Congenital central hypoventilation syndrome
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Abstract
Congenital central hypoventilation syndrome is a failure of automatic control of breathing. This rare disease entity should be considered in children with episodic or sustained hypoventilation and without obvious neuromuscular, metabolic, cardiopulmonary or an identifiable brainstem lesion. The disorder is also known to be associated with other manifestations of autonomic nervous system dysregulation and other neurocristopathies. Remarkable progress has been made in the last couple of years in determining the genetic basis of this syndrome and has led to a breakthrough in the diagnosis and also provides clues to the pathophysiology responsible for this disorder. Understanding of the underlying genotype would help to predict disease phenotype and severity. Early diagnosis and treatment to ensure adequate ventilation are important to prevent serious complications caused by periods of hypoxaemia and to facilitate these children to achieve more productive lives. The current article aims at summarizing the updated information regarding the diagnosis and management of the disease.

Keywords:  Autonomic dysfunction, Congenital central hypoventilation syndrome (Ondine's Curse), Diaphragmatic pacing, PHOX2B gene

Introduction
Congenital central hypoventilation syndrome (CCHS) is a rare disorder of the automatic control of breathing. The literary misnomer “Ondine’s curse” has been used in prior literatures and the disease was first described in 1970 by Mellins et al. The hallmark of the disease is alveolar hypoventilation with insensitivity to hypoxaemia and hypercapnia, most pronounced during sleep, but the clinical spectrum of severity can be wide. For many years, the underlying cause for this disease was a mystery and the disease was mostly diagnosed based on exclusion of other causes of central hypoventilation.

A genetic defect for CCHS has been postulated based on reports of familial cases and concordance in monozygotic twins. It was until 2003 that the mutations in the PHOX2B gene on chromosome 4p12 were found to be responsible for this syndrome. This gene is responsible for the expression regulation of a series of target genes involved in the development of autonomic nervous system and also plays a role in neural crest cell migration. This explains why many patients present with symptoms of autonomic dysfunction in addition to symptoms of hypoventilation. With the increasing recognition of mild or late-onset cases in late childhood or even adulthood, it is now clear that CCHS is no longer diagnosed exclusively in the newborn period. The exact incidence is unknown. A prevalence rate of 1 in 200,000 live births has been reported in France in 2005 but this is likely to be under-reported because milder phenotype may have been missed.

With the rapid expansion of new knowledge and concept about this disease, the American Thoracic Society (ATS) has issued an updated statement on the diagnosis and management of congenital CCHS in 2010. This paper has summarised the recent genetic findings regarding to this disease, including the mechanism, inheritance and genotype-phenotype association. It has also discussed on the available treatment and home health care options.

Clinical presentation
The clinical presentation of patients with CCHS depends very much on the severity of the underlying hypoventilation disorder. Some infants do not breathe at birth, or present with intermittent episodes of apnoea...
with cyanosis. They may not have the classically described sleep-wakfulness differences at this age. Many of them would have required assisted ventilation early in the newborn period. Some infants may even present as apparent life threatening events as they develop respiratory arrest upon falling asleep, or some may die and be categorised as having sudden infant death syndrome. If not recognised in the neonatal period, they will present again at a later age with signs of right heart failure and pulmonary hypertension from prolonged periods of hypoxaemia and hypercapnia.

A proportion of the CCHS children who present in the neonatal period may mature and have a pattern of adequate breathing during wakfulness over time; however, apnoea or central hypoventilation persists during sleep. This apparent improvement over the first few months of life is believed to result from normal maturation of the respiratory system (e.g., improved respiratory mechanics, mechanoreceptor and residual chemoreceptor function) and does not represent a true change in the basic deficit in autonomic respiratory control. However, for those with more severe disease, hypoventilation will persist during wakfulness.

