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Central Hypoventilation Syndromes

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INTRODUCTION

Hypoventilation refers to an increased arterial concentration of serum carbon dioxide due to inadequate gas exchange. Central hypoventilation indicates that a deficiency in the central nervous system, rather than the respiratory system, is the root of the problem. Central hypoventilation is uncommon and may be due to a variety of conditions (Table 1), which can be either congenital or acquired. The following is a review of conditions causing central hypoventilation in children. Although individually rare, these conditions can have serious effects on children if not identified, and understanding the pathophysiology of these conditions will help direct management and provide optimal care.

NORMAL CONTROL OF BREATHING

Control of breathing is governed by a complex system of receptors responding to changes in P_{O_2} , P_{CO_2} , and pH, as well as other factors, such as lung stretch, that has significant redundancy and changes with age and sleep state. Central chemoreceptors, located in multiple areas of the brainstem, respond to small changes in P_{CO_2} , causing stimulation of breathing by the central pattern generator in response to hypercapnia.¹ Central chemoreceptors are thought to be responsible for more than 50% of the hypercapnic ventilatory response. Peripheral chemoreceptors, located at the bifurcation of the carotid arteries, respond to acidemia, transient hypercapnia, or low P_{O_2} in arterial blood.² The central chemoreceptors account for greater than half of the ventilatory response to CO_2 with the peripheral chemoreceptors contributing the remainder of the response.³ The retrotrapezoid nucleus, a sparsely populated collection of neurons at the ventral medullary surface, is an important source of respiratory drive. The neurons in this nucleus are sensitive to changes in both oxygenation and ventilation as it receives input from the carotid bodies, hypothalamus, J receptors, and central pattern generator. The retrotrapezoid nucleus is

hypothesized to be the intrinsic respiratory pacemaker at birth.⁴ The medullary raphe is another central nervous system site potentially responsive to CO₂ changes.

To a degree, the brainstem centers of metabolic control of breathing can be overridden by anatomically distinct centers, which allow for voluntary control of breathing, thus allowing actions such as hyperventilation and breath-holding. In normal individuals, awareness of breathing increases with increased respiratory load, exercise, and upper airway obstruction, and voluntary control is affected by emotions such as laughter or panic. Although metabolic control of breathing is located in the brainstem, voluntary control of breathing is anatomically located in the cerebellum, primary motor cortex, and premotor areas.¹ Final integration of the voluntary and metabolic centers of respiratory control is thought to be located in the spinal motor neurons or the brainstem. The stimuli to the brainstem resulting in the feeling of dyspnea originate from vagal afferents.

In normal individuals, CO₂ tension is the primary trigger for ventilation. Above an apneic threshold, the ventilatory response to CO₂ is linear and is affected by sleep state and hypoxemia.² In response to increasing P_{CO₂}, ventilation will initially increase by greater tidal volume, followed by an increase in respiratory rate. In response to hypoxia, ventilation initially increases but then is reduced over time. In infants, this ventilatory “roll-off” will reach a reduction in ventilation that is below normoxic breathing in the second part of this biphasic response. In older children and adults, however, there is a more modest decline in ventilation after the ventilatory peak in response to hypoxia.⁵ The ventilatory response to combined hypoxia and hypercapnia is multiplicative rather than additive.

At the initiation of sleep, upper airway resistance increases, but withdrawal of the wakefulness stimulus leads to an immediate increase in CO₂, which is not due entirely to changes in pulmonary mechanics.⁶ During rapid eye movement (REM) sleep, there is often a further increase in CO₂ due to loss of accessory ventilatory muscle tone. The presence of sleep also causes the emergence of the apneic threshold, which is overridden by cortical influences during wakefulness. In individuals where there is a narrow gap between eupnic and apneic CO₂ levels, such as infants, unstable breathing patterns such as periodic breathing may emerge. In addition, the ventilatory responses to hypercapnia and hypoxemia are blunted during sleep. During REM sleep, there is less input from brainstem centers and more input from the primary motor cortex, resulting in more variation in the respiratory pattern.⁷ Arousal is an important response to changes in oxygenation or ventilation during sleep. Although hypoxemia is a strong stimulus for arousal in the first few months of life, elevated carbon dioxide levels are the more robust stimuli for arousal in later life.⁸

