

# Sleep-Related Breathing Disorders

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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 (CSA) disorders, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder. However, some patients meet diagnostic criteria for more than one of these groups. For example, patients may 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 and 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 transiently reduced 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 patients, 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 their presentations, diagnostic criteria, courses, 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 central sleep apnea disorders are characterized by disruption of sleep due to repetitive respiratory events characterized by reduction or cessation of airflow due to reduced or absent respiratory effort. Patients with central sleep apnea of various etiologies may also exhibit OSA. In general, central sleep apnea disorders require the presence of symptoms referable to respiratory events because central apnea can be a normal physiologic response to relative hypocapnia, whether caused by the wake to sleep transition, ascent to altitude, or excessive ventilation from PAP therapy. The exception to this requirement for symptoms is Central Sleep Apnea due to Cheyne-Stokes Breathing since this breathing pattern is abnormal and predicts worse clinical outcomes in the setting of heart failure, independent of symptoms.

Contributing mechanisms underlying the central sleep apnea disorders include: 1) an elevated respiratory drive (e.g., due, for example, to hypoxia (as with high altitude periodic breathing); 2) instability of the ventilatory control system (due to wake/sleep instability or prolonged circulation times (as seen in heart failure)); 3) damage or impairment of the neural circuitry that regulates respiration during sleep (e.g., due

to stroke or opioids, respectively); or 4) immature development of that neural circuitry, as in the case of primary central sleep apnea of prematurity or primary central sleep apnea of infancy.

Sleep-related hypoventilation disorders are characterized by an abnormal increase in the arterial PCO<sub>2</sub> (PaCO<sub>2</sub>) during sleep. Because of the impracticalities of arterial blood sampling during sleep, these disorders are typically diagnosed by end-tidal or transcutaneous CO<sub>2</sub> monitoring during sleep. While not uniformly present, sustained nocturnal hypoxemia on pulse oximetry should raise consideration of a sleep-related hypoventilation disorder as the etiology of desaturation. Awake hypoventilation may or may not be present in these disorders. The exception is obesity hypoventilation syndrome, which requires documentation of awake (daytime) hypoventilation.

A notable change from the previous version of the International Classification of Sleep Disorders is that greater significance is placed on distinguishing between sleep-related hypoventilation due to a medical disorder and sleep-related hypoxemia. The distinction between sleep-related hypoventilation and sleep-related hypoxemia has important diagnostic and treatment consequences. Sleep-related hypoxemia disorders are characterized by sustained periods of significantly reduced oxyhemoglobin saturation during sleep without hypercapnia. This diagnostic category is used when sleep-related hypoventilation is either absent or insufficient to explain the severity of hypoxemia (in the latter case, both diagnoses should be used). Sleep-related hypoxemia can occur due to ventilation-perfusion mismatch, low inspired partial pressure of oxygen, shunt, or a combination of these factors. Many diverse etiologies can be associated with both sleep-related hypoventilation due to a medical disorder and sleep-related hypoxemia. There are no longer separate diagnostic categories for each class of pathology that may contribute to hypoventilation or hypoxemia. Instead, the specific underlying disorder should be diagnosed separately, in association with a diagnosis of sleep-related hypoventilation due to medical disorder or sleep-related hypoxemia.

Finally, it is essential to note that diagnosis of a sleep-related breathing disorder must be based, where applicable, on polysomnography or home sleep apnea testing (HSAT) conducted in accordance with the standards of the American Academy of Sleep Medicine.

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## 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 they share the same pathophysiology.

Use of the term Pickwickian syndrome is discouraged because not only has it been applied to those with OSA only, 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, fatigue, insomnia, or other symptoms leading to impaired sleep-related quality of life.<sup>1</sup>
  - 2. The patient wakes with breath-holding, gasping, or choking.
  - 3. The bed partner or other observer reports habitual snoring or breathing interruptions during the patient's sleep.
- B. Polysomnography (PSG) or HSAT<sup>2</sup> demonstrates:
  - 1. Five or more predominantly obstructive respiratory events<sup>3</sup> (obstructive and mixed apneas, hypopneas, or respiratory effort-related arousals [RERAs])<sup>4</sup> per hour of sleep during a PSG or per hour of monitoring (HSAT).<sup>2</sup>

OR

- C. PSG or HSAT<sup>2</sup> demonstrates:

1. Fifteen or more predominantly obstructive respiratory events ((obstructive and mixed apneas, hypopneas, or respiratory effort-related arousals [RERAs]))<sup>3</sup> per hour of sleep during a PSG or per hour of monitoring (HSAT).<sup>2</sup>

## Notes

1. Sleep-related quality of life may be adversely affected by OSA-related symptoms including, but not limited to nonrestorative sleep, snoring, sleep-related choking, insomnia, nocturia, morning headaches, and disruption of bedpartner's sleep. Adverse effects may result in impairments in daytime concentration, memory, driving, social functioning, or work-related productivity.
2. HSAT commonly underestimates the number of obstructive respiratory events per hour compared to PSG because actual sleep time, as determined primarily by EEG, is often not recorded. Therefore, the term respiratory event index (REI) may be used to denote event frequency based on monitoring time rather than total sleep time.
3. Respiratory events are defined according to the latest version of the AASM Manual for the Scoring of Sleep and Associated Events.
4. RERAs and hypopneas based on cortical arousals from sleep cannot be scored using HSAT because arousals by EEG criteria cannot be identified.

## *Essential Features*

OSA is characterized by repetitive episodes of complete (apnea) or partial (hypopnea, respiratory effort-related arousals (RERA)) upper airway obstruction occurring during sleep. These events may result in reductions in blood oxygen saturation and are usually terminated by brief arousals from sleep. By definition, apneas and hypopneas 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 occur more frequently in REM, N1, and N2 sleep than in N3 sleep. Events are usually longer and associated with more severe decreases in oxygen saturation when they occur in REM sleep and when the individual is 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 or comorbid sleep-related hypoventilation or hypoxemia. Snoring between apneas is typically reported by bed partners, as are witnessed episodes of gasping, or choking and body movements that disrupt sleep. There is typically evidence of inspiratory flow limitation or increased upper airway resistance on respiratory monitoring. Patients may awaken in the morning feeling tired and unrefreshed regardless of the duration of their time in bed.

Excessive sleepiness is a major presenting complaint in many but not all cases. Sleepiness is most evident during relaxation or inactivity. With extreme sleepiness, sleep may occur while actively conversing, eating, walking, or driving. The severity of OSA as determined by the frequency of apneas and hypopneas or the 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. Thus, assessment of sleepiness can be difficult. In addition, patients may adapt to sleepiness over time and fail to recognize it as a reportable problem. Furthermore, patient complaints of sleepiness may not always accompany breathing pauses and disruptive snoring observed by the bed partner. Finally, it is important to note that sleepiness is a condition with numerous possible etiologies and a range of manifestations (see Differential Diagnosis).

The predominant symptom may be fatigue or lack of energy due to poor sleep rather than sleepiness. Insomnia, poor sleep quality, and fatigue are more common presenting symptoms in women than men. Generally, quality of life 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 do not endorse any symptoms or confirm 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 the 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, stroke, and transient ischemic attack, and it may be an independent risk factor for these conditions. OSA is associated with cognitive dysfunction, which may be most prominent in older patients. There is also increasing evidence that OSA may be a risk factor for the development and progression of Alzheimer's disease. 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 that disease. Patients with severe OSA may be at risk for developing cor pulmonale, although this is usually seen only in patients with daytime hypercapnia due to comorbid conditions such as obesity hypoventilation syndrome or chronic obstructive pulmonary disease (COPD). However, isolated pulmonary hypertension may be observed infrequently in the absence of comorbid cardiopulmonary disorders. 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.

Increasing evidence suggests that OSA may be linked to worsening of chronic kidney disease. OSA has also been associated with ophthalmologic conditions including glaucoma, nonarteritic ischemic optic neuropathy and floppy eyelid syndrome. However, the nature of the interaction between OSA and these conditions remains uncertain. 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: 1) OSA-induced arousals from non-rapid eye movement (NREM) sleep mimicking a primary disorder of arousal (confusional arousal, sleepwalking, or sleep terrors); 2) OSA-induced arousals from REM sleep mimicking REM sleep behavior disorder; 3) disorders of arousal from NREM associated with slow wave sleep rebound during initiation of nasal continuous positive airway pressure (CPAP) therapy; 4) OSA-induced arousals linked with sleep-related eating disorder; and 5) OSA-induced nocturnal seizures or cerebral anoxic attacks with prominent motor activity.

## *Clinical and Pathophysiological Subtypes*

Analyses of OSA populations have identified symptom clusters consisting of patients with complaints of insomnia or disturbed sleep, those who are minimally symptomatic, and those who report excessive daytime sleepiness. While further study is needed to clearly define the relationship of these symptom clusters to long-term consequences of OSA or response to treatment, current evidence indicates that an excessive sleepiness subtype may be linked to adverse cardiovascular outcomes and mortality.

There has traditionally been little clinical significance in distinguishing between apneas and hypopneas or respiratory events that occur predominantly during REM sleep versus other sleep stages. However, more recent analyses indicate specific characteristics that may predict greater risk of OSA complications and likelihood of response to treatment. These characteristics include shorter duration of respiratory events, greater sleep fragmentation, occurrence during REM, degree of hypoxic burden, and increased blood pressure/heart rate response to respiratory events. The highest risk features remain to be determined, but both symptoms and detailed polysomnographic features should be considered in the diagnosis and management approach to OSA.

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 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 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 with respiratory event-associated arterial oxygen desaturation. However, 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, although the pathophysiologic relationships have not been established. Nevertheless, individuals with both disorders have greater nocturnal oxygen desaturation and daytime hypercapnia for the same degree of bronchial airflow obstruction. They also have an increased risk for pulmonary hypertension and right heart failure. The prevalence rate in the general population for having both conditions has been estimated to be 1-4%.

## *Demographics*

OSA can occur in any age group. Estimates of prevalence are very dependent on study inclusion criteria, the sensor technology used, how sleep-related respiratory events are defined, the event frequency

threshold, and other criteria used to define disease. Data from general population-based studies from several countries indicate that OSA associated with daytime sleepiness occurs in 3% to 7% of adult men and 2% to 5% of adult women. However, many individuals with OSA do not endorse daytime sleepiness, and OSA prevalence estimates based solely on apnea-hypopnea index (AHI) criteria are much higher. For an AHI  $\geq$  15/hour, overall OSA prevalence ranges from 6 – 17% for the entire adult age range, with progressively higher estimates among older age groups. The global prevalence of OSA defined by AHI  $\geq$  15/hour was recently estimated to be approximately 425 million cases.

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 due to 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 Black persons than White persons. The prevalence of OSA in Asian individuals is comparable to that of White people, despite this group having a generally lower body mass index (BMI). Differences in craniofacial features predisposing Asians to developing OSA are likely explanations. OSA prevalence among Hispanic persons is similar to or slightly higher than White people. Data on OSA prevalence among Native American persons and other aboriginal populations are limited, although OSA occurs commonly in these groups.

### *Predisposing and Precipitating Factors*

The major predisposing factor for OSA is excess body weight. It is 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. Various abnormalities of the bony and soft tissue structures of the head and neck may predispose an individual to OSA. These may be hereditary (e.g., mandibular size, mandibular position, palatal height) or acquired (e.g., enlarged adenoids and tonsils). OSA patients with normal or below-normal body weight are more likely to have upper airway obstruction due to localized structural abnormalities such as maxillomandibular deformity (e.g., micro/retrognathia) or adenotonsillar enlargement. Larger neck circumference is a significant risk factor for OSA as well.

Menopause is a risk factor for this disorder in women, even after adjustment for age and BMI. However, the use of hormone replacement therapy may be protective. There are conflicting data concerning smoking as a risk factor for OSA. Endocrine disorders such as acromegaly and hypothyroidism are risk factors for OSA. Adults and children with Trisomy 21 also have a high prevalence of OSA due to multiple risk factors including macroglossia, midline facial hypoplasia, and adenotonsillar hypertrophy. OSA is common in patients with some neurologic disorders that affect peripheral muscles, such as myotonic dystrophy. OSA is also frequent among patients with end-stage kidney disease. This prevalence may reflect a bidirectional relationship in which OSA worsens due to fluid retention and OSA-related hemodynamic and other stresses adversely impacting renal function. Apneas, hypopneas, and snoring may be exacerbated following the ingestion of alcohol or sedating medications before sleep or following

an increase in body weight. Nocturnal nasal restriction or congestion due to abnormal morphology or rhinitis may also worsen OSA.

### *Familial Patterns*

OSA can be a heritable condition, as demonstrated by familial clustering of OSA patients. First-degree relatives of OSA patients are twice as likely to have OSA as relatives of those not affected. Clustering of symptoms 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 OSA include craniofacial morphology and ventilatory control. Familial environmental factors such as physical activity and eating habits may also play a role. 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 as 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. Recent studies have noted that after weight loss and subsequent regain of weight, improvements in OSA severity resulting from the initial weight loss were sustained for a significant period following the recurrent weight gain.

Pregnancy may be associated with the development or worsening of OSA. The prevalence and severity of OSA in women tend to increase with menopause.

OSA has been implicated as a risk factor for multiple conditions (see Associated Features). As previously described, these include incident systemic hypertension, coronary artery disease, congestive heart failure, stroke, and premature mortality. Data suggests that these effects are more evident in men and middle-aged individuals. OSA is associated with cognitive dysfunction, which may be more frequently seen in older patients, and may contribute to the development and progression of Alzheimer's disease. 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 strongly related to the onset and recurrence of atrial fibrillation. There is some evidence that OSA may contribute to an increased rate of expansion of thoracic and abdominal aortic aneurysms and possibly be a risk factor for aortic dissection. Finally, OSA may contribute to the worsening of chronic kidney disease.

OSA may increase the severity of depression. Because of daytime sleepiness, functional impairment commonly occurs, manifested by poor job performance, loss of employment, impaired family



relationships, and reduced overall quality of life. In addition, the risk of occupational injuries and motor vehicle accidents is significantly increased among those with OSA.

OSA has also been linked to increased cancer incidence and mortality in some studies, although data are conflicting. Specific cancer types, such as melanoma, may be more closely linked to OSA. Whether OSA treatment impacts cancer outcomes remains unknown.

### *Developmental Issues*

Pediatric OSA is discussed in a separate section (below). OSA can occur in any age group, but prevalence accelerates between young adulthood and middle age, with a plateau reached after approximately age 65 years. OSA is often underrecognized in elderly patients, but can be associated with daytime sleepiness, neurocognitive dysfunction, falls, diminished quality of life, and mood disturbances.

