to 30 minutes) and occur more frequently, most often at a frequency of more than five per day. In contrast to cluster headaches, chronic paroxysmal hemicrania is exquisitely sensitive to indomethacin. Attacks are also strongly associated with REM sleep.

Hypnic headaches are an uncommon type of headache that awakens the patient from sleep with a generalized or lateralized headache that lasts at least 15 minutes (range, one to 180 minutes) with a frequency of at least 15 times per month. Onset is typically after the age of 50, although similar headaches are described rarely in younger individuals, including children. In comparison to cluster headaches, hypnic headaches are

less severe, often bilateral and not associated with cranial autonomic features. 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. The headaches tend to occur during REM sleep. However, they also have been reported to occur during stage N3 sleep. A positive therapeutic response to lithium, indomethacin, and caffeine has been reported in many patients.

Other medical (e.g., hypertension), neurologic (e.g., brain tumors, arteriovenous malformations, cerebral venous thrombosis and trauma), psychiatric (e.g., depression), and sleep disorders (e.g., snoring and OSA) also can give rise to headaches that may occur during sleep or upon awakening from sleep. Patients with increased intracranial pressure (due, for example, to brain tumor, hematoma, arteriovenous malformations, or cerebral venous thrombosis) may complain of headache in the morning or headache that starts after 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 down or sneezing or with other activities that may cause further increase in intracranial pressure.

Sleep related headaches can disrupt nocturnal sleep, although the exact prevalence of this complication is unknown.

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

Migraine headaches have several predisposing factors that vary from patient to patient. However, stress, relaxation, changes in weather and barometric pressure, changes in sleep pattern, hypoglycemia, and specific foods (e.g., chocolate, Chinese food, alcohol) have been known to trigger migraine headaches. Alcohol can also predispose an individual to having cluster headache and chronic paroxysmal hemicrania. OSA and attendant hypoxia have been reported to be a trigger for cluster headache. However, sleep apnea may also predispose a person to having other types of headache and may independently lead to morning headaches. Change of sleep pattern and insomnia can predispose the patient to developing headaches.

Familial Patterns

There is a positive family history for migraine in up to 80% of patients with this disorder. Familial hemiplegic migraine is inherited in an autosomal dominant pattern with a variety of genetic mutations identified on chromosomes 1 and 19. Cluster headache does not have as strong of a familial disposition as migraine headache, but first-degree relatives of probands with cluster headache are seven times more likely to develop cluster headaches, and the concordance rates in monozygotic twins is 100%. The inheritance patterns of hypnic headache are not known.

Onset, Course, and Complications

Migraine headache usually starts in the second or third decade of life, with a slightly earlier onset in men than in women. The mean age of onset of cluster headache is 28 years. Chronic paroxysmal hemicrania has a wide range of onset, from childhood to old age. Most patients with hypnic headache are elderly, with the age of onset from 40 to 82 years. Brain tumors are more prevalent in the elderly, most occurring from the fifth decade to late life.

Most sleep related headaches are benign and tend to decrease in frequency with age. There may be spontaneous remissions that last from months to years. Pregnancy has a variable effect on these headaches. Migraines tend to decrease with age and, in women, may stop after menopause. Cluster headaches, as the name suggests, occur in clusters and are accompanied by pain-free intervals lasting months to a couple of years. They also tend to decrease with age. Hypnic headache occurs infrequently. Headaches in patients with brain tumors are related to an increase in intracranial pressure and tend to improve with treatment of the primary lesion and a decrease in intracranial pressure. Some patients with OSA report improvement of the headache after treatment of the apnea.

The 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

Not applicable or known.

Pathology and Pathophysiology

Several anatomic areas are common to the physiology of both sleep and headaches; these include the brainstem and diencephalon, specifically the ventrolateral periaqueductal gray and the posterior hypothalamus. From a neurochemical perspective, adenosine, melatonin, and orexin also are involved in both the regulation of sleep and the evolution of headaches. Dysfunction of REM sleep and arousal mechanisms are common to many headache disorders. Data from transgenic models indicate that disruption of sleep occurs in two forms of familial migraine. However, current mechanistic explanations of the relationship between sleep and headache are speculative.