CONGENITAL CENTRAL HYPOVENTILATION SYNDROME

Background and Genetics

Congenital central hypoventilation syndrome (CCHS) is a rare, lifelong condition that causes primary alveolar hypoventilation. First described in 1970 by Mellins and colleagues,⁹ it was discovered in 2003 that the paired-like homeobox 2B (*PHOX2B*) gene on chromosome 4p12 is the disease-defining gene for CCHS.^{10,11} Transmission is through an autosomal-dominant pattern, although most cases of CCHS are de novo or inherited from a mosaic typically unaffected parent.^{10,11} *PHOX2B* encodes a transcription factor that is instrumental in the regulation of neural crest migration and development of the autonomic nervous system. More than 90% of patients with CCHS are heterozygous for an in-frame polyalanine repeat of the 20-residue polyalanine region. Although the normal genotype is referred to as 20/20, these mutated proteins produce genotypes of 20/24 to 20/33. The remaining approximately 10% of *PHOX2B* mutations are nonpolyalanine repeat mutations

(NPARMs) causing missense, nonsense, or frameshifts.¹² The incidence of CCHS is currently unknown, but one French study has estimated a rate of 1 in 200,000 live births.¹³

Clinical Presentation

Children with CCHS usually present during infancy with episodes of cyanosis or apnea, or even cardiorespiratory arrest. Characteristically, children with CCHS have been described as having a square face with a tall, flat forehead, and a deep philtrum with downturned lips.¹⁴ This phenotype is more prevalent with increased polyalanine repeats. There may be ophthalmologic clues to a diagnosis of CCHS as well. Children with CCHS may have a sluggish to absent papillary light reflex, strabismus, anisocoria, or convergence insufficiency. Individuals presenting late in the course may have evidence of right heart failure or developmental delay.

Some children will present outside of infancy and even in adulthood, but a careful history will often reveal signs and symptoms of hypoventilation or disorders of autonomic regulation from the newborn period. Those not diagnosed until much later may present with the sequelae of longstanding hypoventilation and hypoxemia, including epilepsy or cognitive disabilities.¹² CCHS should also be considered in older individuals with hypoventilation associated with respiratory infections or anesthesia. CCHS diagnosed in children over 1 month of age is termed later-onset CCHS. These children usually have the 20/24 and 20/25 genotypes and rarely have NPARMs.

The degree of hypoventilation in patients with CCHS is variable, and although most children ventilate adequately during wakefulness, approximately 15% require ventilatory support even when awake. Typically, a greater number of polyalanine repeats correlate with more severe hypo-ventilation, with those having 20/27 and 20/33 genotypes often requiring ventilatory support during both sleep and wakefulness. Because individuals with CCHS lack the response to hypercapnia and hypoxemia, they do not adequately augment respiratory effort required during ventilatory challenges such as illness or exercise. One study found that during an exercise challenge, children with CCHS, who had absent hypercapnic and hypoxic ventilatory responses during wakefulness, increased minute ventilation by increasing respiratory rate but not tidal volume.¹⁵ Interestingly, this study showed a positive correlation between treadmill pace and respiratory rate. Oxygen saturation decreased and CO₂ tension increased during exercise in patients with CCHS but not controls in this study. A different study of 6 sleeping patients with CCHS demonstrated increased respiratory rate during brief periods of passive lower extremity motion.¹⁶ These studies suggest that mechanoreceptors in the limbs play a role in regulating ventilation in children with CCHS.

The pathophysiology associated with hypoventilation from CCHS is not well understood. Multiple studies have evaluated central and peripheral chemoreceptor function in children with CCHS. Patients with CCHS have been shown to have a peripheral chemoreceptor response similar to controls when given rapid challenges of hyperoxic or hypercarbic gas, suggesting that peripheral chemoreceptors are present and functioning in patients with CCHS who can ventilate adequately when awake.¹⁷ However, classic rebreathing responses to longer hypoxic or hypercapnic challenges are abnormal.¹⁸ One study evaluating respiratory-related evoked potentials found disrupted central integration of the afferent signal during wakefulness and reduced responses during non-REM sleep in patients with central hypoventilation syndrome compared with controls.¹⁹ Another study found that, compared with controls, patients with CCHS had no difference in cough threshold when evoked by fog inhalation, but those with CCHS lacked respiratory sensations or increases in ventilation before coughing.²⁰ Functional magnetic resonance imaging has also been used to evaluate central nervous system signal responses in the brains of people with CCHS. Compared with controls, delayed responses have been demonstrated in the medullary

sensory regions, limbic areas, and cerebellar and pontine sensorimotor coordination areas in patients with CCHS during Valsalva.^{21,22} Functional magnetic resonance imaging studies evaluating response to hyperoxia have shown altered responses in the amygdala, which normally regulates respiratory timing, as well as blunted heart rate responses in patients with CCHS compared with controls.²³ This combination of findings underlies the autonomic dysfunction central to CCHS and supports the hypothesis that deficiencies in central integration of chemoreceptor inputs, rather than the receptors themselves, are likely responsible for the autonomic dysfunction and loss of respiratory drive in CCHS.