### *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. 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 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 tonic 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. Sleep-associated reductions in end-expiratory lung volume may result in smaller upper airway size due to decreased downward traction (tracheal tug). In some patients, unstable ventilatory control (high loop gain) results in ventilatory overshoot following apneas or hypopneas, with resulting hypocapnia that may contribute to the subsequent loss of ventilatory drive and upper airway narrowing upon return to sleep.

The mechanisms of apnea/hypopnea termination are varied. 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<sub>2</sub>, high PaCO<sub>2</sub>) and mechanical (upper airway mechanoreceptors) stimuli leading to restoration of airway patency. In some patients, neuromuscular compensation is impaired, and termination of events may depend on a change of sleep state (arousal) at either a cortical or subcortical level. Conversely, in some patients, an abnormally low arousal threshold may lead to arousal before compensatory mechanisms can dilate the airway and stabilize breathing. In this case, precipitous arousal may perpetuate the cycle of repetitive obstructive events. Recent studies demonstrate that pathophysiologic traits, including impaired neuromuscular response, low arousal threshold, high loop

gain, and anatomic factors, can be identified from clinical sleep recordings. While not yet incorporated into routine PSG analysis, these findings may help define OSA pathophysiologic subtypes or endotypes.

Cortical arousals are associated with changes detectable by EEG, whereas other responses may be detectable only by direct or indirect measures of autonomic activity such as heart rate, blood pressure, or peripheral arterial tone. Although arousals are not required to terminate all obstructive events, sleep fragmentation from arousals is nevertheless believed to be a significant cause of excessive daytime sleepiness.

As an apneic or hypopneic event progresses, the patient gradually becomes more hypoxemic. The degree of oxygen desaturation is dependent not only on the extent of airflow obstruction and duration of the event but also on the patient's baseline oxygen saturation and lung volume, as well as 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 and other mediators as a result of respiratory-related sleep fragmentation, repetitive episodes of oxygen desaturation, and increased sympathetic nervous system activity. These findings may be significant in the pathogenesis of hypertension and cardiovascular disease, cognitive dysfunction, and other changes related to OSA.

### *Objective Findings*

Obstructive apneas are documented by a cessation of airflow with ongoing respiratory effort during PSG or HSAT. 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 typically 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 the administration of positive airway pressure. In others, frequent central apneas persist or emerge, at least during the initial nights of positive airway pressure treatment (see Treatment-Emergent Central Sleep Apnea).

Oxygen saturation typically declines for a variable period 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% to as much as 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 (or flattening of inspiratory flow) and an arousal at event termination may not meet flow reduction 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). They are 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. 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. Bradyarrhythmias or tachyarrhythmias may accompany obstructive apneas and hypopneas; 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*

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

**Other sleep-related breathing disorders** Patients with *central sleep apnea* have predominantly central apneas rather than obstructive apneas, hypopneas, or RERAs as the primary finding on PSG or HSAT. If mixed apneas are predominant, a diagnosis of OSA should be made. Patients with *obesity hypoventilation syndrome* demonstrate daytime hypercapnia. Snoring may not be a prominent feature, although daytime sleepiness can occur. Patients with *sleep-related hypoventilation disorders due to a medical condition* may also show episodic or sustained oxygen desaturation without evidence of airflow obstruction on PSG or HSAT. Confirmation of nocturnal hypercapnia is diagnostic. However, if obstructive apneas or hypopneas are evident, a diagnosis of OSA should be made in addition to the diagnosis of sleep-related hypoventilation.

**Other hypersomnolence disorders** OSA must be differentiated from other causes of sleepiness such as *narcolepsy*, *idiopathic hypersomnia*, and *insufficient sleep*. These conditions may be suspected based on history, but PSG and MSLT or hypocretin determination are required to confirm a diagnosis of narcolepsy or idiopathic hypersomnolence.

**Other causes of nocturnal dyspnea** such as *nocturnal panic attacks*, *nocturnal gastroesophageal reflux*, *asthma*, *paroxysmal nocturnal dyspnea from congestive heart failure* (which may reflect *Cheyne-Stokes breathing*), and *nocturnal angina pectoris* must be considered in the differential diagnosis of OSA. In many cases, the absence of snoring and daytime sleepiness is highly suggestive of etiologies other than OSA. However, the absence of obstructive apneas, hypopneas, or RERAs on PSG definitively excludes OSA as the diagnosis.

## *Unresolved Issues and Further Directions*

Although substantial evidence implicates OSA as a risk factor for impaired cognition, mood disturbances, atrial fibrillation, coronary artery disease, stroke, and transient ischemic attacks, it has not been demonstrated that treatment mitigates these risks. The pathophysiologic mechanisms linking OSA to increased risk of atrial fibrillation, coronary artery disease, and stroke 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. While mood disturbance and cognitive dysfunction are linked to OSA, the impact of OSA treatment on these outcomes needs to be established. Additional studies are required to determine the role of novel OSA metrics other than the AHI and the physiologic impact of obstructive breathing patterns such as sustained inspiratory flow limitation that do not meet current criteria for hypopnea/apnea. Further research is also needed to understand the role of phenotypic clusters, defined either by clinical symptoms or pathophysiologic characteristics, in predicting OSA complications and treatment responses and in targeting therapy to specific pathophysiologic features.

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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, obstructive sleep apnea-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 because not only has it been applied to those with OSA only, but also indiscriminately used to describe persons who are only obese and those with obesity hypoventilation syndrome.

### *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 and other cognitive problems.
- B. PSG demonstrates one of the following:
  - 1. One or more obstructive apneas, mixed apneas, or hypopneas per hour of sleep.<sup>1,2</sup>
  - 2. A pattern of obstructive hypoventilation, defined as at least 25% of total sleep time with hypercapnia ( $\text{PaCO}_2 > 50$  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 are defined according to the latest version of the AASM Manual for the Scoring of Sleep and Associated Events. The manual also provides guidelines regarding the use of pediatric versus adult scoring criteria in adolescents.
- 2. Respiratory effort-related arousals (RERA's) are not included in the PSG criteria for pediatric obstructive sleep apnea because their relationship to signs and symptoms has not been adequately defined for this age group.

### *Essential Features*

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 or normal sleep patterns. 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, consisting of long periods of persistent partial upper airway obstruction associated with hypercapnia, arterial oxygen desaturation, or both. 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 due to this higher arousal threshold, sleep architecture is usually normal, with average 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 normal in young children up to three years old). When upper airway obstruction is long-standing, pectus excavatum can develop. 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.

Overt excessive daytime sleepiness is a less common daytime symptom in young children with OSA than adults, although it may be present in obese adolescents. Sleep disruption more often manifests as hyperactivity or impaired attention in young children. Attentional, learning, and behavioral issues may impair school performance. A mood disturbance may also be present.

### *Associated Features*

Hypoxemia and hypercapnia may be present during sleep and, in rare cases, may be severe. A prominent sinus arrhythmia is often seen, although other arrhythmias are rare. Nocturnal 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 compared with children without OSA, the size of the tonsils and adenoidal tissue does not predict the presence or severity of OSA in individual patients. There is emerging evidence of cardiovascular and metabolic consequences of OSA in children, including abnormal cardiac function, elevated blood pressure, insulin resistance, inflammation, and non-alcoholic fatty liver disease. However, unlike in adults, whether there is a direct relationship between the

severity of OSA determined by AHI and cardiovascular or metabolic consequences has not been well studied.

### *Clinical and Pathophysiological Subtype*

Not applicable or known.

### *Demographics*

OSA 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 adolescents is likely similar but less certain and is unknown in infants. 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; there is no evidence to suggest differences in prevalence in Hispanic or Asian children compared with White children. The disease can occur at any age, from the neonatal period to adolescence. Some studies suggest a bimodal peak in preschool children associated with adenotonsillar hypertrophy and obesity and, in adolescents, primarily associated with obesity.

### *Predisposing and Precipitating Factors*

Adenotonsillar hypertrophy and obesity are the most common predisposing/precipitating factors for OSA in otherwise healthy children, with adenotonsillar hypertrophy more relevant to younger children. Obesity may be a more important risk factor in older children and adolescents but is also relevant in younger children. Additional risk factors include prematurity, allergic disease, and anatomic features, including narrow or high arched palates. Underlying neurological conditions associated with reduced upper airway tone, including neuromuscular weakness/hypotonia and cerebral palsy, are associated with increased risk for OSA. Children with syndromic or genetic craniofacial microsomia, particularly micrognathia and midfacial hypoplasia (such as with Treacher Collins and Pierre Robin syndromes), are at increased risk, as are children with craniosynostosis syndromes, including Apert, Crouzon, Pfeiffer, Nuenke, and Saerthe-Chotzen syndromes. Multiple other genetic disorders and syndromes are associated with an increased risk for OSA, including trisomy 21, Prader-Willi syndrome, achondroplasia, muscular dystrophies, and mucopolysaccharidosis. OSA is highly prevalent in children with trisomy 21, who exhibit multiple underlying risk factors, including hypotonia, macroglossia, and increased risk for obesity. These children should be screened frequently for symptoms of OSA with a low threshold for diagnostic testing. Children with neuromuscular diseases often have upper airway muscle weakness, predisposing to airway collapse. Children with cerebral palsy may be predisposed to OSA because of spasticity, weakness, or incoordination of the upper airway muscles. Other medical conditions such as 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 and air pollution exposure have been



associated with snoring and OSA. There are disparities in the prevalence and outcomes of OSA with elevated risk in children from minority populations and lower socioeconomic groups.

### *Familial Patterns*

As in adults, heredity is a significant risk factor for OSA in children. There is a 2-4-fold increased risk of OSA in children with affected close family members. Potential mechanisms for familial aggregation include heritability of predisposing skeletal, soft tissue, body habitus, or respiratory control characteristics. Heritability may be significant in overweight compared with normal-weight individuals. Incidence rates in children with a sibling with OSA are elevated, although the relative roles of genetic factors versus environmental factors have not been determined.

### *Onset, Course, and Complications*

Longitudinal studies describing the natural history of prevalent and incident OSA in children are limited. The natural history of preschool-onset OSA is likely to differ from adolescent-onset OSA. Data from randomized controlled trials and a long-term follow-up study of pediatric OSA suggest spontaneous resolution is more common in non-obese children, females, and White children. Although it is difficult to quantify the impact of pediatric OSA on subsequent health outcomes due to a lack of longitudinal studies, data suggest there may be long-term sequelae. OSA can cause growth failure in early childhood, especially when associated with a comorbid genetic or craniofacial disorder. In addition, pediatric OSA is associated with cognitive and behavioral sequelae, including 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 are less common in children than adults but can include pulmonary hypertension, cor pulmonale, left ventricular hypertrophy, and systemic hypertension.

### *Developmental Issues*

Developmental issues are reviewed within individual sections.

### *Pathology and Pathophysiology*

In children, as in adults, OSA results from abnormal neuromuscular control of ventilation, arousal threshold, 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. There is a decrease in ventilatory drive and neuromuscular tone during sleep, facilitating upper airway collapse. Children are more able to maintain

airway patency than adults in the presence of OSA, with hypopneas or obstructive hypoventilation seen more often than apneas. In addition, children are less susceptible to cortical arousals and can better maintain normal sleep architecture than adults. Nevertheless, the resultant recurrent hypoxemia, hypercapnia, and sleep disruption may lead to neurobehavioral, cardiovascular, and growth abnormalities. Childhood OSA may also be associated with metabolic and inflammatory abnormalities.

Upper airway narrowing in most otherwise healthy children is primarily due to adenotonsillar hypertrophy. However, adenotonsillar hypertrophy alone does not lead to OSA, and OSA can occur without adenotonsillar hypertrophy. There is no direct relationship between tonsil size and OSA severity. The lack of relationship may be due to the interaction of tonsillar obstruction with other anatomic structures and non-anatomic factors such as ventilatory control. However, studies that clarify these relationships are limited. Obesity is a risk factor for childhood OSA. Other causes of upper airway narrowing include craniofacial microsomia such as 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. EEG arousals that meet the three-second duration criterion may or may not be present following apneas, especially in young children; however, 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 normal during NREM sleep. Obstructive events are frequently associated with desaturation and hypercapnia.

Delineation of the site of obstruction by radiography, advanced imaging, or drug-induced sleep endoscopy may help direct treatment. However, there is less evidence for this approach in children than adults. In addition, echocardiography may show evidence of right, left, or biventricular hypertrophy.

### *Differential Diagnosis*

**Isolated snoring** Pediatric OSA must be differentiated from *isolated snoring* (*i.e.*, snoring without apneas, hypopneas, or gas exchange abnormalities on PSG). 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. Assessment of symptoms alone or in combination does not reliably distinguish OSA from primary snoring; polysomnography is needed to make this distinction. Nocturnal pulse oximetry and HSAT are not equivalent to attended PSG but may be useful in resource-limited environments.

**Other sleep-related breathing disorders** *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 challenging to separate nonobstructive hypoventilation and desaturation from OSA, especially because the two conditions may coexist. Children with nonobstructive hypoventilation typically do not snore and do not have paradoxical inward rib cage motion during inspiration, although the latter may be present in children with neuromuscular disease.

**Other hypersomnolence disorders** 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 with 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 work defining scoring criteria for respiratory events in infants and data regarding the prevalence in infants and adolescents is needed. The natural course of the disease, the optimal techniques for monitoring patients during PSG, and the effects of mild OSA require further study. Consideration of diagnostic criteria in addition to or as an adjunct to the AHI is warranted. The use of alternatives to PSG for diagnosis, an approach to severity classification, and the threshold necessitating treatment should also be further investigated. The role of genetic, environmental, and social determinants of health in the pathophysiology of childhood OSA must be further explored. Finally, additional work is needed to understand phenotypes and endotypes of pediatric OSA and the role of personalized therapies.

No specific clinical phenotypes have been identified for pediatric OSA. This is due, in part, to the fact that most children treated with adenotonsillectomy for snoring and obstructed breathing do not undergo polysomnography before surgery, limiting the amount of clinical and PSG data.

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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 -E satisfy the criteria

- A. The presence of one or more of the following:
  - 1. Sleepiness.
  - 2. Difficulty initiating or maintaining sleep or nonrestorative sleep.
  - 3. Awakening short of breath.
  - 4. 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 the following:
  - 1. Five or more central respiratory events<sup>1</sup> (central apneas or central hypopneas) per hour of sleep.
  - 2. The total number of central apneas plus central hypopneas is > 50% of the total number of apneas and hypopneas.<sup>2</sup>
- D. The pattern of ventilation meets criteria for Cheyne-Stokes breathing (CSB).<sup>1</sup>
- E. The disorder is not better explained by another current sleep disorder, medication (e.g., opioids), or substance use.