Unlike other sleep-related hypoventilation disorders, the hypoventilation in CCHS is classically produced by a pattern of decreased tidal volume and is most severely affected during non-rapid eye movement (non-REM) sleep as it is controlled entirely by the autonomic nervous system whereas there may be increased excitatory inputs to the respiratory system during REM sleep. These CCHS patients also have absent or negligible ventilatory sensitivity to hypercapnia and hypoxaemia during sleep and wakfulness. They lack arousal responses and sensations of dyspnoea to the endogenous challenges of hypercapnia and hypoxaemia, so they do not exhibit signs of respiratory distress when challenged with these stimuli.

In the past decade, there have been increasing reports on the late-onset form of CCHS, which likely represent the mildest form of disease which was not recognised before. They were usually discovered because of an unexpected, profound hypoventilation triggered by intercurrent respiratory infection, or after exposure to sedative/anaesthetic agents. In retrospect, many of these patients had history of ventilatory disturbances in infancy that resolved spontaneously, eg breath holding spells. These late-onset CCHS can present in late childhood, adolescence or even adulthood and the diagnosis can now be confirmed by the PHOX2B genetic testing.

CCHS is also associated with a number of other conditions affecting the autonomic nervous system. They may have abnormalities in heart rate, blood pressure, and pupil diameter control. Some of them exhibit an increased frequency of arrhythmia, primarily sinus bradycardia and transient asystole. The enteric nervous system may also be abnormal owing to defective migration of neural crest cells. Haddad syndrome, in which CCHS occurs concurrently with Hirschsprung’s disease, was first reported in 1978 by Haddad et al. It is estimated that about 16-20% of patients with CCHS have associated Hirschsprung’s disease. In cases of defective neural cell differentiation, neural crest tumours may arise, which are present in about 5% of patients with CCHS. The most common types of neural crest tumours identified are neuroblastosoma, ganglioneuroma, or ganglioneuroblastoma. Neuroblastomas in CCHS typically present before age 2 years, whereas ganglioneuromas are often incidental findings observed at later ages. Other clinical associations include seizures, esophageal dystomility, gastro-oesophageal reflux, recurrent syncope, and lack of circadian temperature variation.

Diagnosis

The clinical diagnosis of CCHS depends on the documentation of hypoventilation during sleep in the absence of primary neuromuscular, lung, cardiac or metabolic disease, or an identifiable brainstem lesion. However, since PHOX2B has been identified to be the disease-defining gene for CCHS, genetic testing has become the crucial investigation. While awaiting for the genetic result, the initial evaluations would include a detailed neurological evaluation that may require a muscle biopsy, chest X-ray, fluoroscopy of the diaphragm, electrocardiogram (ECG), echocardiogram, metabolic screening and magnetic resonance imaging (MRI) of the brain and brainstem.

In view of the central nature of the hypoventilation, multiple attempts have been made over the years to identify structural brain or brainstem abnormalities, but so far no definite gross anatomical lesion accountable for the unique manifestations of this syndrome could be found. Some subtle changes (e.g. restricted regional perfusion of the brain or impaired response to the application of specific ventilatory challenges) have been reported by the newer MRI imaging modalities or other functional MRI techniques. For example, Kumar et al demonstrated damaged or maldeveloped tissue in
limbic, cerebellar, and brainstem regions using MRI T2-relaxometry and diffuse tensor imaging. Macey, Woo and Harper et al demonstrated that CCHS patients had aberrant responses and functional MRI signal changes in multiple brain areas when presented with a variety of ventilatory challenges. However, these results need to be interpreted with caution as they were usually based on small sample size and it was difficult to judge whether these changes were secondary to the previous hypoxaemic events or the restricted perfusion itself be a byproduct of autonomic neural dysfunction resulting in impaired vascular control.

A comprehensive respiratory physiology study should be arranged to document the degree of hypoventilation. This also helps to determine the level of ventilatory support that will be required. It basically includes all aspects of routine polysomnography including electroencephalogram, respiratory effort, oronasal airflow measurements, ECG, oxyhemoglobin saturation and end-tidal or transcutaneous carbon dioxide (CO₂) monitoring. Blood gas parameters can be measured from an indwelling arterial line. Testing should be ideally performed during wakefulness, REM and non-REM sleep. As described earlier, the central hypoventilation is typically worse in non-REM sleep. They can also demonstrate impaired responses to hypercapnia and hypoxaemia in the circulation, but complex ventilatory response testing is usually used in research setting.