Sleep Findings

During sleep, infants with CCHS usually have reduced tidal volumes with regular respiration and periods of central apnea. Hypoventilation is present during wakefulness but is more profound during sleep (**Fig. 1**). A study of 9 children breathing spontaneously during sleep found more pronounced hypoventilation during non-REM than REM sleep, although significant hypoventilation was seen in all sleep stages.¹⁹ The cause of this state dependency is unknown, but may be related to a REM-related ventilatory drive not yet well understood. However, ventilatory support is required throughout all sleep stages.

Associated Conditions

A variety of other autonomic nervous system dysregulations has been associated with CCHS, including Hirschsprung disease in about 20% of patients and neural crest tumors, which are usually in individuals with NPARMs.¹² Other symptoms of autonomic dysfunction, including temperature instability, cardiac arrhythmias that may require a pacemaker, reduced pupillary light response, esophageal dysmotility, and abnormal perception of discomfort or anxiety, are also seen.^{12,24}

Diagnostic Evaluation

A diagnosis of CCHS should be considered in any child who has hypoventilation without known dysfunction of the brainstem, neuromuscular weakness, cardiopulmonary, or metabolic cause to explain the finding. A 2-stage blood test is available for the diagnosis of CCHS and should be sent in any case where the diagnosis is considered. The *PHOX2B* Screening Test, which is a gel electrophoresis that evaluates for the polyalanine repeat mutations and the most common NPARMs, is capable of identifying 95% of CCHS cases. If this test is negative and the phenotype supports the diagnosis, the *PHOX2B* Sequencing Test can be performed.¹² Hemoglobin and hematocrit for polycythemia and blood gas with bicarbonate level should be considered to evaluate for respiratory acidosis and metabolic alkalosis as ongoing evaluations. Echocardiogram, electrocardiogram, and brain-type natriuretic peptide levels should be considered annually to evaluate for pulmonary hypertension.

Polysomnography is extremely useful in the evaluation of CCHS. This study should include evaluation of wakefulness, REM, and non-REM sleep to assess the degree of hypoventilation. Ventilatory response testing has been used as a research tool to assess the patient's ventilatory responses to both hypercapnia and hypoxia.

The differential diagnosis is broad and includes primary pulmonary, cardiac, neurologic, or metabolic disease. To evaluate for underlying lung disease, chest imaging with radiography or computed tomography should be considered, as well as pulmonary function testing if possible. Intracranial lesions should be evaluated with magnetic resonance imaging. Inborn errors of metabolism can be evaluated with metabolic testing and potentially muscle biopsy.

Management of CCHS

All patients with CCHS require mechanical ventilation; therapy with oxygen or respiratory stimulants is not adequate. Infants may require continuous ventilation because of an immature respiratory system and circadian rhythm. Many infants will require tracheostomy to achieve adequate ventilation, but older children may be able to be ventilated with noninvasive ventilation (see Management of central hypoventilation syndromes section). CCHS is a lifelong condition and although the ventilatory system will become more stable with age, patients will not develop normal ventilatory responses to hypoxia or hypercarbia. Mortality is highly variable, and the main causes of death are cor pulmonale, pneumonia, and aspiration.¹³ With adequate ventilation and well-coordinated care, however, many patients with CCHS can expect to lead productive lives. There is a growing cohort of patients with CCHS surviving to adulthood and even having children of their own. Genetic counseling is important, especially considering the dominant nature of transmission.