Objective Findings

Polysomnographic aspects of sleep related headaches need to be better defined. Migraine headache is reported to occur in association with REM sleep or stage N3 sleep. An excess of stage N3 sleep also has been reported in patients with migraine. However, large controlled studies are not available. Fifty percent of cluster headaches and a majority of chronic paroxysmal hemicrania are associated with REM sleep. OSA and hypoxia during sleep may aggravate other sleep related headaches or may be an independent cause of headache. Hypnic headache occurs during sleep, with recent reports of headache during REM sleep and uncommonly during stage N3 sleep. Thus, the majority of sleep related headaches seem to have some relationship with REM sleep, but there are no defining or pathognomonic polysomnographic aspects of individual headache syndromes.

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 may cause headaches.

Differential Diagnosis

Sleep related headaches are a heterogeneous group of different headache entities with a common expression of occurrence 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*, *head trauma*, *alcohol intoxication*, or *bruxism*. Although the initial presentation may be one of headache, detailed history and examination will identify one of these contributing conditions.

Tension-type headaches are bilateral headaches with a feeling of a band-like tightening sensation around the head. In patients older than 50 years, *giant cell arteritis* may

present with lateralized or bilateral headache with tenderness over the temporal area, accompanied by polymyalgia rheumatica and visual problems, including loss of vision.

Exploding head syndrome is in the differential diagnosis of headache because it may occur in association with the sleep period. Patients report hearing an explosion in the head which is unaccompanied by pain.

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 may have frequent laryngeal stridor (which may be difficult for families to differentiate from snoring), associated tachypnea, and intermittent upper airway blockage.

Associated Features

Fear and panic upon awakening often accompany events and may, at times, lead to insomnia. In some cases of sleep related laryngospasm, gastroesophageal reflux has been identified. Less commonly, sleep related laryngospasm has been related to underlying OSA.

Clinical and Pathophysiological Subtypes

Sleep related laryngospasm may be associated with multisystem atrophy, a neurodegenerative disorder.

Demographics

Prevalence data do not exist. Typical age of onset is unknown, although when the condition is due to multisystem atrophy, affected individuals are typically older.

Predisposing and Precipitating Factors

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

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

Laryngospasm is a common cause of death in multiple system atrophy.

Developmental Issues

Not known.

Pathology and Pathophysiology

When not associated with neurodegenerative disorders of known pathology (e.g., multisystem atrophy), the pathology and pathophysiology is uncertain. 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 and multisystem atrophy can cause laryngeal dysfunction, resulting in sleep related laryngospasm.

Objective Findings

Sleep related laryngospasm may be observed on PSG with accompanying audio recording. It is seen in all stages of sleep but is most severe in REM sleep. Laryngospasm can appear to be 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, PSG or sleep-deprived EEG may demonstrate seizures that manifest solely as nocturnal laryngospasm. Endoscopy of the upper airway is necessary to examine vocal cord function and to exclude upper airway pathology. Gastroesophageal studies may reveal evidence of reflux.

Differential Diagnosis

OSA may cause awakenings, with choking or gasping for air, excessive daytime somnolence, restlessness, or insomnia. If OSA is a diagnostic consideration, sleep study 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." One possible cause of sleep related laryngospasm may be 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)* may be in the differential diagnosis of laryngospasm, but is generally recognizable by polysomnographic features of RBD and a history of dream enactment.

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 cross the lower esophageal sphincter (LES) into the esophagus and, potentially, into more proximal sites during sleep time. Symptoms are usually noticed during arousals or awakenings. Symptoms may include heartburn, substernal burning, chest discomfort, a sour or bitter taste in the mouth, regurgitation, water brash, coughing, choking, or unexplained excessive daytime sleepiness, even in the absence of typical reflux symptoms. Sleep related GER is associated with sleep onset and sleep maintenance insomnia, early morning awakenings, sleep disturbances, arousals, unrefreshing sleep, daytime functioning difficulties, and excessive daytime sleepiness. GER is a potential asthma trigger, predisposes to aspiration, and is a cause of cough. 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 prevalent in patients with OSA.