#### 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 should 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. Most patients with CSA-CSB have heart failure (either reduced or preserved ejection fraction). In systolic heart failure, the cycle length is more prolonged (due to a longer respiratory phase) than in patients with diastolic heart failure. There is often a delay in the nadir of the associated oxygen desaturation. Patients with CSA-CSB have normal or low daytime arterial PCO<sub>2</sub> (PaCO<sub>2</sub>). A diagnosis of CSA-CSB requires that events are predominantly central apneas and hypopneas with an average frequency of at least five events/hour during a full-night diagnostic PSG or on the diagnostic or therapeutic portion of a split-night study. For patients with a mixture of OSA and CSA-CSB, central apneas may persist or increase in frequency after elimination of upper airway obstruction on positive airway pressure. In patients with CSA-CSB, arousal from sleep tends to occur at the zenith of respiratory effort between contiguous central apneas or hypopneas. These arousals can result in sleep fragmentation. As a result, 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 up to 60% of patients with symptomatic heart failure have some form of sleep apnea (CSA-CSB and/or obstructive), a high index of suspicion for these disorders is indicated. A CSB pattern can also occur during wakefulness and can be observed at the 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 indicate that it can be noted after stroke (though this often resolves spontaneously). CSA-CSB can rarely present in an idiopathic form or associated with renal failure.

As in other forms of CSA, apneas and hypopneas are characterized by absent or reduced ventilatory effort, respectively, due to diminished central respiratory drive during the events. 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 attenuates during REM sleep. In patients with both OSA and CSA-CSB, the relative amount of central and obstructive apnea can vary from night to night or even within the same night.

### *Clinical and Pathophysiological Subtypes*

Some patients have combined OSA and CSA, and the CSA-CSB may not fully 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. The use of  $\beta$ -blockers and angiotensin-converting enzyme inhibitors to treat 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 in 26% to 50% of patients in the acute period following stroke.

### *Predisposing and Precipitating Factors*

The most important predisposing factors are 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, atrial fibrillation, and daytime hypocapnia (i.e., awake PaCO<sub>2</sub> of 38 mm Hg or less). Greater pulmonary congestion (higher left ventricular end-diastolic pressure) generally predicts lower PaCO<sub>2</sub>. 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 of CSA with CSB. However, because it occurs 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 systolic congestive heart failure, CSB is associated with a poor prognosis, as indicated by a greater adjusted relative risk for mortality/cardiac transplantation than seen in patients without CSB. These data suggest that the CSB pattern during sleep could participate in the pathophysiology and progression of heart failure. However, others have argued that CSB might only represent a marker or compensatory response to substantial heart failure. CSB in the setting of acute heart failure may resolve with treatment of acute heart failure. CSB may also improve after optimizing

treatment in chronic heart failure (e.g., after cardiac resynchronization therapy or post-transplantation). 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.

### *Developmental Issues*

Although there are reports of CSB in children, the condition is extremely rare in this age group. 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. However, 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<sub>2</sub> and PaO<sub>2</sub> (due to increased circulation time) are likely the major factors. This breathing disorder tends to occur in individuals with a chronically low PaCO<sub>2</sub> when awake and asleep. Hyperventilation occurs due to an increase in the responsiveness of the peripheral and central chemoreceptors (higher controller gain). The increased responsiveness is believed to be due to both increased sympathetic tone and stimulation of vagal receptors in the lungs by pulmonary congestion. The eupneic PaCO<sub>2</sub> in individuals with CSB pattern and heart failure is closer to their apneic threshold than those without CSB pattern (primarily due to a smaller sleep-related rise in PaCO<sub>2</sub> in those with CSB) so that even modest increases in ventilation can drive PaCO<sub>2</sub> below the apneic threshold. The most common trigger factor for central apnea is an arousal from sleep, which abruptly augments ventilation and drives PaCO<sub>2</sub> below the apneic threshold.

The crescendo-decrescendo pattern of tidal volume results from prolonged lung-to-chemoreceptor circulatory delay, resulting in very slow transmission of changes in PaCO<sub>2</sub> in the lungs to the chemoreceptors. This, in turn, results 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 preserved 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 associated with these medical disorders are believed to be due to a reduction in PaCO<sub>2</sub> 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 N1 and N2. It tends to dissipate in N3 and REM sleep. In N3 sleep, the sleeping PaCO<sub>2</sub> 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<sub>2</sub> below the apneic threshold.

Arousals are frequently seen 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 more prolonged 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 signs of flow limitation or obstruction such as 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 N3 sleep. Additionally, PaCO<sub>2</sub> 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 course of the night and is associated with a fall in the sleeping PaCO<sub>2</sub>. The gradual decrease in sleeping PaCO<sub>2</sub> is thought to be due to a progressive increase in pulmonary congestion over the course of the night with stimulation of juxtacapillary (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*

**Other sleep-related breathing disorders** *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<sub>2</sub> ≥ 45 mm Hg and/or sleep-related hypoventilation. Patients with CSA-CSB usually have an awake PaCO<sub>2</sub> < 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, but 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 preserved ejection fraction and the extent to which it contributes to impaired quality of life, sleepiness, or worsening heart failure. Whether targeted treatment of CSB improves cardiovascular outcomes in heart failure is also unclear.

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## Central Sleep 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<sup>1</sup>:
  1. Sleepiness.
  2. Difficulty initiating or maintaining sleep, frequent awakenings, or nonrestorative sleep.
  3. Awakening short of breath.
  4. Witnessed apneas.
- B. PSG shows all the following:

1. Five or more central respiratory events<sup>2</sup> (central apneas or central hypopneas) per hour of sleep.
  2. The total number of central apneas plus central hypopneas is > 50% of the total number of apneas and hypopneas.
  3. Absence of CSB.<sup>2</sup>
- C. The disorder occurs as a consequence of a medical or neurological disorder and is not better explained by medication/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 Cheyne-Stokes breathing (CSB)) is classified here. CSB has a classical crescendo-decrescendo pattern in respiratory effort, typically repeating every 45-60 seconds. In contrast, central apneas without Cheyne-Stokes breathing tend to be abrupt, ataxic, and have a shorter cycle length. Typically, CSA occurs in the setting of known neurological disorder such as stroke or hindbrain/spinal cord lesion. Some of the medical conditions that can lead to CSA (e.g., stroke, end stage renal disease, muscular dystrophy) can predispose to CSA with or without a Cheyne Stokes pattern of breathing. For example, myotonic dystrophy might lead to congestive heart failure and CSA in a Cheyne Stokes pattern, or decreased brainstem sensitivity to CO<sub>2</sub> that causes CSA not in a Cheyne Stokes pattern.

#### *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 witnessed apnea and awakening with shortness of breath. The presentation varies with the cause of the central sleep apnea disorder and may include neurological findings.

## *Clinical and Pathophysiological Subtypes*

None. Some of the common medical and neurological disorders causing central sleep apnea without CSB are listed in *Pathology and Pathophysiology* (below).

## *Demographics*

The prevalence and demographics of this disorder vary with the underlying etiology. For example, 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, and the following list is not considered exhaustive. Often, some abnormality is present at or proximate to the respiratory control centers of the central nervous system. The most common predisposing conditions are brainstem lesions of developmental, vascular, neoplastic, degenerative, demyelinating, or traumatic etiology. For example, 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. Patients with CM exhibit obstructive, central, or a mixture of obstructive and central apneas. Some patients exhibit nocturnal hypoventilation but rarely daytime hypoventilation. Similarly, high spinal cord lesions causing tetraplegia are also associated with CSA.

Some medical conditions may predispose to either CSA or OSA, with CSA predominating in certain pathophysiological subtypes. Acromegaly generally predisposes to OSA; however, CSA is also described, perhaps due to hormonal changes affecting breathing. Chronic kidney disease is similarly associated with OSA and CSA, the latter sometimes in a Cheyne-Stokes pattern (which would be classified elsewhere). Finally, some disorders such as muscular dystrophy may demonstrate OSA and central sleep apnea with or without concomitant sleep-related hypoventilation. In this last case, muscle weakness can cause hypoventilation events that appear to meet the criteria for central apneas. These events reflect profound muscle weakness making respiratory effort difficult to detect despite some degree of preserved central respiratory drive. Hypoventilation in such cases may be most prominent throughout REM sleep with reduced activation of accessory muscles and reliance on a weakened diaphragm. Thus, careful consideration of the underlying medical condition and sleep data is necessary to establish this diagnosis.

## *Familial Patterns*

None known.

### *Onset, Course, and Complications*

Onset, course, and complications vary with the different etiologies. In CM the presentation is typically 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 hypersomnolence, 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. Patients with Prader-Willi syndrome may have central sleep apnea as infants but convert to predominantly OSA later in childhood due to obesity. Patients with muscular dystrophy will worsen over time and will require progressively greater levels of ventilatory support or a backup rate as inspiratory triggering becomes weaker and weaker.

### *Developmental Issues*

Not known.

### *Pathology and Pathophysiology*

While the cause of CSA depends on the specific medical disorder, the underlying abnormality is generally caused by dysfunction of central ventilatory control centers. The presence of sleep may unmask ventilatory control abnormalities with the loss of the wakefulness stimulus. In addition, other medical conditions may contribute to altered control of breathing that result in transient cessation of respiratory drive despite normally functioning ventilatory control centers in the brainstem.

Sleep-related hypoventilation or daytime hypoventilation may coexist with CSA due to medical or neurological disorder without CSB, in which case both diagnoses should be made.

As noted above, in the case of muscular dystrophy or other neuromuscular disorders, diaphragmatic weakness may be profound, particularly during phasic REM. There may be no apparent airflow or detectable respiratory effort, giving rise to events that appear to meet criteria for central apnea despite intact neural output from CNS ventilatory control centers. In the appropriate clinical context, more sensitive measures of respiratory effort may be required to appropriately distinguish these hypoventilation episodes from central apneas.

## Objective Findings

The polysomnogram of the patient with CSA due to medical or neurological condition—not CSB—demonstrates recurrent (five or more per hour) central apneas or central hypopneas. Runs of recurrent central apneas separated by periods of ventilation may occur. The inter-event respiratory phase is typically brief, consisting of only several breaths. The central apneas do not have the pattern of CSB.

Measures of respiratory effort (e.g., diaphragm EMG or esophageal manometry) may be used to differentiate between lack of respiratory effort due to lack of central drive to breathe (i.e., central apnea) versus difficult-to-discern respiratory effort due to neuromuscular weakness. However, even with advanced modalities to detect effort, it can become virtually impossible to distinguish lack of neural output from brainstem ventilatory control centers from lack of ability to convert that neural signal to inspiratory effort in patients with advanced neuromuscular disease.

## Differential Diagnosis

**Other sleep-related breathing disorders** Patients with CSA due to medical or neurological disorder—without 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 a daytime hypercapnia<sub>2</sub>. Finally, in those with neuromuscular disorders, consideration should be given to carefully evaluate whether events appearing to reflect central apneas actually reflect hypoventilation episodes with severe neuromuscular weakness limiting ability to detect effort, rather than a loss of central respiratory drive. In certain diseases such as myotonic dystrophy, both hypoventilation due to neuromuscular weakness and central sleep apnea may co-exist.

Although CSA may arise in the setting of stroke, OSA is still much more common, accounting for more than 90% of all diagnoses of sleep apnea after stroke.

## 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 generally not well characterized, sometimes without clear distinction between CSA with and without Cheyne Stokes breathing.

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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. The breathing disturbance occurs at high altitude.<sup>1</sup>
- B. The presence of one or more of the following:<sup>2</sup>
  1. Sleepiness.
  2. Difficulty initiating or maintaining sleep, frequent awakenings, or nonrestorative sleep.
  3. Awakening with shortness of breath or morning headache.
- C. Witnessed periodic breathing or PSG performed at altitude demonstrates recurrent central apneas or central hypopneas, with a central AHI  $\geq 5$  events/hr.
- D. The disorder is not better explained by another current sleep disorder, medical disorder, medication (e.g., narcotics), or substance use.

### Notes

1. Typically, at least 2500 meters (8,202 feet), although some individuals may exhibit the disorder at altitudes as low as 1500 meters.
2. Periodic breathing is a common response to altitude. Therefore, associated symptoms (Criterion B) are required to diagnose the disorder.
3. A diagnosis of CSA due to high-altitude periodic breathing does not exclude a diagnosis of OSA.



### *Essential Feature*

High-altitude periodic breathing is characterized by alternating periods of central apnea and hyperpnea associated with being at high altitude. The pattern of periodic breathing is an expected response 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 2500 meters (8,202 feet), and virtually 100% demonstrate periodic breathing at 4000 m (13,123 feet). Periodic breathing has been described at altitudes as low as 1500 meters (4900 feet). Chronic exposure to altitude above 2500 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 altitude include a reduction in stage N3 sleep and increased arousal frequency. Although total sleep time is generally preserved, it will decrease at altitudes higher than 3500m. Of note, the degree of both subjective and objective impairment of sleep quality was not correlated with the severity of periodic breathing in several studies.

### *Clinical and Pathophysiological Subtypes*

None known.

### *Demographics*

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 is more common in men than women. As stated above, periodic breathing will occur in virtually anyone ascending to higher than 4000 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 at altitude. This hyperventilation leads to a hypocapnic alkalosis that, during sleep, inhibits ventilation. Thus, repetitive cycles of apnea and hyperpnea develop during NREM sleep. The obvious precipitating factor for 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, there is likely to 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 is generally evident during sleep immediately after ascent to altitude. The occurrence and onset of breathing disturbance depend to some extent on the rapidity of the ascent, the elevation, and individual predisposition. However, it is often present on the first night at altitude. The breathing pattern may become more regular over time at moderate altitude, although it is likely to persist more than one year at extreme altitude. One study found that periodic breathing increased 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 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 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 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 demonstrated both 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 might have a lower hypocapnic apnea threshold 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 2500 meters, the atmospheric pressure is approximately 570 mm Hg, and the ideal alveolar  $PO_2$  is 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 robust hypoxic responses tend to demonstrate this respiratory pattern more commonly. 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 throughout the night. The respiratory pattern is often improved during REM sleep with reduced cycling. This improvement is likely due to the decreased hypoxic and hypercapnic responsiveness characteristic of REM sleep. One study found that the hypoxic ventilatory response continued to increase up to seven days after ascent to altitude, resulting 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 periodic breathing increases over three days to two weeks of acclimatization despite improvements in oxygen saturation. The increase in periodic breathing and oxygen saturation is thought to be due to increased controller gain of the respiratory system.