RAPID-ONSET OBESITY WITH HYPOTHALAMIC DYSFUNCTION, HYPOVENTILATION AND AUTONOMIC DYSREGULATION

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD), also known as late-onset central hypoventilation with hypothalamic dysfunction, is a rare disorder presenting in childhood with rapid weight gain, hypothalamic endocrine dysfunction, and severe hypoventilation. Children often present in crisis, such as respiratory failure or cor pulmonale. This condition was first described in 1965²⁵ but has only recently been distinguished from CCHS as a separate condition.^{26,27} Although CCHS typically presents during infancy, the clinical findings associated with ROHHAD begin after 1.5 years of age, with a mean age of approximately 3 years.²⁶ Rapid onset of obesity is typically the first clinical sign in ROHHAD and is striking, often with 15 kg or more of weight gain in a single year (**Fig. 2**). Additional hypothalamic dysfunction may precede or follow weight gain and may include growth hormone deficiency, hyperprolactinemia, central hypothyroidism, disordered water balance, precocious/delayed puberty, thermal dysregulation, or corticotrophin deficiency. Because of these important features, children in whom ROHHAD is being considered should be evaluated and followed by an endocrinologist. Developmental delay and regression as well as behavioral problems are also common. Children with ROHHAD are also at risk for neural crest tumors, including ganglioneuromas and ganglioneuroblastomas.²⁸ Similar to CCHS, ophthalmologic abnormalities may be seen in individuals with ROHHAD.²⁶

In addition to hypothalamic dysfunction, children with ROHHAD develop hypoventilation. The respiratory phenotype of ROHHAD includes an absent or attenuated response to hypercarbia and/or hypoxemia and can be evaluated with hypercapnic ventilatory response testing. In one of the largest series reported, about half of patients with ROHHAD required tracheostomy for positive pressure ventilation.²⁶

Unlike CCHS, mutations of PHOX2B are characteristically lacking from individuals with ROHHAD.²⁹ To date, no candidate genes have been identified as a cause of ROHHAD³⁰ and studies continue to attempt to identify the presumed genetic basis of ROHHAD.

The prognosis of ROHHAD has improved with earlier identification and treatment of the condition. Significant morbidity exists from a progressive neurologic or psychiatric decline in a subset of cases, including seizures, depression, psychosis, hallucinations, and emotional lability. Autonomic nervous system dysregulation can cause severe bradycardia in some patients. The care of individuals is complex and should be multidisciplinary, focus on the

endocrine and ventilatory abnormalities, and include assisted ventilation when hypoventilation occurs.

FAMILIAL DYSAUTONOMIA

Familial dysautonomia (FD) is a rare autosomal-recessive condition primarily affecting the Ashkenazi Jewish population, that was first described in 1949.³¹ FD is caused by mutations in the gene that encodes for I-K-B complex associated protein, affecting the development of primary sensory neurons. As a result, people with FD have severe blood pressure instability, impairment in temperature perception, sense of taste, and ability to swallow, as well as ataxia.³² Individuals with FD are prone to developmental abnormalities, renal disease, and left ventricular hypertrophy, in addition to vomiting attacks from surges in sympathetic activity.^{33,34}

Patients with FD have been shown to have abnormal ventilatory responses to hypoxia and hypercapnia. One study of 22 subjects with FD showed that progressive hypoxia resulted in blunted increases in ventilation and paradoxical decreases in heart rate and blood pressure. Hyperventilation induced prolonged apneas with profound desaturations.³⁵ A study using inductance plethysmography and electrocardiogram at home in 25 children with FD found an increased respiratory frequency and greater daytime respiratory variability in those with FD compared with controls.³⁶ Children with FD have more apnea and desaturation than controls during sleep.³⁷

There is no definitive therapy for FD and treatment is supportive, but early recognition of FD is related to better survival rates.³⁸ Because of swallowing difficulty, chronic lung disease secondary to chronic aspiration is a concern in young children. Gastrostomy tube and/or fundoplication should be considered.³⁹ Because of associated autonomic neuropathy, there are a host of potential surgical complications involving the respiratory, cardiovascular, and renal systems. Perioperatively, adequate pain control is important to prevent crises from sympathetic surges.⁴⁰ Pulmonary causes of death are common, frequently during sleep. Sudden unexplained deaths are reported in nearly a third of cases.³⁸

CHIARI MALFORMATION

In a Chiari type II malformation (CM II), the cerebellar vermis, caudal brain stem, and fourth ventricle herniate through the foramen magnum, obstructing flow of cerebrospinal fluid and causing hydrocephalus. This type of malformation is usually associated with myelomeningocele, where the meninges and spinal cord protrude through open vertebral arches leading to paralysis and significant morbidity and mortality.⁴¹

