Published in final edited form as:

Sleep Med Clin. 2008 December 1; 3(4): 601–615. doi:10.1016/j.jsmc.2008.08.006.

Central Alveolar Hypoventilation Syndromes

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Keywords

Central alveolar hypoventilation; Congenital central hypoventilation syndrome

The ventilatory control system is tightly regulated. Three elements known to regulate this system include (1) sensors, such as peripheral and central chemoreceptors, and mechanoreceptors; (2) central controllers that receive input and integrate the response from the above sensors; and (3) effectors, including the muscles of respiration, that respond to the commands of the central controllers.

Thus, alveolar ventilation is regulated most of the time involuntarily by the respiratory centers located beneath the ventral surfaces of the pons and medulla, that receive afferent input from the sensors and control ventilation automatically (chemically) via the respiratory muscles. This chemical control regulates breathing during non-rapid eye movement (NREM) sleep. Voluntary control by cortical centers can also occur, particularly during wakefulness and during rapid eye movement (REM) sleep.

Central alveolar hypoventilation disorders denote conditions resulting from underlying neurologic disorders affecting the sensors, the central controller, or the integration of the signals. Such disorders can lead to insufficient ventilation and an increase in PaCO₂ (hypercarbia), as well as a decrease in PaO₂ (hypoxemia). The condition may be congenital or acquired, and affected children may be at risk from the neonatal period. Central alveolar hypoventilation may be present during sleep alone or in more severe cases during sleep and wakefulness.

It is important to make an early diagnosis of central hypoventilation to prevent the deleterious effects of hypercapnia, acidosis, and hypoxemia on cardiovascular and neurocognitive function. This review discusses the current knowledge on central alveolar hypoventilation syndromes, particularly in children, with special emphasis describing the recent knowledge about congenital central hypoventilation syndrome (CCHS) and rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD).

CONGENITAL ALVEOLAR HYPOVENTILATION DISORDERS

Congenital Central Hypoventilation Syndrome

CCHS or congenital central alveolar hypoventilation syndrome has also been referred to as Ondine's curse and has been recognized in the literature for more than 30 years.¹ Ondine's curse (also known as Undine) was referenced to the story of a water sprite from European lore who cursed her unfaithful lover to lose all automatic functions and therefore stop breathing

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when he fell asleep. This rather apt description of the plight of subjects with CCHS has now become a part of medical mythology, but does not accurately reproduce the fable of Ondine. The identification of associated features including Hirschsprung's disease, which is considered a neurocristopathy or developmental anomaly of the neural crest,³ neural crest tumors, and autonomic nervous system (ANS) abnormalities has led to CCHS also being regarded as a neurocristopathy.⁴⁻⁶ Subsequent work identifying abnormalities in a gene (PHOX2B) involved in the development of the ANS in the majority of cases of CCHS, if not all, has confirmed this concept.^{7,8}

Epidemiology—CCHS is a rare disorder that is present across the world, with an estimated incidence of 1 per 200,000 live births in France.^{9,10} Reliable estimates of prevalence in the United States and other countries are not currently available. The male to female ratio in many countries is reported to be 1:1.^{9,10}

Ventilatory disturbances in congenital central hypoventilation syndrome—

Ventilatory disturbances in CCHS have a characteristic pattern. The prominent respiratory disruption in children with CCHS is hypoventilation during sleep, although severely affected children may also have wake hypoventilation. Minute ventilation is reduced during sleep in CCHS because of a reduction in tidal volume with a relatively preserved breathing frequency. This pattern is much more apparent in NREM sleep when chemical control of breathing maintains respiration, than in REM sleep when a significant cortical component regulates breathing.¹¹⁻¹³ These findings suggest some type of alteration in chemosensitivity or alteration in regulation of the chemical ventilatory response in these subjects. Sleep hypoventilation results in significant endogenous hypercarbia and hypoxemia in CCHS, but these chemical changes characteristically do not lead to arousals and awakening from sleep.⁴ Interestingly, arousals in response to exogenous hypercapnia are relatively preserved, indicating at least some functioning chemoreceptor activity.¹⁴ Paton and colleagues¹⁵ found that the absence of chemical ventilatory control in CCHS extends to wakefulness with no change in ventilation in response to hypercarbia or hypoxemia in wake children (Fig. 1 and Fig. 2). In addition, they reported a remarkable lack of dyspnea or discomfort in the children studied. The urge to breathe after a breath hold has been termed "air hunger" and the urge to breathe after exercise has been termed "shortness of breath." Shea and colleagues¹⁶ found that children with CCHS did not have "air hunger" on inhalation of carbon dioxide and were able to hold their breath much longer than controls. However, if they were able to exercise heavily, they did report symptoms akin to "shortness of breath." Ventilatory response to exercise in CCHS is abnormal: increase in minute ventilation commensurate with exercise is seen up to the lactate threshold, but beyond this level it tends to lag resulting in carbon dioxide retention and hypoxemia. This response is accompanied by lower increase in heart rate as compared with controls.¹⁷⁻¹⁹ Shea and colleagues²⁰ investigated the importance of voluntary control of breathing in CCHS and reported that distracting mental activities did not compromise breathing in patients with CCHS, suggesting the presence of some mechanisms of involuntary ventilation. The ability of children with CCHS to increase minute ventilation in response to exercise is, at least in part, in response to movement of the extremities. Gozal and colleagues^{21,22} showed elegantly that passive movement of the extremities, during wakefulness and sleep, induces increases in minute ventilation.