**Genetics: mechanism, inheritance and genotype-phenotype association**

A mutation in the PHOX2B gene is now required for the diagnosis of CCHS according to ATS guidelines. The role of PHOX2B gene was initially identified in PHOX2B mutant mice that died in utero with absent autonomic nervous system circuits. The paired-like homeobox PHOX2B gene is located on chromosome band 4p12 which encodes for a transcription factor that consists of 314 amino acids with 2 short and stable polyalanine repeats of 9 and 20 residues, respectively. This transcriptional factor is responsible for regulating expression of genes involved with the development of the autonomic nervous system, such as dopamine-ß-hydroxylase, PHOX2A, and TLX-2. Some studies have shown that increased polyalanine repeat expansion mutation has been associated with decreased transcription of these genes. The exact pathophysiology is still under investigation but preliminary animal and human physiological studies predicted that the defect in CCHS likely lies in central integration of the central and peripheral chemoreceptor signals, whose development and function are controlled by PHOX2B.

Approximately 90% of individuals with the CCHS phenotype will be heterozygous for a polyalanine repeat expansion mutation (PARM) in the second polyalanine repeat sequence in exon 3 of PHOX2B. The normal allele will have 20 alanines (the normal genotype would be referred to as 20/20) and the affected allele will have 24-33 alanines (genotypes 20/24-20/33), with the most common being 25, 26, and 27. The remaining approximately 10% of individuals with CCHS will have a non-polyalanine repeat expansion mutation (NPARM) in the PHOX2B gene, these will be missense, nonsense, or frameshift.

Most individuals with CCHS are heterozygous for a de novo PHOX2B mutation. The inheritance pattern for the remainder is autosomal-dominant, some may have an affected parent and 5%-10% have an asymptomatic parent who has mosaicism for a PHOX2B mutation. Parents of children with a known PHOX2B mutation should be tested for the family-specific mutation to determine their risk for later-onset CCHS or mosaicism. Proper genetic counseling should be offered to the family. For example, affected individual with CCHS has 50% chance of transmitting the mutation, hence the disease phenotype, to each offspring. If an unaffected parent is found to be mosaic for a PHOX2B mutation, there will be up to a 50% chance of recurrence in any subsequent child.

The specific manner in which the PHOX2B gene mutates also predicts the severity and form of the disease. Studies have shown a correlation between the number of expansion and the need for continuous ventilatory support. In general, individuals with 25-polyl alanine repeat expansion mutation rarely require 24-hour ventilatory support, those with 26-poly alanine repeat expansion mutation have a variable need for ventilatory support during the awake time periods based on their activity levels, and those with 27-33-poly alanine repeat expansion mutations require 24-hour ventilatory support. Individuals with NP ARM also tend to require 24-hour ventilatory support. Mild- and late-onset CCHS has been associated with 24-poly alanine and 25-poly alanine repeat expansion mutations. A subset of CCHS patients, especially for those with NP ARM type mutations, apart from associated with severe forms of CCHS, they often have extensive Hirschsprung’s disease and are at very high risk for developing malignant neural crest derived tumours, such as neuroblastoma.
seems to have relationship with the type of mutation. For example, it was found that the R-R intervals on ECG were prolonged in 83% of CCHS patients with 27-polyalanine repeats, 19% with 26-repeats but none of those with 25-repeats. Furthermore, 67% of those with 27-repeats, 25% with 26-repeats, and none with 25-repeats required a cardiac pacemaker for prolonged R-R intervals, and two of three with sinus pause >3 seconds died suddenly. Improved understanding of the molecular basis of the PHOX2B mutations and this genotype-phenotype relationship will allow physicians to anticipate the clinical phenotype for each affected individual.