Individuals with myelomeningocele and CM II have blunted ventilatory response to hypercapnia and hypoxemia, which suggests abnormalities of central chemoreceptors. In a study of 7 infants with myelomeningocele and Chiari malformation, arousal to hypercapnia occurred in only 37.5% of subjects compared with 100% of controls. Arousal to hypoxia was also diminished, with only 18.2% of those with myelomeningocele arousing compared with 89% of controls.⁴² The cause of central hypoventilation in patients with Chiari malformation is thought to be due to dysgenesis of neural structures or damage to the brainstem and cerebellum during the herniation, causing impairment of the respiratory centers.⁴³

Individuals with CM II are also at risk for sleep-disordered breathing. In a population-based study of 73 children, 16% had central hypoventilation, but 41% and 27% had obstructive and central apnea, respectively.⁴⁴ This study also reported several children who had sleep-related hypoxemia not related to apnea or hypoventilation. A recent study of 16 children

with CM II reported a relatively high mean central apnea index of 5.9 ± 7.3 events/h, but this study did not report CO₂ measurements.⁴⁵ Individuals with myelomeningocele have also been shown to have a high rate of restrictive lung disease and many have respiratory muscle weakness.⁴⁶

Children with CM II have variable presentation, with the most severely affected patients presenting in infancy with apnea, bradycardia, and vocal cord paralysis.⁴⁷ Children with meningomyelocele should be evaluated with a polysomnogram that includes CO₂ monitoring. If abnormalities are seen, an evaluation of hydrocephalus should be made. If abnormalities persist despite correction of hydrocephalus, cervical decompression may be considered. However, the abnormalities may be secondary to dysplasia of the brainstem rather than compression and may not resolve after surgery.⁴⁴ Some children with CM II, particularly those with myelomeningocele and without spontaneous ventilation in infancy, will require mechanical ventilation, as there is an increased mortality in this population due to hypoventilation and central apnea.

There is no definitive evidence to suggest that Chiari type I (CM I) malformation is related to hypoventilation, but there are reports of significant sleep-disordered breathing in patients with CM I malformations. One case report documents a young man with a CM I with syringomyelia who presented with obstructive sleep apnea and hypoventilation after acute respiratory failure. The patient underwent posterior fossa decompression and had improvement in arterial P_{co2} during wakefulness from 65 to 45 mm Hg but his severe obstructive sleep apnea did not improve.⁴⁸ There are several reports of children with CM I having significant bradypnea and central apnea.^{49,50} Other reports have identified mixed obstructive and central apneas.^{51,52} Posterior fossa decompression has been successful in some reports, but there is no large series evaluating ventilation during sleep in CM I.

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a condition caused by a deletion of paternally expressed imprinted genes at chromosome 15q11–q13 that results in a phenotype including infantile hypotonia and failure to thrive. As children get older, they develop hyperphagia and obesity as well as developmental delay and behavioral problems.⁵³ Craniofacial features include a narrow nasal bridge and micrognathia.

Patients with PWS have been shown to have an abnormal ventilatory response. Although eucapnic at rest during wakefulness, individuals with PWS have been shown to have a paradoxical response to hyperoxia and no change in minute ventilation in response to hypercapnia.⁵⁴ Obese patients with PWS have a flattened slope of the ventilatory response curve, but both lean and obese people with PWS begin to increase ventilation at a higher P_{co2} than controls.⁵⁵ During sleep, children with PWS have a higher arousal threshold to hypercapnia than control.⁵⁶ In response to hypoxia during sleep, people with PWS are less likely to arouse and have a blunted increase in heart rate and respiratory rate compared with controls.⁵⁷ These findings suggest abnormal function of both peripheral and central chemoreceptors.

Children with PWS are at risk for a variety of sleep disorders, including altered sleep architecture and both central and obstructive sleep apnea.⁵⁸ Obstructive sleep apnea and obstructive hypoventilation may be due to unique features of PWS, including morbid obesity, a small nasopharynx, and hypopharyngeal hypotonia. Young children with PWS may be at risk for developing worsening of sleep-disordered breathing soon after the initiation of growth hormone⁵⁹ and there have been reports of sudden death in this population,^{60,61} so children with PWS should have a polysomnogram to screen for sleep-disordered breathing before starting therapy.⁶² After initiating growth hormone, patients

should be closely monitored for signs of sleep-disordered breathing and repeat polysomnography should be considered.