Taken together, these findings have led to the speculation that poor integration of signals in brainstem rather than affected chemoreceptor function explains the ventilatory disturbances in CCHS.²³ Using functional magnetic resonance imaging (MRI), Harper and colleagues and Macey and colleagues^{24,25} studied the responses to hypercapnia and hypoxia and cold forehead stimulation (that bypasses central chemoreceptors) in subjects with CCHS. They reported significant roles of midbrain, cerebellar, thalamic, basal ganglia, and limbic sites in response to these chemical stimulations that are deficient in subjects with CCHS.

Autonomic disturbances in congenital central hypoventilation syndrome—

Patients with CCHS have multiple disturbances of autonomic dysfunction including abnormal heart rate variability (HRV), attenuated increase in heart rate in response to exercise and increased frequency of sinus bradycardia and transient asystole.^{18,26,27}

Reduced wake blood pressure and attenuation of the night time dip in blood pressure was demonstrated on 24 hour blood pressure monitoring in children with CCHS.²⁸ Pulse arterial tonometry (PAT) studies have shown reduction in the attenuation of PAT pressures with vital capacity sigh and exposure of the hand to ice cold water which lead to endogenous sympathetic stimulation.²⁹

Pathology—Autopsy studies have not been contributory to the etiology of the disorder. Normal white matter or, in other cases, diffuse central nervous system astrocytosis, gliosis, and atrophy, but no primary brain stem abnormality, have been reported.¹¹ One report suggested small carotid bodies and an increase in lung receptors in two cases on autopsy.³⁰

Clinical features of congenital central hypoventilation syndrome—Most cases present in infancy, usually in the newborn period, occasionally in childhood, and rarely in adulthood. Trochet and colleagues³¹ have proposed that onset of hypoventilation after the newborn period (28 days of life) be classified as late-onset congenital hypoventilation syndrome. The common clinical features of CCHS are presented in Table 1.

Although most patients present with symptoms in infancy, some patients, including parents of children with CCHS, have been detected to have CCHS as adults.^{31,32} Clinical clues to the diagnosis of late-onset CCHS include the ability to hold breath for prolonged periods without discomfort, episodes of cyanosis, daytime sleepiness and fatigue, unexplained seizures with normal electroencephalogram, evidence of right heart failure, apnea or delayed recovery after anesthesia or anticonvulsant therapy, and signs of autonomic dysfunction such as postural hypotension and low body temperature.³² Late diagnosis is frequently associated with cognitive impairment.³²

Genetics—Reports of CCHS in identical twins,³³ female siblings,³ and male–female half siblings,³⁴ as well as mother–daughter transmission^{35,36} strongly suggested a genetic basis for CCHS. A formal segregation analysis of ANS dysfunction in families of children with CCHS suggested an autosomal codominant inheritance pattern.³⁷ Initial studies focused on the genes that had known associations with Hirschsprung's disease, such as receptor tyrosine kinase, endothelin signaling pathway genes, and glial-derived neurotrophic factor.⁸ These did not identify abnormalities that were seen exclusively in subjects with CCHS and were not present in control subjects.

The search was then directed to genes involved in the development of the ANS, and Amiel and colleagues⁷ in 2003 reported heterozygous polyalanine repeat abnormalities in the PHOX2B gene mapped to chromosome 4p12 in CCHS subjects that were not found in control subjects. PHOX2b is a homeobox gene; it contains DNA sequences that are involved in the regulation of development. It has an early role in the promotion of pan-neuronal differentiation, repression of expression of inhibitors of neurogenesis, and regulation of the noradrenergic phenotype in vertebrate neural cells, including expression of tyrosine hydroxylase, dopamine β-hydroxylase, and receptor tyrosine kinase.^{38–40} PHOX2b has two short and stable polyalanine repeats of nine and 20 residues (27 and 60 base pairs respectively) in exon 3.⁷ Heterozygous expansion of the 20 residues to 25 to 33 residues (15 to 39 additional base pairs) is seen in most (about 90%) subjects with CCHS and is not seen in normal controls, suggesting a loss of function with the expansion.^{7,41,42} Polyalanine expansions have been implicated in other inherited diseases such as X-linked mental retardation and seizures.⁴³ Polyalanine expansions are

thought to function as spacers or protein-binding elements; expansions may thus lead to proteins that can bind DNA but have impaired functioning and interfere with functioning of the normal protein produced by the normal allele (a dominant negative effect). In this scenario, larger polyalanine expansions would result in greater phenotypic changes, which has been observed in patients with CCHS.⁸ Reports of patients with deletions of the chromosome 4p region that included the PHOX2B gene but did not have CCHS provide evidence for a dominant negative effect rather than a haploinsufficiency model.⁴⁴