PHOX2B mutations can now be detected by two methods: Targeted mutation analysis and Sequence analysis. The former, also referred to as the "PHOX2B screening test", amplifies the region encoding the polyalanine repeat and determines the polyalanine repeat length. Because more than 90% of individuals with CCHS have a PHOX2B polyalanine expansion mutation and because this PHOX2B polyalanine expansion testing is a more sensitive test for detection of mosaicism, such testing should be performed first. Only if a PHOX2B polyalanine expansion mutation is not found in an individual with the CCHS phenotype should sequencing of the entire coding region and intron-exon boundaries of the PHOX2B gene be performed that detects a subset of NPARMs.

Screening and monitoring

Patients with CCHS need at least annual, or more frequently in young infants or children who are symptomatic, polysomnographic monitoring to assess adequacy of ventilator support and to guide titration. The severity or chronicity of the central hypoventilation may also be assessed by screening the patient for polycythemia (hemoglobin and hematocrit levels) and chronic respiratory acidosis and metabolic alkalosis (bicarbonate levels). Echocardiogram and ECG will determine if there is any evidence of pulmonary hypertension or cor pulmonale as a result of chronic hypoxaemia. Neurocognitive testing should be performed if there is evidence of developmental delay or learning disability.

They should also be screened for evidence of other autonomic dysfunction. Barium enema or rectal biopsy should be performed for patients with constipation or abdominal distension to rule out Hirschsprung's disease. Holter monitoring (72-hour) should be performed if there is clinical suspicion of cardiac arrhythmias, including bradycardias that may necessitate pacemaker insertion. Chest and abdominal imaging should be requested early if there is any possibility of a neural crest tumour, particularly in patients with the corresponding mutations. A comprehensive ophthalmologic examination will identify any eye involvement and allow for early intervention to avoid interference with learning. The ATS guideline has also suggested clinical evaluations based on the type of PHOX2B mutation.

Management

The goal of treatment for CCHS is to ensure adequate oxygenation and ventilation during both wakefulness and sleep. This will improve long-term prognosis by reducing the risks of cor pulmonale and neurological insult from chronic hypoxaemia. Respiratory stimulants are ineffective in CCHS. Supplemental oxygen alone is not sufficient treatment for hypoventilation and will not prevent pulmonary hypertension. They must rely on assisted ventilation. Though some CCHS children may gradually develop the ability to breathe adequately during wakefulness, they still suffer from hyperventilation during sleep with impaired ventilatory responses to hypoxaemia and hypercarbia. Hence, weaning these patients off mechanical ventilation totally is not a realistic goal.

Positive pressure ventilation (PPV) via tracheostomy is the commonest mode of ventilation used, particularly in infants and younger children, as this is the safest form of ventilation to ensure adequate ventilation and oxygenation during the first few years of life while the respiratory and central nervous systems are maturing. Currently available home positive pressure ventilators are portable and can be battery operated, thus facilitate the transition to home care. Uncuffed tracheostomy tubes are typically used to permit a leak large enough to use a Passey-Muir valve to facilitate subsequent speech development of the child.

For those CCHS patients who only require ventilatory support during sleep can be considered potential candidates for bi-level non-invasive ventilation (NIV). This type of ventilation is best started after 5-6 years of age, when the clinical course of CCHS is usually more stable. They would need well-fitting mask/prongs for successful delivery of the ventilation. Bi-level ventilation should not be used for 24 hour a day because the mask interferes with daily activities and social interaction and may cause some mid-face hypoplasia. As with PPV,
NIV settings should be determined and titrated periodically in the sleep laboratory. Patients with CCHS are unlikely to trigger the ventilator adequately during sleep so the ventilator mode should provide a set rate with a set inspiratory time. For some CCHS patients, successful transition from PPV to NIV may allow for tracheostomy decannulation.