Associated Features

Associated features of this disorder include dysphagia, odynophagia, laryngopharyngitis, laryngospasm, 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, excessive daytime sleepiness, daytime fatigue, poor daytime functioning, and reduced work productivity. Patients with sleep related GER also have a decrease in health-related quality of life and more health care visits.

Clinical and Pathological Subtypes

Not applicable or known.

Demographics

GER symptoms affect up to 44% of adults in the United States monthly, and 20% weekly. Among patients with weekly heartburn, 79% report GER symptoms during sleep time, 57% report waking up during sleep, and 40% report that GER during sleep time affected their ability to work the next day. Among the 15,315 subjects of the Sleep Heart Health Study, 25% reported heartburn during sleep. In a review of 5 large

population studies, the mean prevalence of heartburn during sleep time was 54% ± 22% (standard deviation). In patients with OSA, sleep related reflux symptoms are present in up to 62%. Furthermore, in a trial examining consecutive asthmatics, 50% had awakenings from sleep because of heartburn. Thus, GER symptoms during sleep time are common. There is no known predilection for men or women. However, men are more likely than women to develop Barrett esophagus.

Predisposing and Precipitating Factors

Predisposing factors for sleep related GER include 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 insomnia, hypertension, asthma, snoring, or daytime sleepiness. 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. 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, compared to infants and children without GER. The incidence of GER increases with age. GER may be more severe and is associated with more complications in older adults.

GER is a chronic disease which is rarely cured, but it may be controlled with lifestyle, and medical and/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 esophagus, which is thought to be 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 esophagitis, and esophageal adenocarcinoma, compared to diurnal reflux. Extraesophageal complications include pulmonary complications previously discussed in the Essential Features section.

Pathology and Pathophysiology

Two major pathophysiologic mechanisms cause individual reflux episodes. Transient LES relaxations (LES relaxations occurring without esophageal contractions) account for 53% to 74% of GER episodes. Transient LES relaxations decrease the LES pressure to the 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, resulting 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 through the impairment of 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. Sleep increases the vagal threshold for triggering transient LES relaxations, so they usually do not occur during stable sleep and are usually confined to arousals. When GER events occur during sleep, esophageal refluxate clearance is prolonged and an 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, does not occur during sleep and is dependent on an arousal. Sleep also delays gastric emptying by disrupting gastromyoelectric function. Events causing arousals, including periodic limb movements and apneas, could 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.

The pathology of GER includes abnormal esophageal manometry, endoscopy, and esophageal biopsy findings. Esophageal manometry findings include an increased frequency of transient LES relaxations, altered or decreased esophageal peristaltic contraction amplitude, and a decrease in LES pressure. Endoscopic findings include changes ranging from mild erythema, erosions, and ulcerations to severe erosions with stricture. Barrett esophagus is identified when columnar tissue replaces the normal squamous epithelium of the distal esophagus.

Objective Findings

Diagnostic testing is not required for sleep related GER. The diagnosis can be made if typical symptoms of heartburn and/or regurgitation are present during sleep time.

PSG is not indicated. Esophageal pH monitoring, which may be combined with esophageal impedance, objectively measures individual GER events. Esophageal monitoring is recommended in difficult, refractory cases, or when symptoms continue despite therapy.

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 in the left side down position.

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 approximate 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 when the pH drops to less than 4.0, and this variable is reported as time (%) where pH is less than 4.0. The percent time where pH is less than 4 is reported over the total recording time, upright time and supine time. Note that supine (in this testing) is defined as the period of time that the patient is in bed. Symptom correlation is also helpful using the event marker on the device or diaries. Normal esophageal pH times during the "supine" 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. Esophageal pH monitoring also can be performed simultaneously with actigraphy to correlate acid reflux events with sleep and wake periods. Catheter-free wireless pH systems are also available and are deployed into the esophagus, usually by endoscopy.

Esophageal impedance monitoring can be combined with pH probes detecting liquid, gas, or liquid gas in the esophagus, and can assess both acid and nonacid reflux events. Use of esophageal impedance monitoring is often performed in esophageal centers, and this technique would be difficult to integrate with polysomnography.