The majority of PHOX2B mutations occur de novo, but Weese-Mayer and colleagues^{8,42} have shown mosaicism for polyalanine expansion in 10% of unaffected parents of children with CCHS with transmission of the polyalanine expansions from affected mother to affected child. Other types of PHOX2b mutations that confer CCHS include missense, nonsense, and frame shift mutations in exons 2 and 3 and are less common (about 8%).⁴⁴ These mutations, in general, result in truncated or dysfunctional proteins with loss of protein function.⁸

Broad genotype–phenotype correlations can be made; mutations with a greater number of polyalanine repeats are more likely to have more severe disease (number of ANS symptoms), increased R–R interval, severity of ventilatory dependence, and rarely, neural crest tumors.^{8, 42,44–46} Most of the limited number of cases of CCHS that have been shown to present later in childhood or were detected in adulthood have had five polyalanine repeats, the least necessary that has been shown to result in CCHS.^{32,45,47,48} Nonpolyalanine expansion mutations causing CCHS lead to greater disruption of PHOX2b function and are associated with more severe ventilatory disruption, greater incidence of Hirschsprung’s disease (87% versus 34%, respectively), and neural crest tumors (50% versus 1%, respectively).^{44,47} Thus, Hirschsprung’s disease and neural crest tumors are strongly predictive of nonexpansion mutations, and patients with nonexpansion mutations should be monitored closely for neural crest tumors. However, some frameshift mutations are associated with milder manifestations.^{31,44}

The percentage of CCHS subjects with PHOX2b abnormalities had been reported initially to range from 40% to 97%.^{7,41,42} This discrepancy may be related to incomplete analysis of the gene, technical issues, or selection of patients that share the features of CCHS but may not have had all the ventilatory abnormalities.⁴⁴ In the largest series of 201 CCHS patients with genetic analysis, all patients had PHOX2b mutations, attributed to strict selection criteria for the diagnosis of CCHS.⁴⁴

Diagnosis—Early detection of CCHS is important because of the significant morbidity, especially neurologic, and the risk of death in the undiagnosed subject. The American Thoracic Society published an official statement to increase awareness and promote early detection of CCHS.⁴ The salient features of CCHS include (1) generally adequate ventilation while the patient is awake but alveolar hypoventilation with shallow breathing (diminished tidal volume) during sleep (more severely affected children hypoventilate both while awake and asleep); (2) better ventilation in REM sleep than in NREM sleep and progressive hypercapnia and hypoxemia with sleep; (3) absent or negligible ventilatory sensitivity to hypercarbia and hypoxemia during sleep; (4) lack of an arousal response to the endogenous challenges of isolated hypercarbia and hypoxemia, and to the combined stimulus of hypercarbia and hypoxemia; (5) generally absent awake ventilatory responsiveness to hypercarbia and hypoxemia; and (6) generally absent perception of asphyxia (ie, behavioral awareness of hypercarbia and hypoxemia) even when awake minute ventilation is adequate.⁴ Patients, particularly infants, may initially have only isolated symptoms such as extreme breath holding spells or temperature instability that may warrant further evaluation or careful follow-up. All cases of late-onset congenital hypoventilation should be tested for PHOX2B abnormalities. Of

note, the diagnosis of CCHS is made in the absence of primary neuromuscular, lung, or cardiac disease or an identifiable brainstem lesion.⁴

CCHS can mimic many treatable diseases, and it is important to evaluate carefully for these conditions: (1) neuromuscular disease: discrete congenital myopathy, myasthenia gravis, or diaphragm dysfunction; (2) pulmonary disease: altered airway or intrathoracic anatomy; (3) cardiac disease: congenital cardiac disease; (4) brainstem lesions: structural posterior brain or brainstem abnormality or Möbius' syndrome; (5) specific metabolic diseases: Leigh disease, pyruvate dehydrogenase deficiency, and discrete carnitine deficiency; and (6) confounding variables including asphyxia, infection, trauma, tumor, and infarction should be distinguished from CCHS.⁴

The initial evaluation should include a detailed neurologic evaluation (that may require a muscle biopsy), chest x-ray, fluoroscopy of the diaphragm, electrocardiogram, Holter recording, echocardiogram, MRI of the brain/brainstem, and ophthalmologic evaluation to assess for pupillary reactivity and optic disk anatomy.⁴ A rectal biopsy should be considered in the event of abdominal distention and delayed defecation to assess for Hirschsprung's disease.⁴ Thorough airway evaluation (bronchoscopy, imaging) and evaluation of inborn errors of metabolism airway (such as serum and urinary carnitine levels or muscle biopsy for carnitine deficiency) may be necessary during initial evaluation.