Several studies have found that the impairment of sleep architecture does not correlate with the degree of periodic breathing. One study found that periodic breathing was greater on the third night at altitude compared to the first night. However, both the nocturnal oxygen saturation and amount of N3 sleep also increased on the third night compared to the first night. It has been hypothesized that hypoxia rather than periodic breathing might be the most significant 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, 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 is much more common during NREM sleep than REM sleep. The apneas and associated hyperpnea can lead to recurrent arousals from sleep, although several studies suggest that the frequency of periodic breathing may be substantially greater than the arousal frequency. A slight to moderate reduction in N3 sleep is the most reported alteration in sleep structure. REM sleep duration is generally preserved, as is total sleep time, at least at moderate altitudes.

### *Differential Diagnosis*

**Other sleep-related respiratory disorders.** The major distinguishing factor between high-altitude periodic breathing and other SRBDs is, of course, occurrence at high altitude. An individual with OSA is likely to continue to have this nocturnal respiratory problem at altitude. Altitude might even exacerbate underlying OSA. Patients with *chronic mountain sickness* demonstrate relative hypoventilation at altitude (i.e., breathe less than is encountered in normal individuals at a similar altitude). They are more hypoxic than normal individuals (i.e., those who demonstrate a more robust ventilatory response to the same ambient hypoxia). During sleep, these individuals often show further arterial oxygen desaturation. Some 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 significant factor impairing sleep quality. However, further studies relating changes in sleep and periodic breathing at altitude over time 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-D must be met

- A. The patient is taking an opioid, ticagrelor or other medication known to impact respiratory control.
- 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. Witnessed apneas.

- C. PSG shows all the following:
  - 1. Five or more central respiratory events<sup>1</sup> (central apneas or central hypopneas) per hour of sleep.
  - 2. The total number of central apneas plus central hypopneas is > 50% of the total number of apneas and hypopnea
- D. The disorder is not better explained by another current sleep disorder or medical disorder.

#### Notes

- 1. As defined by the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events.
- 2. Abnormal breathing patterns including ataxic breathing (irregular variations in respiratory cycle time and tidal volume), Biot's breathing (irregular tidal volume), cluster breathing, or Cheyne Stokes breathing may be observed.
- 3. Nocturnal or daytime hypoventilation may be present but is not required. If sleep-related hypoventilation is present, a diagnosis of sleep-related hypoventilation due to medication or substance use can be made in addition to a diagnosis of central sleep apnea due to a medication or substance.
- 4. A diagnosis of CSA due to a medication or 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 and individuals treated with fentanyl patches or continuous narcotic infusions. Suboxone (a combination of buprenorphine and naloxone) is often used to treat patients with narcotic dependence and pain and can also cause medication-induced central apnea. Many individuals use multiple drugs (prescribed or illicit) that can synergistically affect sleep and breathing. For example, approximately 30% of long-term opioid users are prescribed sedative-hypnotic medications concurrently. Due to the potential risks of extreme sleepiness, respiratory depression, and death associated with this combination of medications, the FDA has required additional warnings to the labeling of opioids and benzodiazepines. In addition to opioids, the antiplatelet agent, ticagrelor, has also been identified as a cause of central sleep apnea.

#### *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. Many patients present with a combination of both OSA and CSA. CSA and sleep-related hypoventilation can also co-exist. In those with sleep-related hypoventilation coexisting with CSA, daytime CO<sub>2</sub> levels may be elevated or normal. Daytime

oxygen saturation has been observed to be lower among chronic opioid users. 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, sleepiness may not substantially improve even if the central apnea is treated successfully. One study of patients on chronic methadone maintenance found that the average Epworth Sleepiness Scale score was within normal range. In these patients, who manifested mild to moderate OSA (average AHI about 18/hour), the degree of sleepiness correlated with depressive symptoms but not with blood methadone levels. However, a case series of patients treated with opioids for chronic pain observed 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 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*

A recent systematic review found that the prevalence of CSA among chronic opioid users was 24%. Among individuals taking opioids, older age, lower BMI, and male sex have been associated with more central apnea events.

### *Predisposing and Precipitating Factors*

The use of a potent, long-acting opioid is the major causative factor. A linear relationship between opioid dose and central apnea events has been observed, with a substantial risk of CSA in patients taking a morphine equivalent daily dose of 200 mg or more. If patients are successfully withdrawn from the offending medication, the central apnea may resolve. Chronic opioid users with existing OSA are at increased risk for comorbid CSA. The frequency of central apneas is also higher among patients taking benzodiazepines and chronic methadone than those chronically taking methadone alone. While the semisynthetic opioid partial  $\mu$ -agonist buprenorphine has been increasingly widely prescribed (at least in part due to the perception that it is less likely to cause respiratory suppression), a case series of 70 consecutive patients prescribed buprenorphine found moderate or severe sleep apnea (AHI  $\geq 15$ , including both obstructive and central events) in 33% of the group, with central apneas predominating. Higher levels of morphine equivalents have been associated with more central apnea events in opioid users. Recently, ticagrelor, a P2Y<sub>12</sub>-receptor antagonist, has been described in multiple case reports and case series to be associated with an increased risk for central sleep apnea. These effects are specific to ticagrelor and are not observed with other antiplatelet agents.

### *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 opioids, with the Centers for Disease Control and Prevention reporting that opioids were involved in 69.5% of drug overdose deaths in 2018. There has been a significant increase in deaths associated with methadone due to the increasing use of this medication for chronic pain. Many of these deaths occur during sleep. Greater restrictions on prescription of opioids has led many patients with opioid-related CSA to turn to illicit sources. The increased prevalence of potent synthetic opioids such as fentanyl and carfentanil has greatly increased the risk of both overdose and related fatalities.

### *Developmental Issues*

Information regarding the presentation of this disorder in children is limited. However, 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 the various breathing abnormalities during sleep with opiates is the respiratory depression that occurs through the action of the drugs on the  $\mu$ -receptors on the ventral surface of the medulla, in the pre-Bötzinger complex. 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 compared to controls who were not taking opioids. The difference was not due to a lower tidal volume but instead, 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. Ticagrelor increases ventilatory sensitivity to CO<sub>2</sub> by increasing controller gain and thereby contributing to central apnea. This increased chemoreflex sensitivity also can contribute to the sensation of dyspnea.



## *Objective Findings*

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 several types of irregular breathing patterns. Although definitions vary, Biot's breathing is generally meant to indicate an irregular tidal volume. Ataxic breathing is characterized by an irregular breathing rhythm as well as an irregular tidal volume. In cluster breathing, respiratory frequency is high, with regular tidal volumes followed by periods of apnea. All these patterns are commonly observed with opioid use. Cheyne-Stokes breathing, and central apneas may also be seen. 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 N3 sleep. Unlike other forms of central apnea, drug-induced central apneas may occur during N3 sleep. Morning dosing of extended-release opioids may reduce the frequency of apnea events without compromising pain control and sleep quality/quantity.

## *Differential Diagnosis*

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

## *Unresolved Issues and Further Directions*

There are conflicting data on baclofen as a cause of CSA. Further research on the role of baclofen in causing CSA in the typical clinical contexts of its use. Further study is also needed to determine risk factors and pathogenesis for CSA in users of long-acting opioids. These sleep-disordered breathing patterns are suspected of playing a role in the unexplained increased mortality in chronic opioid users. Well-controlled trials are still needed to determine whether medication-induced CSA has meaningful clinical impacts on patient-centered outcomes and optimal therapies.

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## Primary Central Sleep Apnea

*ICD-9-CM code : 327.21*

*ICD-10-CM code: G47.31*

### *Alternate Name*

Idiopathic central sleep apnea.

### *Diagnostic Criteria*

Criteria A-D must be met

- A. The presence of at least one of the following<sup>1</sup>:
  1. Sleepiness.
  2. Difficulty initiating or maintaining sleep, frequent awakenings, or nonrestorative sleep.
  3. Awakening short of breath.
  4. Witnessed apneas.
- B. PSG demonstrates all the following:

1. Five or more central respiratory events<sup>2</sup> (central apneas or central hypopneas) per hour of sleep.
  2. The total number of central apneas plus central hypopneas is > 50% of the total number of apneas and hypopneas
  3. Absence of CSB.<sup>2</sup>
- C. There is no evidence of daytime or nocturnal hypoventilation.
- D. The disorder is not better explained by another current sleep disorder, medical disorder, medication or substance use.

#### 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 respiratory events, defined as a reduction or cessation of airflow during sleep associated with a diminished or absent 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 and frequent awakenings. Patients may present with a complaint of insomnia, daytime sleepiness, or both. Other signs and symptoms that are often, but not invariably, present include witnessed apnea and awakening with shortness of breath. Central sleep apnea with CSB and CSA due to a known medical or neurological disorder, opioid use, or other substance uses are classified elsewhere.

#### *Associated Features*

Patients with primary CSA tend to have low normal arterial PaCO<sub>2</sub> during wakefulness (less than 40 mm Hg).

#### *Clinical and Pathophysiological Subtypes*

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

#### *Demographics*

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 difference. In children, case series suggest that primary CSA is very rare.

### *Predisposing and Precipitating Factors*

CSA in these patients occurs because of transient decreases in the arterial  $\text{PCO}_2$  ( $\text{PaCO}_2$ ). During wakefulness, drops in  $\text{PaCO}_2$  do not result in apnea. However, when the  $\text{PaCO}_2$  drops below the apnea threshold during sleep, respiratory effort ceases. For most people, the apnea threshold is within a few mm Hg of the baseline sleep  $\text{PaCO}_2$ . Any factors that narrow the gap between the sleeping  $\text{PaCO}_2$  and the apnea threshold level predispose to the development of a central apnea. Additionally, a high ventilatory response to  $\text{CO}_2$  seems to be a major predisposing factor in the development of primary CSA and can lead to instability in ventilation. Frequent arousal may also predispose to recurrent central apneic events. Ventilatory response to  $\text{CO}_2$  increases with the transition from sleep to wake. Increased ventilation associated with arousal can result in a  $\text{PaCO}_2$  that is below the apnea threshold after the return to sleep, resulting in a central apnea. The apnea results in a rise in  $\text{PaCO}_2$ , arousal from sleep, and a repeat of the cycle. Thus, any disorder that results in sleep-wake instability may worsen CSA. Because ventilatory drive is lower during REM than NREM sleep,  $\text{PaCO}_2$  rises. The higher  $\text{PaCO}_2$  in REM reduces the likelihood of central events. Some studies have also suggested a worsening of primary CSA in the supine position, but this observation has been more clearly documented in patients with CSB.

### *Familial Patterns*

Some data suggest that ventilatory chemoresponsiveness is directly inherited. Because elevated  $\text{CO}_2$  responsiveness is a predisposing variable in the development of primary CSA, it would seem likely that there would be a familial pattern in this respiratory abnormality. However, there are no data addressing this issue.

### *Onset, Course, and Complications*

Very little information regarding onset, course, or complications is available. The apneas can lead to sleep fragmentation, yielding 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. It should be noted that central apnea is defined 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 premature and term infants until respiratory centers in the brain mature. Brief central apneas (typically under 10 seconds) with arousal or desaturation occur as a normal physiologic response to relative hypocapnia in infants and children. These events may be seen in wake-to-sleep transition, following movements, or following sighs in sleep. These apneas may be interpreted as physiological despite meeting criteria for scoreable events.

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 increased sensitivity of the respiratory control system to carbon dioxide that leads to 1) increased responsiveness to changes in CO<sub>2</sub> (leading to exaggerated ventilation to small changes in CO<sub>2</sub>) and 2) a PaCO<sub>2</sub> during sleep that lies closer than average to the apnea threshold. Both may contribute to transient drops in PaCO<sub>2</sub> below the apnea threshold, yielding a cessation of ventilation. In addition, arousal from sleep (and associated changes in ventilation between wake and sleep) are also contributory, as discussed above. Because respiratory control is more stable in N3 and REM sleep, central apnea in patients with primary CSA most often occurs during N1 and N2 sleep and is rare in other stages.

### *Objective Findings*

The PSG of the patient with primary CSA demonstrates a central apnea/hypopnea index of > 5 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 intervening respiratory phase is typically brief with a maximum of five breaths and 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 increased N1 and N2 sleep at the expense of 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<sub>2</sub> 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. Most normal individuals should not have more than five central apneas per hour of sleep.

**Other sleep-related breathing disorders** Primary CSA must be distinguished from other respiratory disorders in sleep and is considered a diagnosis of exclusion. Some patients with predominantly OSA have central apneas during diagnostic or positive airway pressure titration studies (see Treatment-Emergent CSA). 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 observed 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 more prolonged respiratory phase between central apneas. In primary CSA, the apnea is often terminated abruptly by a large breath, and there are usually no more than 4 to 5 breaths between apneas. Furthermore, most patients with Cheyne-Stokes respiration have a history of congestive heart failure or a neurological disorder.

Patients with *central apnea due to medication or substance use*, particularly potent long-acting narcotics, may exhibit periodic breathing with central apneas of similar appearance to primary CSA. However, the underlying breathing pattern 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 N3 sleep 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). Absent an identified comorbid disorder, 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 few other symptoms. Thus, primary CSA is a diagnosis based on the exclusion of other causes of CSA.

In *sleep-related hypoventilation and hypoxemic syndromes*, patients have normal or increased daytime PaCO<sub>2</sub> with the onset or worsening of hypoventilation during sleep. Daytime hypoventilation is defined as a PaCO<sub>2</sub> > 45 mm Hg. Patients with primary CSA usually have an awake PaCO<sub>2</sub> < 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 reduced tidal volume (shallow pattern of breathing), often without a compensatory increase in respiratory rate. There is usually significant oxygen desaturation secondary to hypoventilation 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. The treatment options that are most effective remains unknown. Furthermore, the benefits of treatment beyond symptom management remain to be determined.

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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 terms “brief resolved unexplained events (BRUE)” and “apparent life-threatening event (ALTE)” should not be used. Although some infants with primary sleep apnea present with a BRUE, there are many other causes of BRUE, and some children with sleep apnea do not have BRUE.

### *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 gestational age of at least 37 weeks.



- C. PSG or alternative monitoring such as portable apnea monitoring shows one of the following:
  - 1. Recurrent, prolonged (> 20 seconds duration) central apneas.<sup>1,2</sup>
  - 2. Recurrent central apneas of shorter duration associated with bradycardia or oxygen desaturation.<sup>2</sup>
  - 3. Periodic breathing<sup>2</sup> for  $\geq 5\%$  of total sleep time after a chronological age of 3 months
- D. The disorder is not better explained by another sleep disorder, medical 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 born by at least 37 weeks gestational age. These events are typically associated with physiological compromise (hypoxemia, bradycardia) or the need for intervention such as stimulation or resuscitation. Obstructive or mixed apneas or obstructive hypopneas may also be seen, although central events are the predominant finding. It is a disorder of respiratory control associated with immaturity of the brainstem respiratory centers.