Achondroplasia

Achondroplasia is an autosomal-dominant condition caused by a mutation in the gene encoding fibroblast growth factor receptor type 3 and affects longitudinal growth and craniofacial, vertebral, and neurologic development. Clinical characteristics include mid face hypoplasia, hypotonia, lumbar spinal stenosis, and characteristic short limbs with short, broad fingers (brachydactyly). There may be contraction of the base of the skull with a small foramen magnum.^{63,64}

Patients with achondroplasia are at risk for a variety of respiratory conditions. One study of 88 children with achondroplasia found that 47% had abnormal polysomnograms, with hypoxemia being the most common finding, which may be related to mild restrictive lung disease due to a relatively small thorax.⁶⁵ A smaller number of patients have obstructive or central apnea, although there is significant variability between studies and prevalence is difficult to estimate.⁶⁶

Disproportion between the size of the skull and its base puts these children at risk for compression of the spinal cord or brainstem at the foramen magnum. This complication of achondroplasia has been implicated in more significant respiratory complications, including sudden death due to apnea in infancy⁶⁷ as well as hypoventilation, which can be severe.^{68,69} Any child with achondroplasia who has hypoventilation or central apnea should have imaging of the brain and spinal cord to evaluate for impingement. If present, cervicomedullary decompression may be required.⁷⁰

Mitochondrial Disorders

Disorders affecting mitochondrial metabolism may also result in central hypoventilation. Leigh syndrome, also known as subacute necrotizing encephalopathy, first described in 1951, is a rare, progressive neurodegenerative disorder marked by functional brainstem decline. This condition is now recognized to be a group of disorders marked by focal, necrotizing lesions. Patients are often normal during infancy but present with psychomotor regression, weakness, hypotonia, intention tremor, and lactic acidosis during the first 2 years of life.⁷¹ Respiratory failure is a frequent feature of Leigh syndrome, which may be attributed to involvement of the brainstem or respiratory muscle weakness as the condition progresses. Although there are reports of patients surviving until adulthood, in most cases, the condition causes death by 5 years of age.⁷¹ There is no causal therapy for Leigh syndrome and the benefits of mechanical ventilation must be weighed against the poor prognosis.

Central hypoventilation has been described in other disorders of mitochondrial metabolism, including pyruvate dehydrogenase deficiency, Kearns-Sayre syndrome, ophthalmoplegia plus, and other inherited mitochondrial myopathies.^{72–75}

Acquired Conditions Causing Central Hypoventilation

In addition to congenital conditions causing central alveolar hypoventilation, damage to respiratory centers in the brain can produce a similar phenotype in previously healthy children. Conditions causing acquired central hypoventilation include brain tumors, central nervous system infections, encephalitis, trauma, and sequelae from neurosurgical procedures.^{76–80} The degree of resultant hypoventilation varies from mild to severe depending on the respiratory centers affected and the degree of damage. Some patients will have intermittent apneic episodes and others will require mechanical ventilation, but most

ventilatory abnormalities will worsen during sleep. Hypoventilation should be considered in patients with tumors affecting respiratory control centers or those who have a history of central nervous system malignancies and respiratory disease.

MANAGEMENT OF CENTRAL HYPOVENTILATION SYNDROMES

Ventilatory Support

Positive pressure ventilation—The goal of treatment for all patients with central hypoventilation syndromes is adequate ventilation and oxygenation during both sleep and wakefulness in a way that maintains a high quality of life and maximizes the child's ability to participate in school and recreational activities (**Fig. 3**). The amount of ventilatory assistance required in central hypoventilation syndromes is highly variable. In CCHS, for example, although infants usually require continuous mechanical ventilation, older children often achieve adequate ventilation during wakefulness as the respiratory system and circadian rhythm mature.

Positive pressure ventilation via tracheostomy is the most efficacious mode to ensure adequate ventilation when continuous ventilation is required. Difficulties with this type of ventilation include the requirement for the continuous presence of trained caregivers and the risk of death due to tracheostomy decannulation, infection, and speech delays.⁸¹ Advantages of this method include the ability to have the patient's face free of a mask and to use a portable, battery-operated ventilator and deliver high pressures if needed.