The availability of genetic testing that identifies most, if not all, cases has made the diagnosis of CCHS much easier. A screening test for polyalanine expansion is relatively easily performed, and more detailed sequencing is indicated when clinical suspicion is high, and the screening test is negative.^{42,47} Current information about genetic testing resources regarding CCHS is available at www.genetests.org, a National Institutes of Health–funded Web site sponsored by the University of Washington, Seattle, Washington. Most mutations arise de novo, but about 5% of parents have somatic mosaicism for a PHOX2B mutation and rarely have a germline CCHS mutation. Therefore, both parents should be screened for mutations and physiologically evaluated if they have mutations, and they should be regularly monitored even if asymptomatic. Children of patients with CCHS have a 50% chance of CCHS development, whereas children of subjects with somatic mosaicism have a less than 50% chance. Prenatal testing can be done if a mutation is identified.

Management—A careful evaluation of spontaneous breathing during sleep (NREM and REM) and wakefulness is essential to determine if the need for ventilatory support is during sleep only or during sleep and wakefulness. The change in tidal volume and respiratory frequency response to the endogenous challenges of hypercarbia and hypoxemia may negate the need for exogenous challenge testing. Before discharge, adequate parental training (eg, basic life support, tracheostomy care), backup ventilation, appropriate nursing assistance, and monitoring equipment need to be arranged. Pulse oximetry and end tidal carbon dioxide monitoring can provide objective evidence of early decompensation of ventilation such as with intercurrent infections, especially because this may be masked by the lack of dyspnea in patients with CCHS. In addition, these parameters can detect at an early stage the need to increase ventilatory support with growth.⁴

Ventilatory support—Ventilatory support can be provided by a mechanical ventilator via a tracheostomy, noninvasive ventilation via face/nasal mask, negative pressure ventilators, and diaphragmatic pacing. Ventilatory support may be needed continually or only when asleep.

Infants who require 24-hour ventilatory support will need mechanical ventilation via tracheostomy. With increased mobility, it may be feasible to transition them to daytime diaphragmatic pacing with a better quality of life. Speech can be attempted in children with

diaphragmatic pacing with one-way speaking valves such as the Passy-Muir speaking valve (Passy-Muir, Irvine, California); readiness for speech may be assessed by capping the tracheostomy tube and allowing the child to breathe around the uncuffed tracheostomy tube. Periodic surveillance of the tracheostomy site for complications such as granulation tissue can help anticipate problems with ventilation, tracheostomy care, and speech with a speaking valve. As the child matures, it may be possible to manage ventilation with daytime pacing and nighttime non-invasive mask ventilation.

Children who require support only at night were initially been managed by tracheostomy and mechanical ventilation but now often are managed with noninvasive ventilation (NIV) with Bilevel Positive Airway Pressure (BLPAP) devices via a face mask. BLPAP ventilation is set up so that the difference between inspiratory and expiratory pressure generates adequate tidal volume with an expiratory pressure sufficient to maintain adequate functional residual capacity. A backup ventilatory rate is dialed in to guarantee minute ventilation. The use of NIV has become more widespread, and in an international survey of patients with CCHS, Vanderlaan and colleagues⁹ reported that 14% of patients had never been tracheotomized and were managed by noninvasive ventilation. Children with CCHS who are maintained on nocturnal ventilation need close monitoring at the age of 2 to 3 years because they may have a greater need for wake ventilatory support during this time.⁴ Adenotonsillar hypertrophy is also common at this age and may interfere with mask ventilation. Facial growth should be regularly assessed by craniofacial experts in infants and younger children receiving mask ventilation because of the potential for midfacial hypoplasia.

The suggested target for ventilatory support is to maintain oxyhemoglobin saturation at or above 95%. End tidal carbon dioxide levels in the 30- to 45-mm Hg range are recommended to provide a safety margin for adequate ventilation in the home environment.⁴ A target level of 30 to 35 mm Hg at night has also been advised based on potential improvement in daytime ventilation brought about by mild nocturnal hyperventilation.²³

Children who need only nocturnal NIV may be candidates for nocturnal diaphragmatic pacing that may become the sole mode of ventilatory support for these children.²³ These children may need additional daytime support via NIV or more aggressive support by endotracheal intubation in the presence of illness or lower respiratory tract infections. Diaphragmatic pacing stimulates the patient's phrenic nerves by an external transmitter, antenna, receiver, and electrode. The external transmitter sets the respiratory rate and length of inspiration. It transmits the signal and energy by inductive coupling across intact skin via the antenna to the subcutaneous receiver. The phrenic nerves are then stimulated by the implanted electrodes. The diaphragmatic musculature needs to be trained by gradually increasing the duration of stimulation to overcome fatigue. Pacing is usually limited to 12 to 16 hours at a stretch, although 24-hour stimulation has been done.²³ Diaphragmatic contractions reduce upper airway pressure and have the potential to cause upper airway obstruction. Pacing equipment can malfunction, and a backup mode of ventilation is important as is proximity to a team that can manage the malfunctions.²³

Negative pressure ventilators expand the chest and abdomen by external negative pressure. This can be delivered by an external shell (cuirass) or a wrap and is also available as a relatively portable product (Porta-Lung Inc., Lakewood, Colorado; <http://portalung.com/>). These ventilators are more cumbersome, limit access to the body, and may cause upper airway obstruction during sleep.²³ However, there may be an option for patients who do not tolerate positive pressure ventilation.