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

#### *Associated Features*

Primary CSA of infancy is state-dependent. It can occur during NREM sleep, although the frequency of respiratory events may increase during REM sleep. Infants may also present with a BRUE (defined by the American Academy of Pediatrics as an event occurring in an infant younger than 1 year of age where the observer reports a sudden, brief, and now resolved episode of one or more of the following: [1] cyanosis or pallor; [2] absent, decreased, or irregular breathing; [3] marked change in tone (hyper- or hypotonia); and [4] altered level of responsiveness. However, many infants with primary CSA of infancy will not have

a BRUE, and many BRUEs are not associated with apnea. In fact, many infants with a history of BRUE will not have evidence of a sleep-related breathing disorder on polysomnography.

Paradoxical chest wall movements are common during REM sleep in infants due to the increased chest wall compliance. These movements may cause a fall in arterial oxygen saturation due to reduced functional residual capacity leading to lowered oxygen stores and changes in ventilation-perfusion relationships. In addition, underlying comorbidities (e.g., chronic lung disease or abnormal neurological status) can predispose the infant to a more severe or prolonged course for apnea. A small upper airway exaggerates the obstructive elements of this disorder.

### *Clinical and Pathophysiological Subtypes*

None known.

### *Demographics*

Less than 0.5% of full-term newborns experience symptomatic apnea. During the first six months of life, 2% of healthy full-term infants experience at least one apnea event lasting at least 30 seconds 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 infants of all races and ethnic groups.

### *Predisposing and Precipitating Factors*

Apnea in the neonate or infant may be exacerbated or precipitated by a variety of medical conditions, such as anemia, hypoxemia, metabolic disorders, neurologic disorders (seizures or intracranial pathology), sedating medications, anesthesia, genetic (congenital central hypoventilation syndrome), or infection (including sepsis, meningitis, respiratory syncytial virus infections, and pertussis). Infection with respiratory syncytial virus and pertussis, in particular, can increase the frequency and the duration of apneas. Children with chromosomal abnormalities or chronic lung disease may also be predisposed to apneic episodes.

If another medical condition appears to be the cause rather than an exacerbating factor for the CSA, the condition should be classified as CSA due to a medical or neurological condition or CSA due to a medication or substance.

### *Familial Patterns*

None known.

### *Onset, Course, and Complications*

Apnea onset is usually in the first few days or weeks of life. Some infants may be diagnosed by nursing observations or routine monitoring soon after birth. Older infants may present with a BRUE or may have failure to thrive. The prognosis is generally good, with resolution of apnea over the first year of life and no residual sequelae. Persistent severe apnea may indicate an underlying medical condition and should prompt further evaluation. Patients with persistent severe apnea may develop sequelae related to hypoxic events. Central apneas in the pattern of periodic breathing (typically absent the first week of life) begin around 2-4 weeks of age and become rare by 6 months of age.

### *Developmental Issues*

This disorder is a condition of infancy that usually 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.

### *Objective Findings*

Apnea is predominantly central, but obstructive and mixed apneas may occur. Apneas are seen most frequently during REM sleep. Periodic breathing is seen most frequently during NREM sleep. Other diagnostic tests, such as an EEG, evaluation for feeding difficulties, or esophageal motility studies, may be appropriate in individual cases.

### *Differential Diagnosis*

**Normal respiratory pauses** are observed during sleep in infants and should be distinguished from Primary CSA of infancy. 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.

**Brief resolved unexplained events (BRUE)** Primary CSA of infancy should be distinguished from BRUE, which is characterized by a report of a sudden, brief, resolved episode of at least one of the following:

cyanosis or pallor; absent or decreased or irregular breathing, marked change in tone (hyper- or hypotonia); or altered level of responsiveness.

**Central sleep apnea due to a medical condition** Recurrent, severe infant sleep apnea is usually due to other comorbid conditions, such as metabolic disease, or unrecognized neurological conditions such as seizures, brainstem malformation, or neurodegenerative condition; thus, an evaluation for these conditions should be performed.

**Factitious disorder imposed by another** This form of child abuse is manifest as imposed upper airway obstruction or attempted suffocation and should be considered in the differential.

**Sudden infant death syndrome** Primary CSA of infancy should be disassociated from the postmortem diagnosis of *SIDS*. Although a small percentage of *SIDS* victims experience apnea symptoms before 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. Larger cohort studies of infants are needed to further characterize normative indices of prolonged central apneas (>20 seconds), shorter central apneas associated with desaturations or bradycardia, and duration and extent of periodic breathing.

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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 gestational 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.<sup>1,2</sup>
  2. Recurrent central apneas of shorter duration associated with bradycardia or oxygen desaturation.<sup>2</sup>
- D. The disorder is not better explained by another sleep disorder, medical disorder, or medication use.

### Notes

1. Normative data concerning the number of prolonged central apneas per hour are not well established because of variations by gestational and post-natal ages.

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*

Primary CSA of prematurity is characterized by prolonged, predominantly central apneas in children born at less than 37 weeks gestational age. These events are typically associated with physiological compromise (hypoxemia, bradycardia), or the need for intervention such as stimulation or resuscitation. Obstructive or mixed apneas or obstructive hypopneas may also be seen, although central events are the predominant finding. It is a disorder of respiratory control due to immaturity of the brainstem respiratory centers.

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 with maturation of brainstem respiratory centers postnatally.

### *Associated Features*

Central apneas may appear within the pattern of periodic breathing. This may be seen as prolonged central pauses that may lead to development of sustained desaturation. These pauses may occur amidst clusters of shorter respiratory pauses or periods of respiratory instability during wake to sleep transitions.

Paradoxical chest wall movements are common during REM sleep in neonates due to the increased chest wall compliance in infants. These movements may cause a fall in arterial oxygen saturation due to reduced functional residual capacity leading to lowered oxygen stores and changes in ventilation-perfusion relationships. In addition, underlying comorbidities (for example, chronic lung disease or abnormal neurological status) can predispose the infant to a more severe or prolonged course for apnea. 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 gestational age. In studies, approximately 25% of infants who weigh less than 2,500 g at birth and nearly all 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 corrected age, and 98% by 40 weeks, with resolution in most infants by 43 weeks. 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, anemia, hypoxemia, metabolic disorders, neurologic disorders such as seizures or intracranial pathology, sedating medications, anesthesia, genetic disorders such as congenital central hypoventilation syndrome, dysphagia, or infection (including sepsis, meningitis, respiratory syncytial virus infections, and pertussis). 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 corrected age should raise suspicion of additional etiologic factors. Gastroesophageal reflux is frequently seen in preterm infants; however, studies show reflux episodes and apneas are rarely temporally related and that reflux does not worsen or prolong apnea in premature infants.

### *Familial Patterns*

Higher concordance is observed in monozygotic twins than dizygotic twins.

### *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 corrected age but may persist for several weeks beyond term, especially in infants born before 28 weeks gestational age. Apnea beyond 43 weeks is rare. Although no exact timeline exists, the earlier the gestational age at birth, the longer the central sleep apnea of prematurity may persist. 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 treated 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. Untreated apnea may result in failure to thrive, cognitive impairment or cor pulmonale.

## *Developmental Issues*

This is a condition related to prematurity that usually 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.

## *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. Primary CSA of prematurity is state-dependent, and the frequency of respiratory events increases during REM sleep.

## *Differential Diagnosis*

**Normal respiratory pauses** are observed during sleep in infants and should be distinguished from Primary CSA of infancy. Normative respiratory data from several large studies show that healthy asymptomatic infants commonly have brief 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.

**Brief resolved unexplained events (BRUE)** Primary CSA of infancy should be distinguished from BRUE, which is characterized by a report of a sudden, brief, resolved episode of at least one of the following: cyanosis or pallor; absent or decreased or irregular breathing, marked change in tone (hyper- or hypotonia); or altered level of responsiveness.

**Central sleep apnea due to a medical condition** Comorbid conditions should be suspected whenever apneas are severe or continue beyond 43 weeks corrected age. Recurrent, severe infant sleep apnea is usually due to other comorbid conditions, such as metabolic disease, or unrecognized neurological conditions such as seizures, brainstem malformation, or neurodegenerative condition; thus, an evaluation for these conditions should be performed.

**Factitious disorder imposed by another** This form of child abuse is manifest as imposed upper airway obstruction or attempted suffocation and should be considered in the differential.



**Sudden infant death syndrome** 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. Larger cohort studies of infants are needed to further characterize normative indices of prolonged central apneas (>20 seconds), shorter central apneas associated with desaturations or bradycardia, and duration and extent of periodic breathing.

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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-D must be met

- A. Diagnostic (PSG) or HSAT<sup>2</sup> demonstrates five or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or respiratory effort-related arousals [RERAs])<sup>1</sup> per hour of sleep during a PSG or per hour of monitoring (HSAT).
- B. PSG during use of continuous positive airway pressure shows significant resolution of obstructive events and emergence or persistence of central apnea or central hypopnea with all of the following:
  1. Five or more central respiratory events<sup>1,2</sup> (central apneas or central hypopneas) per hour of sleep.
  2. The total number of central apneas plus central hypopneas is > 50% of the total number of apneas and hypopneas.
- C. The presence of at least one of the following symptoms or signs thought to be attributable to the central events:
  - a. Sleepiness.
  - b. Difficulty initiating or maintaining sleep, frequent awakenings, or nonrestorative sleep.
  - c. Awakening short of breath.
  - d. Witnessed apneas.
- D. 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 to the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events.
2. The diagnosis of TECSA should not rely solely on the treatment device report to detect central events. When a report suggests clinically significant new or residual central apnea, repeat PSG may be warranted in the appropriate clinical context.
3. Prior to making a diagnosis of TECSA and proceeding with targeted therapy (e.g., ASV), potential contributing issues including mask leak and excessive CPAP pressures should be addressed.
4. A diagnosis of treatment-emergent central sleep apnea does not exclude a diagnosis of OSA. That is, a co-existing diagnosis of OSA can be made based on the diagnostic sleep study.
5. In most patients, TECSA will resolve weeks to months after initial therapy for OSA; however, approximately a third will have persistent events.

### *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 continuous positive airway pressure, 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). In addition to the breathing disturbances observed on physiologic testing, some adverse impact of the central apneas is required for diagnosis. This can include nocturnal awakenings with or without a sense of dyspnea, unrefreshing sleep, or persistent daytime sleepiness.

The presence of frequent central respiratory events from downloads of positive airway pressure devices may suggest the possible presence of TECSA. However, the accuracy of device downloads in differentiating central from obstructive events is questionable. Therefore, ideally, central events should be verified by further testing (i.e., polysomnography) prior to diagnosis.

### *Associated Features*

Patients with treatment-emergent CSA have several characteristics when placed on positive airway pressure. A high number of arousals persist on PAP treatment, and the AHI is often higher during NREM than REM sleep. This is because treatment-emergent central apneas almost invariably occur during NREM sleep. If patients can attain N3 sleep, central apneas often decrease until interrupted by an arousal or transition to a lighter stage of sleep that precipitates another series of central apneas or hypopneas. Patients with treatment-emergent CSA can have persistent sleep fragmentation on CPAP treatment and may report limited symptomatic 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 4% to 20%, depending on the characteristics of the group studied and the methodology. In most patients, TECSA will resolve weeks to months after the initial titration; however, approximately a third (14-46%) will have persistent events (1-4% of OSA patients on CPAP).

### *Predisposing and Precipitating Factors*

Several 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, predisposing to ventilatory oscillations and intermittent hypocapnia below the apneic threshold. Studies have found that often a small increase in end-tidal PCO<sub>2</sub> 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.

Potential risk factors for TECSA include male sex, lower body mass index, older age, and a variety of PSG parameters from the baseline study (higher AHI, higher arousal index, and higher central apnea index). However, identified risk factors for treatment-emergent CSA vary from study to study.

Emergence of central apnea can also be seen after treatment of obstructive sleep apnea with oral appliances, tracheostomy, maxillomandibular advancement, and hypoglossal nerve stimulation. A case report of the development of central apnea following nasal surgery in a patient with known obstructive sleep apnea has also been published.

### *Familial Patterns*

None known.

### *Onset, Course, and Complications*

The recognition of treatment-emergent CSA typically follows PAP titration. Although the exact percentage of patients with central apneas on initial PAP titration whose central events persist on long-term PAP treatment is not known precisely, the available data suggest that about 25-35% of those patients will have persistent central events on long-term PAP. 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. In addition, nocturnal oximetry at home on PAP treatment may show arterial oxygen desaturations due to these central apneas that persist over weeks to months despite PAP therapy. 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 because of this.

### *Developmental Issues*

Treatment-emergent sleep apnea has been described in children, but the overall prevalence is unclear.

### *Pathology and Pathophysiology*

The pathophysiology is not clearly defined. A low arousal threshold, which may destabilize breathing, and difficulty reaching stage N3 sleep may predispose to sleep instability. A high ventilatory response to PaCO<sub>2</sub> (increased controller gain) and a small difference between the sleeping PaCO<sub>2</sub> and the apnea threshold may also predispose patients to treatment-emergent central apneas. Induction of hypoxemia through treatment with excessive positive airway pressure or large mask leak may trigger treatment-emergent central apneas in susceptible individuals.

### *Objective Findings*

PSG or HSAT 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) 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 should not be applied to patients who manifest central sleep apnea on PAP treatment if 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 N1 and N2 sleep. In some patients, progressive increases in pressure to prevent 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 most cases, the central AHI is neither  $\geq 5$ /hour nor are central events  $\geq 50\%$  of the total number of apneas and hypopneas.

**Other central sleep apnea disorders** Some 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 and 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. Several 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? Further study is required to better understand the contribution of persistent central apnea to symptoms and long-term health outcomes, and the role of various treatment options. The accuracy of current CPAP machines to detect central events and enable diagnosis of TECSA also needs further study.

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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<sub>2</sub>) 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<sub>2</sub>) ≥ 45 mm Hg. In the sleep-related hypoventilation disorders other than OHS, daytime hypoventilation may or may not be present.