Other objective measures include esophageal endoscopy with or without biopsy in order to evaluate for esophagitis and other esophageal complications. A histologic evaluation is required to establish a diagnosis of Barrett esophagus.

Differential Diagnosis

The differential diagnosis is primarily with *peptic ulcer disease* and *angina*. The chest pain associated with GER is sometimes indistinguishable from that of angina. *Duodenal ulcer disease* is commonly associated with a burning epigastric pain, and this can sometimes be similar to the pain experienced by patients with GER. Other conditions that may be associated with GER include OSA, *sleep related abnormal swallowing*, and *sleep related laryngospasm*. PSG evaluation 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, 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, typically during sleep. The symptoms of sleep related myocardial ischemia are very similar to those that characterize episodes 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 and jaw and to 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 that wakes the patient from sleep and that may be secondary to left ventricular diastolic dysfunction or ischemic mitral regurgitation. Other related features depend on the trigger for the cardiac ischemia. Ischemic events related to OSA may present during those times of sleep when nocturnal desaturation is most severe. Cardiac ischemia related to hemodynamic changes or vasospasm occurring during REM sleep may present in the early hours of the morning, around the time of waking, when REM sleep is most likely to occur. Ischemia associated with nocturnal hypotension is most likely to occur during slow wave (N3) sleep, when blood pressure is lowest.

Clinical and Pathophysiologic Subtypes

None known.

Demographics

The specifics of prevalence, sex ratios, and age ranges have not been comprehensively evaluated. 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 referred to as 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 with severe vasculopathy who are taking multiple antihypertensive medications, and especially those in whom autonomic dysfunction (related to either age or diabetes) may impair blood pressure homeostatic mechanisms.

Predisposing and Precipitating Factors

Predisposing factors include established coronary artery disease or valvular disease such as aortic stenosis. Because coronary filling occurs during diastole, conditions associated with reduced diastolic blood pressure, such as severe aortic regurgitation, may elicit nocturnal angina, particularly in the presence of preexisting coronary artery disease. Similarly, any predisposition to hypotension, which is most likely to occur during slow wave (N3) sleep, may heighten risk. 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 be a trigger for myocardial infarction and sudden death that occurs at night. Deeper oxyhemoglobin desaturations, which may be encountered in REM, particularly with coexisting pulmonary disease or truncal-abdominal obesity, are more likely to trigger cardiac ischemia. In patients with vasospastic angina, use of 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 prior to sleep, may contribute. Finally, in the proper clinical context, abuse of drugs such as amphetamine, cocaine, and other stimulants, needs to be considered in the evaluation of 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 both the sleep apnea and the coronary artery disease are sufficient to elicit sleep related myocardial ischemia. This is likely to be most common in middle-aged to older men, particularly those who are overweight, although several studies have documented life-threatening OSA related cardiac ischemia in women. It is notable that several 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 and pulmonary edema, arrhythmias, and even progression to myocardial infarction and death.

Pathology and Pathophysiology

For sleep related myocardial ischemia related to OSA, the apnea-related hypoxemia and surges in blood pressure and heart rate at termination of apnea may all result in relative myocardial oxygen deficiency. A substrate of preexisting severe coronary artery disease is expected to exacerbate this problem. Variant angina may be more likely to occur during sleep because of the significant and abrupt fluctuations in cardiovascular neural control during REM sleep. For nocturnal angina related to hypotension, perfusion of the coronary arteries during diastole makes maintenance of diastolic pressures during sleep important for adequate myocardial perfusion. Autonomic insufficiency due to old age, diabetes, and medication effects blunts the ability of the cardiovascular system to maintain adequate blood pressure.

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 (silent ischemia) and may be incidentally noted on either 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 with a normal-appearing single ECG channel should be further evaluated with multichannel ECG.

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 can be associated with ischemia. Sleep related breathing disorders, particularly OSA, may elicit oxygen desaturation and consequent sleep related myocardial ischemia. The presence of cardiac arrhythmias should prompt an evaluation for nocturnal ischemia.

Differential Diagnosis

Sleep related myocardial ischemia must be differentiated from *gastroesophageal reflux*, which may also be associated with chest discomfort. The nature of the pain, associated symptoms and prior history are helpful in making a distinction, although 12-lead ECG may be necessary in some cases. *Nocturnal panic attacks* may be associated with chest wall pain and respiratory distress. Although the majority of 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 transition from N2 to N3 sleep.