Long-term management—Patients with CCHS have so many special needs that it is advisable to coordinate their care with a center that has the expertise in managing CCHS.⁴ These needs include the following:

1. Close monitoring of growth and development including detailed neurocognitive testing for impairments that may be caused by CCHS or is secondary to hypoxemia.
2. Regular echocardiography to gauge pulmonary arterial pressure and ambulatory electrocardiographic monitoring to assess for asystole, particularly with symptoms of dizziness and syncope. These evaluations may inform the need for better ventilation and cardiac pacing.^{4,46}
3. Careful periodic ophthalmologic evaluation because of the high incidence of ocular abnormalities.^{4,49}
4. A high index of suspicion for the management of infection in children with CCHS because of the impaired ability to sense hypoxemia, poor perception of respiratory distress in response to lower respiratory infections, and unpredictable temperature control. Management is optimized by objective evaluation of respiratory status by pulse oximetry and end tidal carbon dioxide monitoring and by well-informed, skilled, and consistent care at home.
5. Limitation of sporting activity to noncontact sports and to moderate exercise with many rest periods because of the potential inability to adapt to greater exercise loads and lack of recognition of hypoxemia, hypercarbia, and acidosis. Swimming carries significant risk and, if allowed, should only be done under close supervision by a competent caretaker who limits submersion time and ensures frequent rests.⁴
6. Children with nonpolyalanine expansion mutations should be screened for Hirschsprung's disease and surveilled for neural crest tumors in infancy and childhood.
7. Close attention and objective monitoring after sedation and anesthesia is necessary because of the potential of prolonged apneas.³²
8. Counseling and advising abstinence from alcohol is important because of the potential for adverse outcomes including coma and death, particularly during adolescence.⁵⁰

Support groups can very useful to help parents and children cope with these unique problems.

Prognosis—The first few years of life are associated with the greatest need for medical attention, and long-term outcome is variable.^{4,23} Children with CCHS do not outgrow the need of ventilatory support during sleep and remain technology dependant, and, internationally, support varies widely across various regions of the globe.⁹ The long-term outcome of neurodevelopment with optimal ventilatory support has not been established. Overall, once the condition is identified, with appropriate support, the outcome has improved with a reasonable quality of life.

Myelomeningocele with Arnold Chiari Type II Malformation

Arnold-Chiari malformation (ACM) is a congenital brain malformation involving a deformity of the brainstem caused by herniation of the medulla and cerebellum through the foramen magnum. Arnold Chiari malformation type II is associated with myelomeningocele, hydrocephalus, and herniation of the cerebellar tonsils; caudal brainstem; and fourth ventricle through the foramen magnum. These patients are at risk for alterations in ventilatory control because of the involvement of respiratory centers located within the affected areas or involvement of brainstem nuclei controlling upper airway motor musculature and sensation. It has been speculated that both traction from the myelomeningocele and increased intracranial

pressure caused by hydrocephalus may cause compression of respiratory centers controlling the ventilatory patterns. Alternatively, it has been proposed that a primary deficit in brain stem structure may be responsible for respiratory deficits observed in these subjects.

Ventilatory patterns during sleep—Sleep disordered breathing including obstructive sleep apnea and hypoventilation has been reported in subjects with ACM type II. The exact prevalence is unknown. A large report by Hayes and colleagues,⁵¹ suggests that about 5.7% (35 of 616) children have evidence of significant central ventilatory dysfunction including vocal cord paralysis, stridor, apnea, hypoventilation, and bradyarrhythmia. In another study of asymptomatic patients with ACM type II, Ward and colleagues⁵² noted hypoventilation in up to 70% of children. Interestingly, in about 30% of cases, these symptoms may be reversible once children undergo treatment for the hydrocephalus or decompression of the brainstem.⁵³

Ventilatory responses—Significant blunted ventilatory responses to hypercapnia and, to a lesser degree, hypoxia have been noted by Swaminathan and colleagues⁵⁴ in children with ACM type II. These findings were also observed by Gozal and colleagues⁵⁵ who tested peripheral chemosensitivity in these subjects and noted a few with altered hypoxic responses. They have speculated that central ventilatory controllers may be affected in these subjects by traction of the ACM affecting integration of chemoreceptor output.⁵⁵

Management—Presence of upper airway obstruction and vocal cord paralysis during wakefulness requires immediate medical attention. If not responsive to treatment of hydrocephalus or posterior fossa decompression, tracheostomy and mechanical ventilation are indicated. Children with significant hypoventilation during sleep or wakefulness will require chronic mechanical ventilation to sustain an adequate life quality.⁵³

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a genetic disorder resulting from a parental imprinting abnormality of chromosome 15 in the Prader-Willi critical region (PWC). The prevalence of the disorder is estimated at 1 per 10,000 to 1 per 25,000 births. Clinically, PWS is characterized by mental retardation, severe hypotonia, and feeding difficulties in early infancy followed later by excessive eating and gradual development of morbid obesity. It is believed that a primary hypothalamic dysfunction has a major role in the disorder leading to hyperphagia, growth hormone deficiency and short stature, temperature instability, and hypogonadotropic hypogonadism.