### *General Criteria for 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.<sup>1,2</sup>

Notes

1. Monitoring of arterial PCO<sub>2</sub> during sleep is not practical. Acceptable surrogates include end-tidal PCO<sub>2</sub> or transcutaneous PCO<sub>2</sub>.
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 only, 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 ( $\text{PaCO}_2 \geq 45$  mm Hg) as measured by arterial  $\text{PCO}_2$ , end-tidal  $\text{PCO}_2$ , or transcutaneous  $\text{PCO}_2$ .<sup>1</sup>
- B. Presence of obesity ( $\text{BMI} \geq 30$   $\text{kg/m}^2$ ;  $\geq 95$ th percentile for age and sex for children).
- C. Hypoventilation is not primarily due to lung parenchymal or airway disease, 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. Although a diagnosis of obesity hypoventilation syndrome may be established based on daytime hypercapnia due to obesity, the presence of sleep-related hypoventilation is inferred. The hypoventilation typically worsens during sleep. Although diagnostic criteria can be met based on evaluation during wake alone, sleep testing should be conducted due to the high frequency of comorbid obstructive sleep apnea. If polysomnography with  $\text{CO}_2$  monitoring is performed, sleep-related hypoventilation will be observed.
- 2. When OSA is present, 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  $\text{PaCO}_2 \geq 45$  mm Hg) that cannot be entirely attributed to an underlying cardiopulmonary or neurologic disease. Hypercapnia worsens during sleep and is often associated with severe arterial oxygen desaturation. The majority of OHS patients have comorbid OSA (80% to 90%). In these patients, daytime hypercapnia may improve or even normalize with adequate PAP therapy and sustained adherence to treatment. The minority of OHS patients without OSA exhibit sustained or intermittent episodes of shallow breathing during sleep associated with worsening hypercapnia and hypoxemia. 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 may have few, if any, sleep complaints, or may present with considerable sleep disturbance including reduced sleep efficiency and frequent awakenings. Patients with OHS commonly complain of hypersomnolence. The severity of hypersomnolence may not correlate closely with the degree of hypercapnia. Other symptoms include nonrestorative sleep, nocturia, morning headaches, fatigue, mood disturbance and impairments of memory or concentration. Physical examination may reveal severe obesity with decreased airway area and features suggestive of cor pulmonale or circulatory congestion, such as plethora, scleral injection, and peripheral edema. Compared to patients with OSA alone, individuals with OHS more often complain of dyspnea, are hypoxemic and have signs of cor pulmonale. Laboratory testing often shows elevated serum CO<sub>2</sub> on electrolyte testing (≈ serum bicarbonate) and less commonly, polycythemia. Cardiopulmonary findings include reduced forced vital capacity and lung restriction; right heart strain, right ventricular hypertrophy and right atrial enlargement; and pulmonary hypertension and right ventricular dysfunction. Consequences of chronic hypercapnia and hypoxemia include pulmonary artery hypertension, cor pulmonale, and neurocognitive dysfunction.

### *Clinical and Pathophysiological Subtypes*

The majority of OHS patients have co-morbid severe OSA. Repeated obstructive events without sufficient time between events to clear CO<sub>2</sub> may play a predominant role in the pathogenesis of OHS, as evidenced by the efficacy of CPAP in resolving both the OSA and OHS in this population. A subgroup of 10-20% of OHS patients do not have substantial OSA, and other factors such as direct effects of obesity on respiratory mechanics or central leptin resistance may play a predominant role in the pathogenesis of OHS in this population. The effectiveness of CPAP therapy (as opposed to non-invasive ventilation) in this subgroup is unclear.

### *Demographics*

OHS may be underdiagnosed if CO<sub>2</sub> analysis is not performed in obese patients presenting with complaints suggestive of OHS. The prevalence of OHS in populations of patients with OSA ranges between 10% and 20%, with higher prevalence among more severely obese populations. The prevalence of OHS is similar in men and women, in contrast to the greater risk for OSA in men compared to women. Nearly half of hospitalized medical inpatients with BMI > 50 kg/m<sup>2</sup> have OHS.

### *Predisposing and Precipitating Factors*

Obesity is believed to be the primary pathophysiologic factor responsible for hypoventilation and hypoxemia. Greater degrees of obesity are associated with worse sleep-related hypoventilation, but individual variation in the severity of hypercapnia at similar weights is seen. In addition, 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 invariably become even

more so during sleep, particularly during REM sleep. However, the relationship between wake SaO<sub>2</sub>/PaCO<sub>2</sub> 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 usually 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. Delays in diagnosis and misdiagnosis (e.g., diagnosis of COPD instead of OHS) commonly occur and may explain the greater utilization of healthcare resources prior to diagnosis among patients with OHS. 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. Reduced quality of life, prolonged hospital admission rates, and extended time in ICU have also been observed. Although the risk of increased morbidity and mortality increases 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<sub>2</sub>. 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. Surgical mortality may also be higher in patients with OHS compared to patients without OHS or OSA.

Many patients with OHS respond to CPAP or bilevel PAP with improvement in daytime PaCO<sub>2</sub>. In a multicenter, open label randomized controlled trial of patients with OHS and co-existing severe OSA who were randomly assigned to CPAP or non-invasive ventilation (NIV), long-term effectiveness was similar regardless of treatment modality. The mean reduction in PaCO<sub>2</sub> was similar whether CPAP or NIV was used, with PaCO<sub>2</sub> ranging between 42-46 mm Hg when measured up to 3 years after treatment initiation. In another study, 34% of OHS patients using PAP more than 4.5 hours per night had normalization of the PaCO<sub>2</sub>. In contrast, hypercapnia may worsen with oxygen therapy alone for the associated hypoxia.

Compared to OSA patients without OHS, those with OHS often have a higher AHI and lower forced expiratory volume in 1 second (FEV<sub>1</sub>) and vital capacity, suggesting that greater OSA severity and ventilatory restriction may predispose to OHS.

### *Developmental Issues*

Obesity hypoventilation syndrome can be seen in children, most often during adolescence in the setting of morbid obesity. To establish the diagnosis, hypoventilation during sleep should be scored using pediatric criteria in the current AASM Manual for the Scoring of Sleep and Associated Events. Children with underlying syndromes that are characterized by both obesity and abnormal ventilatory response to hypoxia or hypercapnia, such as Prader Willi Syndrome and Late-Onset Central Hypoventilation with Hypothalamic Dysfunction should be excluded before making the diagnosis of obesity hypoventilation syndrome.

### *Pathology and Pathophysiology*

The pathophysiology of OHS is related to several mechanisms, including changes in the respiratory system related to obesity, abnormal breathing during sleep, and impaired respiratory drive. However, the relative importance of these factors to developing and maintaining hypoventilation likely varies among patients.

Obesity itself increases CO<sub>2</sub> production and is associated with several factors that predispose to CO<sub>2</sub> retention. Excess adiposity in the chest wall and abdomen impairs respiratory function by reducing respiratory system compliance, increasing lower airway resistance, and causing a cephalad displacement of the diaphragm. These changes are accompanied by early airway closure during exhalation leading to increased closing capacity as well as ventilation perfusion mismatch with lower lobe atelectasis and increased work of breathing.

Among patients with co-existing OSA, sustained nocturnal hypercapnia can result from insufficient ventilatory compensation (i.e., CO<sub>2</sub> unloading) following obstructive events, which are often relatively long in duration with a short recovery period between apneas.

Abnormal ventilatory control (blunted hypercapnic ventilatory response) allows hypercapnia to persist into wakefulness after the cause of acute hypercapnia is no longer present. Chronic hypercapnia stimulates renal absorption of bicarbonate. Although this blunts the degree of acidosis due to an elevated PaCO<sub>2</sub>, it reduces the compensatory CO<sub>2</sub> 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. Resistance to leptin, a ventilatory stimulant, has been observed in OHS and may also contribute to hypoventilation. Thus, numerous factors impair CO<sub>2</sub> 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, including leptin resistance.

### *Objective Findings*

In untreated patients, arterial blood gas testing during wakefulness shows hypercapnia and often, mild hypoxemia. The characteristic polysomnographic finding is sleep-related hypoventilation and arterial oxygen desaturation during sleep with or without obstructive apneas and hypopneas. Hypercapnia and

hypoxemia are often worse during REM than NREM sleep due to sleep state-related control of breathing as well as atonia of accessory respiratory muscles during REM. Worsening hypoventilation during sleep can be documented by an arterial blood gas measurement of PaCO<sub>2</sub> during sleep (rarely performed) or transcutaneous or end-tidal PCO<sub>2</sub> 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 hypoxemia may result in polycythemia. Electrocardiography, chest radiography, and echocardiography may demonstrate evidence of pulmonary hypertension, right ventricular hypertrophy, and right atrial enlargement. Pulmonary function testing may reveal a restrictive pattern, including reduced vital capacity and forced expiratory volume in 1 second (FEV<sub>1</sub>) in severely obese patients.

The serum bicarbonate level is usually elevated due to renal compensation for chronic respiratory acidosis (hypercapnia). A pooled analysis using data from more than 1,300 obese patients with and without OHS demonstrated that a serum bicarbonate level <27 mmol/L has a high negative predictive value, essentially ruling out OHS, particularly when clinical suspicion is less than 20% (e.g., patients with BMI 30-40 kg/m<sup>2</sup>). Among patients who have high clinical suspicion of having OHS, direct measurement of PaCO<sub>2</sub> regardless of serum bicarbonate levels is recommended to make a definitive diagnosis.

### *Differential Diagnosis*

**Other causes of hypoventilation during wakefulness and sleep.** These causes include *pulmonary airway and parenchymal disorders, neuromuscular and chest wall disorders, severe untreated hypothyroidism, use of respiratory suppressants, and congenital or idiopathic central alveolar hypoventilation syndromes.*

**Obstructive and central sleep apnea syndromes** These syndromes can be distinguished from sleep-related hypoventilation by the periodic alterations in airflow and accompanying periodic fluctuations in SaO<sub>2</sub> that occur in OSA and CSA. 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 is needed into the pathogenesis of OHS regarding why some obese individuals develop OHS while others do not, and how coexisting OSA affects patient outcomes. The degree and duration of hypercapnia/hypoxemia necessary to produce adverse consequences, such as pulmonary hypertension, in individual patients remains ill defined. Development of a validated staging and risk stratification scheme

for OHS that can predict clinical outcomes and identify patients who may benefit from intervention is also needed, as are data to inform the choice of modality and timing of treatment for individual patients.

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

### *Diagnostic Criteria*

Criteria A-C must be met

- A. Sleep-related hypoventilation is present.
- B. Central nervous system autonomic dysfunction is present, most often due to a mutation of the *PHOX2B* gene.
- C. The disorder is not better explained by another sleep disorder, medical disorder, medication use, or substance use.

### Notes

1. CNS autonomic dysfunction typically manifests as abnormal ventilatory response to hypercapnia with clinically significant hypercapnia and hypoxemia during sleep. Waking hypoventilation may or may not be present but the PaCO<sub>2</sub> is typically higher during sleep and meets criteria for sleep-related hypoventilation.

2. PSG monitoring demonstrates severe hypercapnia and arterial oxygen desaturation worse in sleep than wake and worse in NREM than REM sleep. The predominant pattern is a reduced tidal volume rather than repetitive central apnea or bradypnea.
3. Although the condition is termed *congenital*, a broader phenotypic presentation has been recognized in recent years, with onset in some cases in later childhood and adulthood. Genotype predicts phenotype in most cases (see Clinical and Pathophysiological Subtypes)

### *Essential Features*

Congenital central alveolar hypoventilation syndrome (CCHS) is a syndrome of global autonomic dysfunction, with abnormal central respiratory control as a defining feature. The condition is fatal if not treated. Almost all cases of CCHS are caused by mutations in the paired-like homeobox 2B (*PHOX2B*) gene, which encodes a transcription factor that is essential for prenatal neuronal differentiation. CCHS is characterized by alveolar hypoventilation with the absence or reduction of ventilatory response to hypercapnia. CCHS typically presents within the first few hours of life with cyanosis, oxygen desaturation and hypercapnia with reduced respiratory effort. The hypoventilation is worse during sleep than wakefulness, and worse during NREM than REM sleep. It is unexplained by primary pulmonary, neurological, or metabolic disease. Later onset CCHS is increasingly recognized, with presentations in infancy, childhood, and even adulthood, most often presenting with respiratory failure following anesthesia or in association with an acute illness. Affected individuals do not perceive dyspnea or show signs of respiratory distress in the face of hypercapnia or hypoxemia. The phenotype of CCHS can be predicted by the genotype as described below.

### *Associated Features*

Patients with CCHS have a spectrum of findings due to autonomic nervous system dysfunction, including Hirschsprung disease, other disorders of GI tract dysmotility, tumors of neural crest origin, cardiac asystoles, bradycardia, metabolic disorders, autonomic dysfunction, and pupillary abnormalities. The risk of these associated disorders varies with *PHOX2B* genotype. Neurocognitive impairment and seizures may develop if hypoventilation is not adequately treated. 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*

Heterozygous mutations in the *PHOX2B* gene are found in almost all cases of CCHS, with more than 90% having polyalanine repeat mutations (PARMs), resulting in an increase from 20 (normal) to between 24 and 33 alanine repeats. An increased number of repeats is associated with more severe phenotypes, and patients with 20/27 to 20/33 mutations typically require ventilatory support 24 hours a day. The majority

require a cardiac pacemaker. Non-polyalanine repeat mutations (NPARMs) include missense, nonsense, frame shift, and stop codon mutations, and typically result in a severe phenotype. Patients with NPARMs are at much higher risk for neural crest tumors and Hirschsprung disease than those with PARMs. Mutations in other genes, including MYO1H and LBX1, have been identified as causative for CCHS in rare cases.

### *Demographics*

The prevalence of CCHS is estimated to be between 1 in 150,000 and 200,00 live births, although this may be an underestimate as individuals with a milder phenotype may not be diagnosed. The condition occurs equally among both sexes and all ethnic/racial groups.

### *Predisposing and Precipitating Factors*

This is a congenital genetic syndrome. Most individuals present shortly after birth. However, individuals with fewer polyalanine repeats (20/24 and 20/25) may present following anesthesia or a systemic illness that precipitates acute respiratory failure.

### *Familial Patterns*

Mutations in *PHOX2B* are de novo in approximately 90% of cases. Affected individuals can transmit the disorder to their offspring in an autosomal dominant pattern with variable penetrance. Mosaicism in unaffected or mildly affected parents has been reported in 5 to 10% of cases. Therefore, parents of newly diagnosed patients should be tested.

### *Onset, Course, and Complications*

Once present, alveolar hypoventilation and the other consequences of autonomic nervous system dysregulation persist throughout life. The clinical consequences of alveolar hypoventilation including cor pulmonale and death can be prevented by providing ventilatory support to normalize PaCO<sub>2</sub> and SpO<sub>2</sub>. Patients with inadequate treatment of alveolar hypoventilation may develop neurocognitive impairment, growth failure, seizures, or cor pulmonale. Because affected individuals do not perceive dyspnea or develop signs of respiratory distress, monitoring for worsening ventilatory control with comprehensive physiological testing is needed frequently during infancy and then at least annually throughout life. The need for ventilatory support may initially lessen following identification and treatment in infancy, but this cannot be easily predicted. Additional support may be needed during times of acute illness and rapid growth. Testing for associated autonomic nervous system disorders including Hirschsprung disease, cardiac dysrhythmias, ophthalmologic disorders, and tumors of neural crest origin is also indicated, with



the frequency of ongoing monitoring directed by genotype. Annual (or more frequent) neurocognitive assessments are recommended in all children with CCHS.