Other causes of *nocturnal respiratory distress*, including heart failure and 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. Chest wall pain may be secondary to a variety of 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 needed to explore the relationship between sleep related myocardial ischemia and the circadian variation in myocardial infarction and sudden death, particularly the role of treatment on outcomes.

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Appendix B: ICD-10-CM Coding for Substance-Induced Sleep Disorders

ICD-10-CM coding for substance-induced disorders is more complex than ICD-9-CM coding. The series F10.xxx-F19.xxx (which is the general section for substance-induced mental and behavioral disorders in ICD-10-CM) contains the pertinent codes for substance-induced sleep disorders. There are specific codes for sleep disorders induced by alcohol, opioids, sedatives, cocaine, other stimulants and other psychoactive substances. However, in the case of cannabis, hallucinogens, nicotine and inhalants, there are no sleep-specific codes. In these instances, the coder must use an "unspecified" or "other" code. A detailed list of the appropriate codes for substance-induced sleep disorders is included in the table below.

Substance	Relevant ICD-10-CM Codes
Alcohol	F10.182 Alcohol abuse with alcohol-induced sleep disorder F10.282 Alcohol dependence with alcohol-induced sleep disorder F10.982 Alcohol use, unspecified with alcohol-induced sleep disorder
Opioid	F11.182 Opioid abuse with opioid-induced sleep disorder F11.282 Opioid dependence with opioid-induced sleep disorder F11.982 Opioid use, unspecified with opioid-induced sleep disorder
Cannabis	F12.188 Cannabis abuse with other cannabis-induced disorder F12.288 Cannabis dependence with other cannabis-induced disorder F12.988 Cannabis use, unspecified with other cannabis-induced disorder
Sedative, Hypnotic or Anxiolytic	F13.182 Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic-induced sleep disorder F13.282 Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or anxiolytic-induced sleep disorder F13.982 Sedative, hypnotic or anxiolytic use, unspecified with sedative, hypnotic or anxiolytic-induced sleep disorder

Substance	Relevant ICD-10-CM Codes
Cocaine	F14.182 Cocaine abuse with cocaine-induced sleep disorder F14.282 Cocaine dependence with cocaine-induced sleep disorder F14.982 Cocaine use, unspecified with cocaine-induced sleep disorder
Other Stimulant (includes amphetamine and caffeine)	F15.182 Other stimulant abuse with stimulant-induced sleep disorder F15.282 Other stimulant dependence with stimulant-induced sleep disorder F15.982 Other stimulant use, unspecified with stimulant-induced sleep disorder
Hallucinogen (includes ecstasy, PCP, phencyclidine)	F16.188 Hallucinogen abuse with other hallucinogen-induced disorder F16.288 Hallucinogen dependence with other hallucinogen-induced disorder F16.988 Hallucinogen use, unspecified with other hallucinogen-induced disorder
Nicotine	F17.208 Nicotine dependence, unspecified, with other nicotine-induced disorders F17.218 Nicotine dependence, cigarettes, with other nicotine-induced disorders F17.228 Nicotine dependence, chewing tobacco, with other nicotine-induced disorders F17.298 Nicotine dependence, other tobacco product, with other nicotine-induced disorders
Inhalant (includes volatile solvents)	F18.188 Inhalant abuse with other inhalant-induced disorder F18.288 Inhalant dependence with other inhalant-induced disorder F18.988 Inhalant use, unspecified with other inhalant-induced disorder
Other Psychoactive Substance (includes polysubstance drug use)	F19.182 Other psychoactive substance abuse with psychoactive substance-induced sleep disorder F19.282 Other psychoactive substance dependence with psychoactive substance-induced sleep disorder F19.982 Other psychoactive substance use, unspecified with psychoactive substance-induced sleep disorder

Glossary

Actigraphy: A measurement of physical activity, typically via a wrist-worn movement sensor, employed to estimate sleep and wakefulness based on relative levels of physical inactivity and activity.