Ventilatory patterns during sleep—Various studies suggest that PWS subjects are at increased risk for the development of obstructive sleep apnea, central sleep apnea, and alveolar hypoventilation during sleep.^{56–58} However, the exact prevalence of sleep-disordered breathing in PWS is not well established.⁵⁸ PWS subjects are at risk for the development of such disorders because of obesity, alterations in cranial structure, hypotonia, restrictive lung disease, and altered ventilatory responses.⁵⁸

Altered ventilatory responses—Ventilatory responses to hypoxia are absent or significantly reduced in subjects with PWS and are independent of degree of obesity.⁵⁹ In contrast, hypercapnic ventilatory responses were shown to be normal in nonobese PWS and blunted in obese PWS subjects compared with controls.⁵⁹ These findings are supported by studies showing absence of peripheral chemosensitivity in PWS⁶⁰ and studies showing poor arousal and cardiorespiratory responses to hypoxia and hypercapnia from slow wave sleep in these subjects.^{57,61} Recent reports document sudden death during sleep in some subjects when treated with growth hormone to improve growth velocity and improve body composition.^{62–68} Although mechanisms leading to sudden death have not been elucidated, abnormalities in

ventilatory control and respiratory infections have been noted. Consequently, polysomnography before treatment with growth hormone and careful monitoring during respiratory infections is recommended.^{66–68}

RAPID-ONSET OBESITY HYPOTHALAMIC DYSFUNCTION AND AUTONOMIC DYSREGULATION

The occurrence of late-onset central hypoventilation syndrome (LO-CHS) with features overlapping with CCHS in association with hypothalamic abnormalities was initially reported in 1965.⁶⁹ It was reviewed by Katz and colleagues⁷⁰ in 2000 when they noted this pattern of later age of onset and associated hypothalamic dysfunction (LOCHS/HD), which distinguished it from CCHS. They also reported that early obesity/hyperphagia was present in all these patients.⁷⁰ Ize-Ludlow and colleagues⁷¹ recently published a detailed study of 15 patients with LO-CHS, identified the consistent early presentation of rapid onset of obesity with associated autonomic abnormalities with hypoventilation, and coined the acronym ROHHAD (Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation) to facilitate identification of this phenotype. They did not find any mutations of PHOX2B or two other candidate genes, BDNF and TRKB, that are involved in neuronal development, in their series of cases. More extensive DNA analysis of two of 15 patients also did not reveal any abnormalities. MRI scans done in patients before cardiorespiratory arrest were not specific; one patient had Rathke's cleft cyst and another had hypointensities in the pons and medulla.⁷¹

Clinical Features

Nine girls and six boys are included in the above report with most having rapid onset of obesity as the initial manifestation followed by hypothalamic dysfunction, then autonomic abnormalities, and eventually hypoventilation. The median age for onset of obesity and hypothalamic dysfunction was 3 years, for autonomic dysfunction 3.6 years, and for hypoventilation 6.2 years. Hypernatremia was a common feature of hypothalamic dysfunction, and ophthalmologic abnormalities were seen in 13 of 15 children. A remarkable finding was the development of neural crest tumors in five of 15 children with this syndrome. A summary of clinical features is listed in Table 2.

All of 9 children tested had central alveolar hypoventilation with mild baseline tachypnea, hypoventilation, and hypoxemia during wakefulness with impaired response to endogenous hypercarbia and hypoxemia during NREM sleep. Seven of the 15 children reported required 24-hour ventilatory support, whereas the rest needed support at night. Of note, 60% of the children were reported to have cardiorespiratory arrest; some of these had some disturbances in respiratory function before arrest, including nocturnal desaturation, obstructive sleep apnea, and cyanotic episodes.

Diagnosis and Management

The diagnosis of ROHHAD rests on the identification of the rapid onset of obesity, hypothalamic dysfunction, and autonomic abnormalities and alveolar hypoventilation in children with normal initial first 2 to 4 years of life. Identification of the pattern of rapid obesity, hypothalamic abnormalities, and autonomic abnormalities is imperative to prevent morbidity and mortality associated with this syndrome.⁷¹ Close monitoring of their ventilatory status is currently recommended at 3- to 6-month intervals in addition to periodic surveillance for neural crest tumors.⁷¹ These recommendations for management may change as understanding of the molecular basis, pathophysiology, prognostic markers, and long-term outcome of this syndrome advances.