Noninvasive positive pressure ventilation (NIPPV) allows ventilatory support to be delivered via nasal or face mask, avoids tracheostomy, and is a good option for many children, especially those who require only nocturnal ventilation.⁸² Children requiring very high ventilatory pressures, who cannot tolerate or be properly fitted for a mask (such as young infants), or who require continuous ventilation are not good candidates for NIPPV. As with ventilation delivered via tracheostomy, NIPPV settings should be determined and titrated periodically in the sleep laboratory or an intensive care setting. Because many children with central hypoventilation syndromes will not trigger the ventilator adequately during sleep, a mode that provides bilevel pressure at a set rate with a set inspiratory time is preferred.⁸³

Negative pressure ventilation—Negative pressure ventilation (NPV) generates a negative inspiratory pressure around the chest and abdomen with a dome-shaped bell, causing inspiration. It was developed to treat respiratory failure during the polio epidemic but there are reports of children with central hypoventilation who have been managed with success using NPV.⁸⁴ Children using NPV must remain supine; the units are not portable, and it may be uncomfortable for some people. The use of NPV has been limited by the risk of asynchrony between vocal cord opening and thoracic inspiratory efforts, causing obstructive sleep apnea.⁸⁵ NPV is used infrequently now that noninvasive pressure ventilation is available.

Diaphragmatic pacing—Diaphragmatic pacing involves electrical stimulation of the phrenic nerve via a battery-operated external transmitter, generating breathing using the child's own diaphragm as the respiratory pump.⁸⁶ Bilateral surgical implantation of phrenic nerve electrodes and diaphragm pacer receivers is recommended in children to achieve optimal ventilation. Pacing is typically initiated 4 to 6 weeks after implantation and requires several months to attain full pacing.⁸⁷ These pacers can be used for approximately 12 to 15 hours a day and can offer freedom from a mechanical ventilator during the day. In some cases, older patients may be able to achieve adequate ventilation with the use of a diaphragmatic pacer at night. Complications of diaphragmatic pacers include equipment

failure, infection, and fibrosis or tension of the phrenic nerve.⁸⁸ Obstructive apnea can occur due to lack of synchronous upper airway skeletal muscle contraction with paced inspiration.⁸⁹

Respiratory stimulants—Although there are case reports of respiratory stimulants treating alveolar hypoventilation,⁹⁰ there is no medication that effectively treats central hypoventilation syndromes.

General considerations—Central nervous system depressants such as opiates and benzodiazepines should be avoided when possible. Conditions that cause metabolic alkalosis will decrease respiratory drive and should be aggressively corrected. Increased risk for hypoxia occurs at high altitudes, airplane travel, underwater swimming, and pneumonia, and families should be counseled about the risks of these activities. As children with central hypoventilation are at high risk for respiratory decompensation from respiratory illness, they should get the seasonal influenza vaccine annually. Similar to patients with lung disease, children with central hypoventilation syndromes should avoid exposure to second-hand smoke and be counseled not to smoke themselves. Due to the complexities of these conditions, many children will require psychosocial support.

Anesthesiologists should be aware of the degree of ventilatory requirements for patients with central hypoventilation. Although children with central hypoventilation syndromes can successfully undergo general anesthesia, these children require careful monitoring of gas exchange during and after anesthesia.^{91,92} They may require an increase in baseline ventilatory support following the procedure. Anesthetic drugs with the shortest half-life should be chosen and regional anesthesia should be used when possible.⁹³

Polysomnography is a useful tool in evaluating hypoxemia and hypoventilation during both wakefulness and sleep and ensuring adequate nocturnal oxygenation and ventilation.⁸³ Guidelines for CCHS recommend comprehensive respiratory evaluation, including polysomnogram, at least annually,¹² and a similar approach could be taken for other causes of central hypoventilation.

SUMMARY

Conditions causing central alveolar hypoventilation are uncommon in children, but have a profound impact on the lives of those affected. As research continues to elucidate the underlying mechanisms behind these conditions, the goal will be better identification and treatment of respiratory and nonrespiratory manifestations. Current therapy for central hypoventilation focuses on achieving normal gas exchange, primarily through mechanical ventilation. Early identification of central hypoventilation and initiation of appropriate ventilation strategies can help to improve outcomes associated with chronic hypoxemia. As with all complex pediatric medical conditions, the difficulties of different modes of mechanical ventilation must always be weighed against the child's overall quality of life to determine the most appropriate therapy. Many children, particularly those with CCHS, are able to lead fulfilling lives with appropriate management.