Alveolar Hypoventilation: A condition in which ventilation of the lung gas exchanging units is decreased relative to the carbon dioxide production (excretion) such that the arterial partial pressure of carbon dioxide is increased. Alveolar ventilation is equal to the minute ventilation (tidal volume × respiratory rate) minus the dead space ventilation.

Apneic Threshold: The value of $PaCO_2$ below which central apnea occurs during NREM sleep.

Ataxic Breathing: A breathing pattern consisting of irregular variation in tidal volume and respiratory rate, characteristic of the effects of opioids on breathing.

Autonomic Arousal: An abrupt shift in autonomic nervous system activity during sleep characterized by an increase in sympathetic activity, including heart rate and blood pressure.

Biological Day/Night: In humans, biological day refers to the internal circadian time when wakefulness and associated functions are promoted (e.g., when endogenous melatonin levels are low). Biological night refers to the internal circadian time when sleep and associated functions are promoted (e.g., when endogenous melatonin levels are high).

Cataplexy: More than one episode of generally brief (< 2 minutes), usually bilaterally symmetrical sudden loss of muscle tone with retained consciousness. The episodes are precipitated by strong emotions, usually positive, with almost all patients reporting some episodes precipitated by emotions associated with laughter.

Chemosensitivity: The sensitivity of the chemoreceptors to increases in PCO_2 or decreases in PO_2. In humans this is measured by increases in ventilation associated with these stimuli.

Chronotype: Individual timing preference for various physical and mental activities, and sleep and wakefulness, over the course of a day. “Morningness” refers to preference for earlier timing of activities and sleep initiation; “eveningness” refers to preference for later timing of activities and sleep initiation.

Circadian Misalignment: Incorrect or inappropriate timing of sleep and wakefulness with respect to internal circadian timing (e.g., the wake episode occurring entirely or partially during the biological night and/or the major sleep episode occurring entirely or partially during the biological day).

Circadian Period (tau): The time it takes to complete one circadian cycle (e.g., time from one circadian phase on day 1 to the same circadian phase on day 2).

Circadian Phase: The time at which a particular event occurs within the circadian cycle (e.g., onset, offset, trough, peak).

Circadian Rhythm: Biological oscillation, with a periodicity near 24 hours, which is clock-driven (i.e., not caused by external or non-circadian clock factors).

Comorbid Insomnia: An insomnia syndrome thought to have partial or total independence from a co-occurring sleep disorder or sleep-disruptive medical, psychiatric, substance dependence/abuse disorder.

Conditioned Arousal: An arousal response developed by the repeated association of a specific setting such as the bedroom with unsuccessful sleep attempts.

Cortical Arousal: An abrupt shift of EEG frequency to a faster frequency lasting at least 3 seconds, indicating cortical activation.

Cyclic Alternating Pattern (CAP): The occurrence in NREM sleep of transient EEG events (phase A, subtypes A1, A2 and A3) interrupting the background activity (phase B). CAP is a sensitive marker of sleep instability, usually increased in sleep disorders that adversely affect sleep continuity.

Dim Light Melatonin Onset (DLMO): A marker of internal circadian phase designated by the rise in melatonin above low daytime levels, typically assessed via blood or salivary melatonin levels. Melatonin levels are reduced by exposure to light and thus need to be assessed in dim light to be accurate.

Dopaminergic: Related to the neurotransmitter dopamine.

Dystonia: Involuntary muscle contractions that result in slow repetitive movements or abnormal postures.

Early Morning Awakening: The termination of sleep at least 30 minutes before the desired rising time with a concomitant reduced total sleep time compared to the usual premorbid sleep pattern.

Electromyogram (EMG): Physiological recording of muscle activity, based on electrical activity that accompanies muscle contraction. For sleep monitoring purposes, EMG is typically recorded from skin surface rather than intramuscular electrodes.

Entrained/Entrainment: The successful end result (entrained) or process of (entrainment) synchronization of an internal circadian clock to the environment (e.g., light dark cycle), producing a stable phase relationship between the circadian clock and environmental time.

Fatigue: A lack of energy, accompanied by a desire to reduce or limit activity levels. This symptom should be differentiated from reports of subjective sleepiness as well as from unintended sleep episodes.