OBESITY HYPOVENTILATION SYNDROME

Obesity hypoventilation syndrome (OHS) is an incompletely understood syndrome of central hypoventilation during wakefulness that is seen in obese patients with sleep disordered breathing. It consists of a combination of (1) obesity; (2) sleep-disordered breathing (SDB) in the form of obstructive sleep apnea hypopnea syndrome (OSAHS) with apnea-hypopnea index greater than 5 per hour and/or sleep hypoventilation syndrome (SHVS) (a 10-mm Hg increase in arterial PCO₂ or persistent oxygen desaturation not explained by obstructive apneas or hypopneas); and (3) stable daytime hypoventilation (arterial PCO₂ > 45 mm Hg).^{72,73}

Most patients with OHS have OSAHS, but about 10% of patients have only SHVS.⁷⁴ OHS is associated with a higher morbidity and mortality rate compared with eucapnic OSAHS patients matched for age, body mass index, and lung function.⁷⁵ Patients with OHS make heavy use of health care resources with reduced use after treatment of OHS.⁷⁶

Pathophysiology

Obesity is associated with reduced respiratory system compliance, increased airway resistance attributed to a reduced functional residual capacity, and an increase in the work of breathing.^{77,78} This increased load is associated with a perturbation of central respiratory drive in patients with OHS; they are unable to increase their respiratory drive in response to hypercapnia.⁷⁹ The causative role of SDB in OHS is seen by the improvement in wake hypercapnia after treatment of OSAHS and SHVS.^{80–82} The precise mechanisms that predispose some patients with SDB to develop OHS are not clearly understood. Genetic factors have been proposed, but relatives of patients with OHS have not been reported to have abnormal ventilatory responses to hypercapnia.⁸³ A pivotal role for leptin in OSAHS has been suggested, because leptin-deficient mice have an impaired ventilatory response to hypercapnia before becoming obese.⁸⁴ In humans, the role of leptin in OHS has not been determined. Treatment of OSAHS in OHS patients has been shown to reduce OHS and leptin levels leading to speculation that OSAHS causes leptin resistance, and this leads to hypoventilation.⁸⁵ However, in OHS patients with SHVS and without OSAHS, treatment of SHVS has been reported to improve OHS and increase leptin levels, suggesting that SHVS may impair leptin production leading to daytime hypercapnia.⁸²

How does SDB cause daytime hypoventilation? SDB results in intermittent hypercapnia with respiratory acidosis, resulting in renal metabolic compensation in the form of increased serum bicarbonate. This compensation has a long half-life that results in increased bicarbonate levels in the daytime. The persistent metabolic alkalosis is thought to blunt the central ventilatory response to carbon dioxide by reducing the change in hydrogen ions for a given change in carbon dioxide, in turn, leading to wake hypercapnia.⁷⁴

Epidemiology

OHS is seen primarily in middle age with a male predominance that is not as prominent as in OSAHS, with an estimated prevalence of 10% to 20% of OSAHS patients that increases with degree of obesity.⁷⁴

Clinical Features

Patients with OHS have symptoms suggestive of OSAHS such as fatigue, daytime somnolence, and loud snoring but are more likely to have dyspnea, daytime desaturation, and edema.⁷⁴ Serum bicarbonate is a useful screening test, and arterial blood gas testing usually reveals compensated respiratory acidosis with a normal pH.^{73,74} Evaluation of lung functions is important to identify obstructive and restrictive lung disease. Patients with COPD and OSAHS

(overlap syndrome) can have daytime hypercapnia. Conditions that can worsen hypoventilation, such as alcohol ingestion, also need to be identified.⁷³

Management

Continuous positive airway pressure may be adequate to treat a subset of patients with OHS.⁸⁶ Patients who continue to have desaturation with CPAP should be provided BLPAP.⁷⁴ BLPAP in patients with OHS is provided as a form of noninvasive ventilation with the difference between inspiratory positive airway pressure and expiratory positive airway pressure being wide enough to provide adequate tidal volume.⁸⁰ Supplemental oxygen may be necessary if BLPAP does not correct oxygen desaturation. Monitoring compliance is an important component of management of patients with OHS because adherence to therapy of OHS is associated with improved outcomes.⁷⁴ Patients who do not tolerate noninvasive positive airway pressure should be considered for tracheostomy. Bariatric surgery, which can result in significant weight loss and improvement of OHS, may be appropriate for selected patients but should be considered carefully because of attendant complications.⁷⁴

OTHER ACQUIRED ALVEOLAR HYPOVENTILATION DISORDERS

Traumatic, ischemic, and inflammatory injuries in the brainstem region can result in acquired central hypoventilation. The term “Ondine’s curse” was first used by Severinhaus and Mitchell⁸⁷ to describe patients who had minimal motor loss and retained the ability to breathe voluntarily after they underwent high bilateral spinothalamic tract cordotomies but became apneic during sleep and had poor ventilatory responsiveness to inhaled carbon dioxide. Unilateral lesions are less likely to have hypoventilation, and damage to C2 fibers is implicated in these cases.⁸⁸ Brainstem infarctions and ischemia can result in central hypoventilation syndromes.^{89–91} Watershed infarcts in the brainstem tegmentum in the human fetal and neonatal brainstem can present with multiple cranial neuropathies, central hypoventilation and apnea, dysphagia and aspiration, Möbius syndrome, and Pierre Robin sequence.⁹¹ Tumors in the region of the brain stem, such as glioma and acoustic neuroma, can lead to central hypoventilation.^{92,93} Children with brain tumors often report sleepiness that may be related to central apneas or hypoventilation.⁹⁴ Hypoventilation may improve after tumor resection.⁹³ Bulbar polio and viral and paraneoplastic encephalitis have can occasionally result in central hypoventilation.^{95–97} The outcome of acquired alveolar hypoventilation cases varies with the etiology and ventilatory management is usually supportive.