For children requiring full-time ventilatory support, newer technology such as the phrenic nerve (diaphragmatic) pacing can be an alternative choice to consider.\(^{39,40}\) Pacing during the day and positive pressure ventilation by mask or tracheostomy at night allows more daytime mobility for active children who require ventilation 24 hours per day. This mode of ventilation involves electrical stimulation of the phrenic nerve that results in diaphragmatic contraction, hence generates breathing using the child's own diaphragm as the respiratory pump. In children, simultaneous bilateral diaphragmatic pacing is generally required to achieve optimal ventilation. Bilateral receivers are then implanted subcutaneously that transmit radio-frequency signals from an external pulse generator to the phrenic nerve electrodes. Pacing is typically initiated 4-6 weeks after surgical implantation to allow tissue reaction around the electrodes to stabilise. Training of the muscle fibers is necessary to sustain pacing for the required 12-16 hours per day, and a period of 3-4 months is usually required to attain full pacing. This sounds an attractive option but patients must have access to the teams with the necessary expertise in maintaining them. Potential complications of pacing include equipment failure, infection and late injury due to fibrosis or tension on the phrenic nerve. In some cases, pacing at night may also permit tracheal decannulation in older patients who only require ventilatory support while asleep. However, in some decannulated patients, obstructive sleep apnoea occurs because vocal fold opening does not occur with a paced inspiration.

For each of the options listed above, their advantages and disadvantages should be discussed thoroughly with the family. The mode of ventilatory support depends very much on the age of the patients and the clinical severity of the hypoventilation. Regular follow up is required with polysomnographic studies to determine that the ventilation remains sufficient. Families should also understand that, even for those older children who have been decannulated from tracheostomy using a combination of NIV and/or diaphragm pacing, they may still need interim endotracheal intubation if respiratory failure develops with intercurrent illnesses. These children must be managed with extreme vigilance due to their lack of objective or subjective responsivity to hypoxaemia and hypercapnia. These limitations emphasise the importance of objective pulse oximetry and preferably end-tidal PCO\(_2\) monitoring, as well as highly skilled and consistent caretakers in the home. A reasonable range is to keep CO\(_2\) around 30 to 40 mmHg and oxygen saturation of 95% or higher. Maintaining low-normal CO\(_2\) level ensures that these patients have some ventilatory reserve when being challenged during their daily activities eg exercise. Apart from being managed by an experienced team, adequate community support should be provided to the family. Caregivers should also be properly trained to manage tracheostomies and ventilators. By providing the most optimal technology that tailors for the child’s needs, it can improve quality of life and also improve long-term prognosis by reducing the risks of sequelae from chronic hypoxaemia. Management of patients with combined neurocristopathies and autonomic complications will be even more complex and require inputs from multiple health care disciplines.

Prognosis

No known cure for CCHS exists and the disorder is life-long. Mortality rates of 8% to 38% have been documented in various CCHS patient cohorts.\(^{6,41,42}\) The main causes of death include cor pulmonale, pneumonia and aspiration. It is usually during the first few years of life that the medical course for CCHS patients being most unstable. With the advent of home mechanical ventilation, the first generation of children with CCHS is now surviving to adulthood. Inadequate management of hypoventilation and chronic hypoxaemia, however, may lead to long-term neurological sequelae and cognitive disabilities.\(^{43}\) Previous studies have demonstrated that many patients with CCHS have learning disabilities but most are in mainstream schools. Some studies showed CCHS patients were associated with an increased risk of adverse neurocognitive outcome, with visuoperceptual reasoning and clerical/visuographic speed appeared particularly vulnerable.\(^{44}\) However, most children with CCHS will have a good quality of life if diagnosed early and managed rigorously.

Prognosis is likely to be further improved by ongoing developments and upgrades in home ventilation and monitoring equipments.

Conclusion

The knowledge on the presentation, pathogenesis and
management of this rare disease continues to evolve. A high index of suspicion is needed in view of the wide spectrum of clinical severity and manifestations. Increased awareness of this unusual clinical entity and a comprehensive evaluation of every patient are critical for early diagnosis and appropriate intervention so as to ensure prompt initiation of respiratory support and prevent complications or late sequelae. As with other rare diseases, further research is needed to allow a better understanding of the phenotypic and genotypic heterogeneities associated with this disorder and to find the best management strategy.

References