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KEY POINTS

- Ventilation is a complex, tightly regulated process involving voluntary and involuntary responses to changes in pH, oxygenation, and P_{CO_2} .
- Congenital central hypoventilation syndrome is caused by a defect in the *PHOX2B* gene and has distinct phenotypic findings.
- Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation is characterized by rapid weight gain and hypoventilation without any mutation in *PHOX2B*.
- There is significant variability in the degree of hypoventilation across conditions, but hypoventilation is worse during sleep in all conditions.
- Mechanical ventilation is the mainstay of therapy for central alveolar hypoventilation, but a multidisciplinary team is often required to manage these complex conditions.

Fig. 1.

One hundred twenty-second polysomnogram epoch of a mechanically ventilated 20-year-old patient with CCHS, 20/26 genotype. When briefly disconnected from the ventilator, there is a dramatic decrease in airflow and the patient desaturates to 77% and ETCO₂ increases by 10 mm Hg. Y-axis parameters: time axis, clock time (in s) with the epoch number superimposed; C3-A2, O1-A2, C4-A1, and O2-A1 are EEG leads; LOC-A2 and ROC-A1 are left and right electrooculograms, respectively. ABDM, abdominal wall motion; CAP, end-tidal P_{CO2} waveform; CHEST, chest wall motion; CHIN, submental EMG signal; ETCO₂, end-tidal P_{CO2} value; PNEUMOFLOW, airflow measured with a pneumotachograph; PWF, oximeter pulse waveform; SAO₂, arterial oxygen saturation.

Fig. 2. Growth curve of a patient with ROHHAD from birth to 36 months. (*From* Katz ES, McGrath S, Marcus CL. Late-onset central hypoventilation with hypothalamic dysfunction: a distinct clinical syndrome. *Pediatr Pulmonol* 2000;29(1):62–8. Copyright John Wiley & Sons; with permission.)

Fig. 3.

Sixteen-month-old boy with CCHS. Many children with central hypoventilation syndromes, including those dependent on positive pressure ventilation, can lead happy and fulfilling lives. Note that this child has a tracheostomy tube with flexible tube extension for greater mobility when ventilated and heat moisture exchanger to provide humidification when not connected to a ventilator. (*Courtesy of Brianne Elizabeth.*)

Table 1

Summary of central hypoventilation syndromes in childhood

Syndrome	Diagnosis/Unique Clinical Features	Age of Onset	Treatment/Prognosis
CCHS	<i>PHOX2B</i> mutation necessary for diagnosis Associated with Hirschsprung disease, neural crest tumors, arrhythmias	Usually at birth	All will require assisted ventilation; diaphragmatic pacing an option for some with 24-h ventilatory needs Good overall prognosis with adequate care but will require ongoing ventilatory support
ROHHAD	No diagnostic test Associated with rapid weight gain, growth hormone deficiency, developmental delay, behavioral problems	Variable after 1.5 y old; symptoms may appear years apart	All will require ventilation; significant neurologic and psychiatric morbidity in some patients
FD	Caused by mutations in I-K-B complex protein Associated with blood pressure instability, temperature instability, ataxia, dysphagia, renal disease	Symptoms present at birth	Supportive therapy; some will benefit from ventilation, may require feeding tube, renal/cardiac evaluation
Chiari malformation	Diagnosis by magnetic resonance imaging CM II associated with myelomeningocele	Usually at birth; milder cases may present later	Posterior fossa decompression successful in treating central apnea in some patients; some will require ventilation, often noninvasive
PWS	Caused by gene deletion at 15q11–13 Patients present with infantile hypotonia and failure to thrive followed by hyperphagia, morbid obesity, developmental delay, and behavior problems	Usually infancy	High risk for obstructive sleep apnea and other sleep disorders; some will require ventilation, usually noninvasive Monitor closely for sleep-disordered breathing after starting growth hormone; significant psychosocial morbidity
Achondroplasia	Caused by mutation in fibroblast growth factor 3 Associated with short limbs with brachydactyly, hypotonia	Usually infancy	Nocturnal hypoxemia is common If hypoventilation or central apnea present, obtain imaging to evaluate for impingement at foramen magnum Overall good prognosis
Mitochondrial disorders	Group of rare disorders affecting mitochondria metabolism Focal necrotizing lesions seen on brain imaging Associated with progressive psychomotor decline	Usually first few months of life	Some will benefit from ventilatory support No specific therapies Poor prognosis