SUMMARY

Central alveolar hypoventilation disorders are rare and complex disorders that may involve alterations in mechanisms of ventilatory control and autonomic dysfunction. These disorders may be congenital or acquired and are associated with significant morbidity and mortality. For many years, the etiology of this group of disorders has not been well understood, and genetic characterization was a blank slate. Recently, CCHS has emerged as distinct neurodevelopmental disorder linked to mutations of the PHOX2B gene. It is anticipated that in the future genetic characterization will be available for other newly described disorders such as ROHHAD. Although respiratory abnormalities and autonomic dysfunction in patients with congenital central alveolar hypoventilation disorders persist throughout life, the prognosis for these children has improved considerably in recent years. This improvement may be attributed to wider recognition of such disorders, specialized centers treating such children, and improved technology to treat and monitor these children throughout life.

Acknowledgments

Dr. Arens is supported by grant number HD-053693 from the National Institutes of Health.

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Fig. 1.

Hypoxic ventilatory response during wakefulness in CCHS. Arterial oxygen saturation (SaO_2) inspired and end-tidal carbon dioxide tension P_{ETCO_2} , inspired and end-tidal oxygen tension P_{ETO_2} $\dot{V}$ (l/s), flow. Inspiratory and expiratory flow are plotted against time. There is irregular breathing without progressive increase in ventilation despite fall in SaO_2 . (Adapted from Paton JY, Swaminathan S, Sargent CW, et al. Hypoxic and hypercapnic ventilatory responses in awake children with congenital central hypoventilation syndrome. *Am Rev Respir Dis* 1989;140(2):368–72; with permission. Copyright © 1989, American Thoracic Society.)

Fig. 2. Hypercapnic and hypoxic ventilatory response during wakefulness in children with CCHS. Minute ventilation (VE) is plotted on the ordinate. End-tidal (alveolar) carbon dioxide tension $P_{ET}CO_2$ is plotted on the abscissa for hypercapnic ventilatory responses. Arterial oxygen saturation (SaO_2) is plotted on the abscissa for hypoxic ventilatory responses. Each row represents one subject. There is no increase in ventilation with hypercapnia or hypoxia. (Adapted from Paton JY, Swaminathan S, Sargent CW, et al. Hypoxic and hypercapnic ventilatory responses in awake children with congenital central hypoventilation syndrome. *Am Rev Respir Dis* 1989;140(2):368–72; with permission. Copyright © 1989, American Thoracic Society.)

Table 1**Clinical manifestations of CCHS**

Respiratory	Nocturnal hypoventilation and daytime hypoventilation ⁴ Breath-holding spells Ability to breath-hold for a very long time with no discomfort
Cardiovascular	Cardiac arrhythmias including bradycardia, brady-arrhythmia asystole, decreased cyclical sinus arrhythmia ²⁷ Need for pacemakers reported in 4% to 6% of patients ^{9,11} Reduced heart rate variability Vasovagal syncope Syncope Cold extremities Postural hypotension ⁹⁸
Gastrointestinal	Constipation without Hirschsprung's disease. Dysphagia Gastroesophageal reflux. Hirschsprung's Disease, about 15% Diarrhea without Hirschsprung's disease ⁹⁸
Ophthalmologic	Nonreactive/sluggish pupils Altered near response ⁴⁹ Altered lacrimation ⁹⁸ Strabismus ^{49,98} Anisocoria, miosis, ptosis ^{49,98}
Neurologic	Developmental delay ⁹⁹ Motor and speech delay Learning disabilities reported in > 25% ⁹ Seizures (primarily during infancy) ⁹ Altered perception of pain ⁹⁸
Malignancies	Tumor of neural crest origin such as ganglioneuroma, neuroblastoma, ganglioneuroblastoma
Temperature instability	Altered temperature control Altered sweating Absence of fever with infections ⁹
Psychological	Reduced anxiety ¹⁰⁰

Table 2**Clinical manifestations of ROHHAD**

Endocrine	Obesity of rapid onset, hyperphagia
	Hypernatremia, polyuria, polydypsia, hyponatremia
	Hyperprolactinemia
	Precocious puberty, delayed puberty
	Hypogonadism, amenorrhea
	Failed growth hormone stimulation test, short stature
	Hypothyroidism
Autonomic	Temperature control abnormalities, altered sweating
	Altered perception of pain
	Cold extremities
	Bradycardia
Ophthalmologic	Pupillary abnormalities and strabismus
Respiratory	Central hypoventilation
	Cyanotic spells
	Cardiorespiratory arrest
	Obstructive sleep apnea
Neuropsychiatric	Behavior disorders
	Autism spectrum disorder
	Developmental delay and regression
	Seizures
	Bipolar disorder, depression
	Psychosis
Gastrointestinal	Constipation
	Diarrhea
Neural crest tumors	Ganglioneuroma
	Ganglioneuroblastoma