Homeostasis: The tendency of a living organism to maintain internal equilibrium by adjusting and regulating its physiological processes.

Hypercapnia: Elevation of the arterial partial pressure of carbon dioxide ($PaCO_2$) to a level > 45 mm Hg during wakefulness.

Hypersomnolence: Excessive sleepiness during the normal wake period.

Hypersomnia: A disorder characterized by excessive sleepiness (e.g. idiopathic hypersomnia).

Hypnagogic Hallucinations: Vivid dreamlike experiences occurring at the transition from wake to sleep.

Hypnopompic Hallucinations: Vivid dreamlike experiences occurring at the transition from sleep to wake.

Myalgia: Muscle pain.

Nonrestorative Sleep: Sleep that is perceived to be poor in quality and unrefreshing, resulting in a sense of feeling unrested upon awakening.

Odds Ratio: A statistical term that provides a measure of the strength of relationship between two variables; the odds of an event occurring in one group compared to the odds of it occurring in another group.

Oneirism: Acting-out of dreams, usually from REM sleep.

Out of Center Sleep Testing: A sleep study performed outside of the sleep center, usually at a patient's home and with limited (typically respiratory related) channels (parameters) recorded.

Parasomnia Pseudo-Suicide: A death, erroneously attributed by authorities to suicide, which results from complex parasomnia, usually from NREM sleep.

Parkinson Disease: A neurodegenerative movement disorder which may result in bradykinesia, rigidity, tremor, and/or postural instability, and eventually cognitive decline.

Phase Advance/Delay: A shift in the timing of the internal circadian clock in which circadian phase is moved earlier (advance, such as required for eastward jet travel or to assume an earlier sleep schedule) or later (delay, such as required for westward jet travel or to assume a later sleep schedule).

Phase Response Curve: Graphic representation that describes the circadian phase shifting response to a time cue (e.g., light) as a function of the internal circadian time at which the cue is presented.

Phase Tolerance: The ability to be awake or asleep at an inappropriate internal circadian time.

Physiological Hyperarousal: A state of chronic physiologic arousal as reflected by measures such as increased mean latency on MSLT, increased metabolic rate and glucose metabolism in the CNS (PET scan), decreased heart rate variability and increased heart rate.

PHOX2B: A paired-like homobox gene, mutation of which is the defining abnormality of Congenital Central Hypoventilation Syndrome.

Prevalence: The proportion of the population affected by a disease or condition at a given time; prevalence indicates how widespread a disease or condition is, thereby serving as a measure of its burden on society.

REM Sleep without Atonia, REM-without Atonia: The intermittent or continuous loss of the normal muscle atonia of REM sleep.

Reverse First Night Effect: A propensity to sleep better than usual on the first night in the sleep laboratory.

Sleep Attacks: Inappropriate falling asleep with few or no prodromal symptoms of sleepiness.

Sleep Diary (sleep log): An instrument used by individuals to keep records of their nightly sleep duration and quality over a period of days to weeks.

Sleep Drunkenness (prolonged sleep inertia): Prolonged difficulty waking up after a night's sleep or a nap with repeated returns to sleep, irritability, automatic behavior and confusion.

Sleep Homeostasis: A process which describes the propensity for sleep driven by duration of prior time awake and sleep history.

Sleep Hygiene: A set of rules/instructions about lifestyle (caffeine intake, alcohol and tobacco use, diet, etc.) and environmental factors (light, noise, temperature) that affect overall sleep duration and quality.

Sleep Onset REM Period (SOREMP): REM sleep occurring within 15 minutes of sleep onset on a multiple sleep latency test or overnight polysomnogram.

Sleep Related Abnormal Sexual Behaviors: Any of a spectrum of sexualized behaviors which arise from sleep, typically NREM sleep.

Sleep Related Violence: Violent behavior which is associated with a NREM parasomnia when the affected individual is accidentally provoked by another person in close proximity – usually a family member.

Suggested Immobilization Test: A procedure for evaluation of periodic leg movements and related sensory components of RLS during resting wakefulness. A standard polysomnogram recording without respiratory measures is used for one hour while the subject sits quietly awake and upright in bed with the legs outstretched.

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