### *Developmental Issues*

While CCHS typically presents in infancy, late onset forms of the disease with milder manifestations are being recognized in later childhood and adulthood.

### *Pathology and Pathophysiology*

The *PHOX2B* gene encodes a tissue-specific transcription factor that is critical for genes involved in the development of the autonomic nervous system, including regions of the brainstem critical for respiratory control. There is extensive ongoing work in animal and cellular models elucidating the mechanism by which *PHOX2B* PARMs and NPARMs result in the various clinical phenotypes.

### *Objective Findings*

Alveolar hypoventilation is the defining feature of CCHS. Hypercapnia and hypoxemia are worse during sleep than waking. Affected individuals have diminished ventilatory response to hypercapnia, hypoxemia, and arousal during waking and 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 are typically more severe during NREM than during REM sleep. Patients may not arouse from sleep despite severe hypercapnia and hypoxemia. Paradoxical breathing and snoring do not usually occur. Hypercapnia and hypoxemia are always present during sleep and may be present during waking in more severely affected individuals.

In patients with inadequate control of alveolar hypoventilation, compensated respiratory acidosis and polycythemia may be present. Pulmonary hypertension and cor pulmonale may develop over time.

Computed tomography and MRI scans of the head are normal. Echocardiography or cardiac catheterization may reveal evidence of pulmonary hypertension because of untreated hypoventilation, but do not show congenital heart disease. Electrocardiograms may show associated arrhythmias due to the autonomic nervous system dysregulation that characterizes the disorder. CCHS is defined by the lack of a primary pulmonary or other cause of alveolar hypoventilation; therefore, chest imaging and pulmonary function testing are generally normal. Chest and abdominal imaging may reveal tumors of neural crest origin.

Genetic testing shows mutations in the *PHOX2B* gene in almost all cases. Genetic testing is essential in making the diagnosis, predicting phenotype, and directing monitoring and therapy. Family members may be offered testing to identify milder (late onset) cases and provide genetic counseling.

## Differential Diagnosis

**Other forms of central hypoventilation** CCHS must be distinguished from *central hypoventilation due to Chiari malformation, other causes of central nervous system disturbance such as trauma or tumors, metabolic conditions such as Leigh disease, other genetic disorders with hypoventilation such as Prader Willi syndrome, and obesity hypoventilation syndrome, as well as other causes of central hypoventilation.*

**Hypoventilation secondary to muscle weakness** due to spinal muscular atrophy, diaphragmatic paralysis or a muscular dystrophy must be distinguished from CCHS.

**Apnea or a brief resolving unexplained event (BRUE)** (see *apnea of infancy/prematurity*) in Infancy may suggest 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.

**Hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome** (see *late-onset central hypoventilation with hypothalamic dysfunction*) shares many features of autonomic dysregulation but is not caused by mutations in *PHOX2B* and must be distinguished from late-onset CCHS.

## Unresolved Issues and Further Directions

There are many unresolved issues regarding CCHS, including prevalence data, precise genotype-phenotype correlations, the 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), rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation with neuroendocrine tumors (ROHHAD-NET).

### 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. Rapid onset obesity after a period of normal growth.
  2. Endocrine abnormalities of hypothalamic origin.
  3. Severe emotional or behavioral disturbances.
  4. Tumor of neural crest origin.
- D. Mutation of the *PHOX2B* gene is not present.
- E. The disorder is not better explained by another sleep disorder, medical disorder, medication, or substance use.

### Notes

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

2. Hypoventilation often develops several years after the rapid onset obesity and endocrine/hypothalamic disorders.

### *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. Patients do not develop dyspnea, anxiety, or overt signs of respiratory distress when hypoventilation is present. 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 occur in approximately 40% of affected individuals.

### *Clinical and Pathophysiological Subtypes*

None known.

### *Demographics*

There are no prevalence data, although this is a very rare condition. There are fewer than 200 cases reported worldwide. The disorder seems to occur equally among males and females. All reported cases have been in children.

### *Predisposing / 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 have normal respiratory control during sleep at birth. Hyperphagia and rapid weight gain typically begin between ages 2 and 4 years as a sign of hypothalamic dysfunction. Other manifestations of hypothalamic dysfunction may include growth hormone deficiency, central precocious puberty, diabetes insipidus, hypothyroidism, and hypogonadotropic hypogonadism. Respiratory failure typically presents several years after the onset of obesity and may be precipitated by general anesthesia or an acute illness. Alveolar hypoventilation requires ventilatory support via face mask or tracheostomy. The respiratory failure does not improve over time. Autonomic nervous system dysregulation is a key feature, and can include altered pupillary responses to light, altered thermoregulation, and gastrointestinal dysmotility. Death has been reported from respiratory failure, cor pulmonale, or hypernatremia secondary to diabetes insipidus. Case series have reported a high mortality. Tumors of neural crest origin occur in at approximately 40% of children, typically ganglioneuroma and ganglioneuroblastoma. Behavioral disorders are common.

### *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, although may show secondary signs of hypoxemia. Genetic, epigenetic, and autoimmune etiologies have all been suggested.

### *Objective Findings*

Hypercapnia and hypoxemia 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 and hypoventilation persists when upper airway obstruction is treated.

Affected individuals have blunted responses to hypercapnia and hypoxemia. Carbon dioxide and oxygen determinations may be normal during wakefulness but will demonstrate hypercapnia and hypoxemia 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 and 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.

### *Differential Diagnosis*

**Other sleep-related hypoventilation disorders** Late-onset central hypoventilation with hypothalamic dysfunction can be distinguished from *late-onset congenital central hypoventilation syndrome* by testing for the *PHOX2B* gene. Genetic testing may also help distinguish the disorder from *Prader-Willi syndrome*, which is characterized by a known genetic abnormality. Most children with Prader-Willi syndrome have facial dysmorphisms and hypotonia at birth, and more severe developmental delay. The disorder can be distinguished from *obesity hypoventilation syndrome* by the pattern of weight gain (rapid in early childhood), the presence of endocrine abnormalities and other associated hypothalamic abnormalities, and the persistence of hypoventilation despite weight loss. In addition, patients with late-onset central hypoventilation with hypothalamic dysfunction 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, nonapneic alveolar hypoventilation, primary alveolar hypoventilation, Idiopathic Sleep-related Central Alveolar Hypoventilation, sleep-related nonobstructive alveolar hypoventilation, idiopathic.

### *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, chest wall disorder, medication use, neurologic disorder, muscle weakness, 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 should 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 and nocturnal hypoventilation are believed to be due primarily to blunted chemoresponsiveness to CO<sub>2</sub> and O<sub>2</sub>. However, reported cases are few and not studied in enough detail to conclusively establish a well-defined etiology. Patients 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*

Prevalence and other demographic factors are not known.

### *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, especially during REM sleep, but the relationship between wake SaO<sub>2</sub>/PaCO<sub>2</sub> and sleep-related desaturation is not sufficiently strong to have substantial predictive value in individual patients.



Some patients with this diagnosis may likely have an underlying anatomic or functional defect affecting respiratory mechanics and ventilatory drive that remains undiagnosed.

### *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 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.

### *Pathology and Pathophysiology*

The etiology of hypoventilation in these patients is not established. Chronic hypercapnia and hypoxemia in idiopathic central alveolar hypoventilation are believed to be due to defective CO<sub>2</sub> and O<sub>2</sub> homeostasis, with impaired CO<sub>2</sub> unloading, reduced chemoresponsiveness to CO<sub>2</sub> and O<sub>2</sub>, 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. As a result, even relatively small decrements in arterial oxygen tension may result in large decrements in oxyhemoglobin saturation. Therefore, sleep-related hypoventilation in these patients may produce more severe oxyhemoglobin desaturation.

### *Objective Findings*

The characteristic polysomnographic finding is demonstration of sleep-related hypoventilation (by arterial blood gas or by a surrogate measure such as end-tidal CO<sub>2</sub> or transcutaneous CO<sub>2</sub>). 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 hypercapnia and hypoxemia. Chronic hypoxemia can be associated with polycythemia. Electrocardiography, chest radiography, and echocardiography may demonstrate evidence of pulmonary

hypertension. Central nervous system imaging is generally unremarkable. Genetic testing for PHOX2B mutations is negative.

### *Differential Diagnosis*

**Other sleep-related hypoventilation disorders** *Obesity hypoventilation syndrome, pulmonary airway and parenchymal disorders, neuromuscular and chest wall disorders, severe untreated hypothyroidism, and use of respiratory suppressants* must be ruled out to establish a diagnosis of idiopathic central alveolar hypoventilation. *CCHS* is associated with an abnormal *PHOX2B* gene. Unlike patients with *late-onset central hypoventilation with hypothalamic dysfunction*, patients with idiopathic central alveolar 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 alveolar hypoventilation can be made.

**Obstructive and central sleep apnea syndromes** can be distinguished from sleep-related hypoventilation by the periodic alterations in airflow and accompanying periodic fluctuations in SaO<sub>2</sub>. In contrast, oxygen desaturation due to sleep-related hypoventilation is generally more sustained, usually several minutes or longer in duration.

### *Unresolved Issues and Further Directions*

A better understanding of the etiology of idiopathic central alveolar hypoventilation is essential to guide preventive and treatment measures. 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 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, 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 hypercapnia. 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 hypercapnia due to prolonged use of medications or substances known to depress ventilatory drive 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 polypharmacy or the concomitant use of alcohol. 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 eventually gives 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 the use of respiratory suppressants are not known. Baseline hypoventilation before initiation of respiratory depressant medication worsens following initiation of the medication. Thus, the prevalence may be higher in patients with more significant perturbations of pulmonary function or neuromuscular weakness. Individuals with chronic hypercapnia during wakefulness experience even greater decrements of alveolar ventilation during sleep. Studies of patients on methadone maintenance have generally found daytime hypoventilation to be absent or mild.

### *Predisposing and Precipitating Factors*

The use of medications or substances that alter respiratory function or drive, including but not limited to opioids, anesthetic agents, benzodiazepines, and muscle relaxants, is the primary pathophysiologic factor responsible for hypercapnia 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  $\text{SaO}_2/\text{PaCO}_2$  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 because of chronic hypercapnia and hypoxemia. An increased risk of death has been reported with the use of potent narcotics, with the CDC reporting that opioids were involved in 69.5% of drug overdose deaths in 2018. By report, many of these deaths occur during sleep, with hypoventilation and terminal apnea presumed to be a major cause.

## *Pathology and Pathophysiology*

Hypoventilation is a direct result of impaired respiratory drive and CO<sub>2</sub> and O<sub>2</sub> chemosensitivity. During sleep, opioids reduce hypercapnic ventilatory response (HCVR) which can reduce ventilation directly but also indirectly through a decrease in upper airway muscle activity. These effects can lead to hypoventilation and hypoxemia. If daytime PaCO<sub>2</sub> is already elevated, further drops in ventilation during sleep can profoundly worsen hypercapnia. Hypercapnia in turn can contribute to hypoxemia. 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<sub>2</sub> or an acceptable surrogate such as end-tidal CO<sub>2</sub> or transcutaneous CO<sub>2</sub> 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 during sleep. Intermittent arousals associated with hypoxemia may be observed. An ataxic breathing pattern may be present during sleep. There is scant literature about daytime or nocturnal PaCO<sub>2</sub> in patients on potent opioids for pain. While severe daytime hypoventilation is thought to be relatively uncommon, 45% of patients in one series had daytime PaCO<sub>2</sub> values > 45 mm Hg.

## *Differential Diagnosis*

**Other sleep-related hypoventilation disorders** These include hypoventilation due to *OHS, pulmonary airway and parenchymal disorders, neuromuscular and chest wall disorders, severe untreated hypothyroidism, and congenital or idiopathic central alveolar hypoventilation syndromes.*

**Obstructive and central sleep apnea syndromes** can be distinguished from sleep-related hypoventilation by the periodic alterations in airflow and accompanying periodic fluctuations in SaO<sub>2</sub>. 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<sub>2</sub> during sleep in patients taking respiratory depressants is not clear. 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, 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. If hypoxemia is out of proportion to severity of hypoventilation, a diagnosis of sleep-related hypoxemia should also be made.
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 with resulting rise in carbon dioxide levels. 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, 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 alveolar 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.

### *Associated Features*

Consequences of chronic hypercapnia and hypoxemia arising because 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<sub>2</sub> at or below 45 mm Hg. In addition, some of these patients have reduced central neural chemoresponsiveness. Hypoxemia may be worsened by the development of atelectasis or aspiration due to defective swallowing associated with some neurologic and neuromuscular



conditions. Similarly, atelectasis may be present in chest wall disorders due to anatomic asymmetries. Substantial hypoxemia due to V/Q mismatch or other pathophysiological processes may increase the alveolar-arterial oxygen gradient (i.e., beyond the level expected due to hypoventilation alone). In such cases, co-morbid sleep-related hypoxemia due to medical disorder should also be diagnosed. This can commonly occur in the setting of parenchymal or airway lung diseases as well as in the setting of secondary pulmonary hypertension.

### *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*

More significant impairments of respiratory function are associated with a greater risk for sleep-related hypoventilation and hypoxemia. However, there is no recognized threshold of pulmonary parenchymal 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 generally become even more so during sleep, particularly REM sleep. However, the relationship between wake  $\text{SaO}_2/\text{PaCO}_2$  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 hypoxemia. 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.

### *Developmental Issues*

Certain disorders causing sleep-related hypoventilation are more likely to present in childhood. These include Duchenne's muscular dystrophy, spinal muscular atrophy, neuromuscular scoliosis and other neuromuscular disorders, bronchopulmonary dysplasia, and cystic fibrosis.

### *Pathology and Pathophysiology*

The pathophysiology of sleep-related hypoventilation in the setting of medical disorders is complex. Factors such as increased dead space and mechanical disadvantage from the underlying medical disorder can increase the work of breathing. These factors, along with underlying neuromuscular weakness in those with neurologic disorders, result in a requirement of increased drive to maintain normocapnia. Loss of the wakefulness drive to breathe with sleep onset can further contribute to sleep-related hypoventilation. Obstructive lung diseases are characterized by hyperinflation which alters force-tension relationships of respiratory muscles. This places these muscles at a mechanical disadvantage that leads to increased work of breathing to maintain normocapnia. Airway disease along with parenchymal destruction can also increase physiologic dead space. Chest wall disorders similarly distort anatomy putting respiratory muscles at a mechanical disadvantage. Finally, interstitial lung diseases increase the work of breathing by increasing the elastic recoil of the fibrotic lung.

In all these conditions, sleep is an added stress by altering the pattern of ventilatory-muscle activation, particularly during REM sleep when there is a disproportionate ventilatory burden placed on the diaphragm due to reduced activation of the intercostal and accessory muscles. Thus, conditions such as Pompe's disease that preferentially affect the diaphragm, will tend to develop sleep-related hypoventilation earlier in the disease course. In all the above diseases, the increased work of breathing leads to greater dependence on accessory muscles of respiration to maintain normocapnia. Loss of the functioning of these accessory muscles leads to greater rise in CO<sub>2</sub> levels than in normal individuals.

The increased work of breathing and/or reduced strength of the respiratory muscles leads to a rapid shallow breathing pattern with increased respiratory rate compensating for decreased tidal volume.

However, this pattern of breathing further increases effective dead space. The normal decline in CO<sub>2</sub> chemosensitivity during sleep is exacerbated in many neurologic and neuromuscular disorders.

By reducing alveolar oxygen tension, hypoventilation syndromes commonly result in hypoxemia. With pure hypoventilation, the alveolar-arterial oxygen gradient is normal or only slightly elevated due to atelectasis or other complications of the underlying disease. Chronic daytime hypoventilation can result in daytime hypoxemia. If sufficiently severe, this may place the patient near or on the steep portion of the oxyhemoglobin dissociation curve. When this occurs, even relatively small changes in ventilation during sleep can result in large decrements in oxyhemoglobin saturation. Thus, sleep-related hypoventilation in these patients may have a relatively great impact on oxyhemoglobin saturation. The development of secondary pulmonary hypertension leads to V/Q mismatch and further exacerbates hypoxemia.

### *Objective Findings*

The characteristic polysomnographic finding is demonstration of sleep-related hypoventilation (by arterial PaCO<sub>2</sub>, transcutaneous PCO<sub>2</sub>, or end-tidal PCO<sub>2</sub>). 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 hypercapnia/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 N3 and REM sleep, 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 hypercapnia and hypoxemia. Chronic hypercapnia and hypoxemia (especially when present during the day as well as at night) can be associated with polycythemia.

Specific respiratory disorders are associated with abnormal findings, with either obstructive or restrictive deficits on pulmonary function testing depending on the underlying etiology. 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. Measures of respiratory muscle strength can help identify neuromuscular etiologies. Measurement of supine vs. seated vital capacity can identify diaphragmatic dysfunction.

Chest radiographic imaging helps define the etiology and quantify the severity of the underlying disease. Suspected neurologic or neuromuscular causes of hypoventilation may be investigated using central nervous system imaging or measures of peripheral nerve or muscular function. Electrocardiography, chest radiography, and echocardiography may demonstrate evidence of pulmonary hypertension.

### *Differential Diagnosis*

**Other sleep-related hypoventilation disorders** These include hypoventilation due to *OHS*, use of medications or substances that can suppress respiratory drive, and congenital or idiopathic central alveolar hypoventilation syndromes.

**Obstructive and central sleep apnea syndromes** can be distinguished from sleep-related hypoventilation by the periodic alterations in airflow and accompanying periodic fluctuations in SaO<sub>2</sub>. 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.

In patients with lung disease such as COPD, nocturnal desaturation may reflect sleep-related hypoxemia, sleep-related hypoventilation, or a combination of the two processes. CO<sub>2</sub> assessment and quantification of the alveolar – arterial oxygen gradient are key to distinguishing between these conditions. These distinctions are important as the diagnosis impacts the therapeutic approach.

### *Unresolved Issues and Further Directions*

Thresholds of impairments of ventilation and respiratory drive producing hypercapnia/hypoxemia need to be identified. In individual patients, the degree and duration of hypercapnia/hypoxemia necessary to produce adverse consequences, such as pulmonary hypertension, are not well defined. The value of routinely measuring PaCO<sub>2</sub> during sleep in these patients is not clear.

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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 oxygen desaturation.

#### *Diagnostic Criteria*

Criteria A and B must be met

- A. PSG, HSAT or nocturnal oximetry shows an arterial oxygen saturation (SpO<sub>2</sub>) during sleep of ≤ 88% in adults or ≤ 90% in children for ≥ 5 minutes.
- B. The desaturation is not fully explained by sleep-related hypoventilation, obstructive sleep apnea, or other sleep-related breathing disorder.<sup>1</sup>

#### *Notes*

1. OSA, CSA, sleep-related hypoventilation, or other sleep-related breathing disorders may be present, but these are not believed to fully explain the hypoxemia.
2. If diagnostic testing reveals hypoxemia during sleep but clinical evaluation (e.g., EtCO<sub>2</sub> or transcutaneous CO<sub>2</sub>) to exclude other causes, in particular sleep-related hypoventilation, has not been performed, the hypoxemia should be noted as a test result finding with further diagnostic evaluation recommended, without making a sleep-related hypoxemia diagnosis.

#### *Essential Features*

On diagnostic testing, significant hypoxemia during sleep is present and the presence of hypoxemia is not better explained by another sleep-related breathing disorder (e.g., OSA) or by sleep-related hypoventilation. 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. Because hypoventilation is a cause of hypoxemia, it is essential to exclude sleep-related hypoventilation as the primary cause of observed hypoxemia. Ideally, physiologic evaluation with an arterial blood gas, transcutaneous PCO<sub>2</sub> or end-tidal CO<sub>2</sub> monitoring is performed to exclude hypoventilation. At the very least, clinical evaluation for causes of sleep-related hypoventilation (e.g., neuromuscular or chest wall disorder) should be performed to exclude this diagnosis. Some patients with sleep-related hypoxemia also exhibit hypoxemia during wakefulness. The presentation of patients with sleep-related hypoxemia varies with the underlying etiology. Chronic hypoxemia can arise from airway or parenchymal pulmonary disease, pulmonary hypertension, congenital and other heart disease, hemoglobinopathies, and environmental exposures such as high altitude. Acute exacerbations of respiratory disorders can accentuate the severity of hypoxemia. Hypoxemia due to underlying lower airway obstructive disease, pulmonary parenchymal disease, pulmonary hypertension, and other causes of sleep-related hypoxemia 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 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*

The underlying cause of the sleep-related hypoxemia will dictate the natural history, including onset, course, and risk of long-term complications. 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. Populations living at high altitude have much higher prevalence due to that exposure. Thus, prevalence may be higher in patients with greater perturbations

of pulmonary function. Individuals with chronic hypoxemia during wakefulness will experience even more significant decrements in oxygen saturation 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 that adequately predicts the risk of sleep-related hypoxemia in individual patients. Patients who are hypoxemic during wakefulness generally become even more so during sleep, especially REM sleep. Among the best predictors of sleep-related hypoxemia is a reduced baseline wake SaO<sub>2</sub>. Obesity, particularly central obesity, increases closing volumes which can lead to lower lobe atelectasis and shunting of blood, thereby predisposing to sleep-related hypoxemia, even in the absence of pulmonary pathology. The combination of risk factors (e.g., patients with chronic obstructive pulmonary disease going to altitude or patients with interstitial lung disease developing secondary pulmonary hypertension) increases the risk of sleep-related hypoxemia.

### *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. Sickle cell disease is an autosomal recessive disorder of hemoglobin that leads to poorly functioning red blood cells. 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 etiology, although substantial variability in course is observed even within the same underlying condition. Many affected individuals with severe hypoxemia develop respiratory impairment, pulmonary hypertension, heart failure, cardiac arrhythmias, and neurocognitive dysfunction. Polycythemia is common in those with chronic hypoxemia. Higher rates of painful crises accompany hypoxemia in children with sickle cell disease. Sleep-related hypoxemia is also an independent predictor of stroke in individuals 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. Of note, patients with co-existing COPD and OSA, often labelled overlap syndrome, have a greater risk of acute COPD exacerbation, pulmonary hypertension, and premature mortality than COPD alone.

## *Developmental Issues*

Certain disorders causing sleep-related hypoxemia are more likely to present in childhood. These include congenital heart disease and sickle cell disease, cystic fibrosis, bronchopulmonary dysplasia, pulmonary hypertension, and diffuse childhood interstitial lung disease.

## *Pathology and Pathophysiology*

Hypoxemia may arise from ventilation-perfusion [V/Q] mismatching, shunt physiology, or low oxygen tension in inspired air, such as when at 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. In patients with chronic obstructive pulmonary disease or other obstructive lung diseases such as bronchiectasis, hypoxemia may be the result of hypoventilation, ventilation-perfusion mismatching, or a combination of the two processes. Pulmonary parenchymal diseases are characterized by altered lung volumes (e.g., reduced functional residual capacity) and abnormal ventilation/perfusion relationships, which can result in hypoxemia during wakefulness. During sleep, decreased lung volumes result in reduced oxygen reserves. In addition, the altered ventilation/perfusion relationships occurring with supine positioning can further exacerbate hypoxemia during sleep. Sleep may be associated with an altered pattern of ventilatory muscle activation, particularly during REM sleep. As a result of reduced activation of the intercostal and accessory muscles, there is a disproportionate ventilatory burden placed on the diaphragm that, in turn, alters ventilation/perfusion relationships within the lung. In patients with chronic obstructive pulmonary disease or other obstructive lung diseases, lung hyperinflation creates a mechanical disadvantage to the diaphragm reducing efficiency of ventilation in REM sleep. In sickle cell disease, decreased oxyhemoglobin affinity, along with pulmonary parenchymal and vascular disease, contributes to desaturation. Finally, daytime hypoxemia, if sufficiently severe, may place the patient near or on the steep portion of the oxyhemoglobin dissociation curve. When this occurs, even relatively small decrements in arterial oxygen tension result in significant decrements in oxyhemoglobin saturation. Thus, the normal, physiologic hypoventilation that occurs at sleep onset, which typically produces a very mild decrease in arterial oxygen tension can produce large decrements in oxyhemoglobin saturation in these patients. In individuals with a patent foramen ovale or atrial septal defect, small changes in arterial oxygen tension due to physiologic ventilatory changes at sleep onset or mild sleep-disordered breathing can raise pulmonary artery pressures sufficiently to cause right to left shunting of blood. This worsens hypoxemia which, in turn, further exacerbates hypoxic pulmonary vasoconstriction in a vicious cycle that can result in severe hypoxemia.

## *Objective Findings*



Various patterns of oxygen desaturation (sustained, intermittent, or episodic) may be observed during sleep. The diagnosis is generally made based on overnight oximetry (alone or as a component of PSG or HSAT). Ideally, CO<sub>2</sub> levels should be concomitantly assessed using arterial blood gas or surrogate such as end-tidal CO<sub>2</sub> or transcutaneous CO<sub>2</sub> monitoring to exclude hypoventilation as the etiology. 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 hypoxemia. 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 hypoxemia 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 rise to hypoxemia during sleep. This includes entities that produce sleep-related hypoxemia such as pulmonary airway and parenchymal disorders, pulmonary vascular disorders, congenital and other cardiac disorders, and high altitude. Identifying the underlying cause of sleep-related hypoxemia is important for prognostic and therapeutic purposes.

**Sleep-related hypoventilation disorders should** be excluded. This includes *neuromuscular and chest wall disorders, OHS, use of medications or substances that can suppress respiratory drive, and congenital or idiopathic central alveolar hypoventilation syndromes*. Exclusion of sleep-related hypoventilation is achieved ideally through physiologic evaluation for evidence of hypoventilation using arterial or venous blood gas, transcutaneous CO<sub>2</sub> monitoring, or end-tidal CO<sub>2</sub> monitoring. Minimally, clinical evaluation should be performed to exclude hypoventilation as the cause of hypoxemia.

**Obstructive and central sleep apnea syndromes can** be distinguished from sleep-related hypoxemia by the periodic alterations in airflow and accompanying periodic fluctuations in SaO<sub>2</sub>. 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 (e.g., COPD can cause both sleep-related hypoxemia through V/Q mismatch and sleep-related hypoventilation), all pertinent diagnoses should be coded.

### *Unresolved Issues and Further Directions*

The degree and duration of 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<sub>2</sub> during sleep is not clear. Except for 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, particularly in the prevention of vascular complications of sickle cell disease.

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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 herein occurs without recurrent 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. As such, it can impact relationship quality and intimacy with the bedpartner and thus lead to psychologic distress. 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.* Both community and clinic-based studies have found snoring, even in those with normal AHI, is associated with excessive daytime sleepiness. Whether this reflects an adverse effect of snoring itself, an unassessed physiologic impact of obstructed breathing on brain function, or inaccurate assessment of OSA due to night-to-night variability in AHI is unclear. 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 HSAT is required 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. However, 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 this 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, including allergic rhinitis and other causes of chronic nasal congestion, increases the risk of snoring. Ingestion of alcohol, muscle relaxants, opioids, 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. Among children, exposure to secondhand smoke increases risk of snoring. Snoring has also been shown to increase during pregnancy. During pregnancy, the prevalence of snoring increases from 8% in the first trimester to 21% in the third trimester. In children, an association has been reported between snoring and adenotonsillar hypertrophy. Breastfeeding is protective of habitual snoring in children. 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 N3 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, several large observational studies that account for OSA found no increased risk of cardiovascular morbidity or mortality in habitual snorers compared to non-snorers. Several studies have suggested snoring may predispose specifically to atherosclerosis in the carotid artery over other arterial beds due to direct vibration trauma. However, this association has not been confirmed by other studies. In pregnancy, snoring is associated with increased risk of gestational diabetes, pregnancy-induced hypertension, and pre-eclampsia but the independent risk of snoring after excluding those with OSA is unclear. Further research is needed to evaluate the long-term health outcomes of habitual snoring in populations where OSA has been excluded including multi-night OSA assessments to understand the extent to which mild OSA may be misclassified as isolated snoring. In addition, longitudinal studies of habitual snorers are needed to determine whether snoring is a risk factor or prodrome for the development of OSA.

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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. Laryngoscopy has confirmed the observed noise is produced by active adduction and vibration of the vocal cords during expiration. 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 apnea are not typically associated with vocalization. Catathrenia is thought to be rare. Onset tends to be in childhood, adolescence, or young adulthood, and there is no apparent gender predisposition. A history of competitive swimming has been identified as a potential risk factor for catathrenia. In those affected, the events occur nearly every night. Several episodes may occur in one night and often occur in clusters. The episodes of catathrenia are not associated with sleep talking or body movement. There are no clear long term health consequences of catathrenia. However, there can be substantial social impact through effects on relationship with the bedpartner and embarrassment.

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