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REVIEW

# The genetics of congenital central hypoventilation syndrome: clinical implications



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**Abstract:** Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder of the autonomic nervous system (ANS) and respiratory control. This disorder, formerly referred to as Ondine's curse, is due to a mutation in the *PHOX2B* gene that affects the development of the neural crest cells. CCHS has an autosomal dominant pattern of inheritance. Majority of the patients have a polyalanine repeat mutation (PARM) of the *PHOX2B*, while a small group has non-PARM (NPARM). Knowledge of the patient's *PHOX2B* gene mutation helps predict a patient's clinical presentation and outcome and aids in anticipatory management of the respiratory and ANS dysfunction.

**Keywords:** diaphragm pacing, noninvasive positive pressure ventilation, genetic counseling, genetic testing, CCHS, PHOX2B, congenital central hypoventilation syndrome

## Introduction

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder of the autonomic nervous system (ANS) and respiratory control due to a mutation in the paired-like homeobox 2B (PHOX2B) gene found on chromosome 4.[1] CCHS patients usually present in the newborn period with apnea, hypoxemia, and hypoventilation that are most severe during sleep, particularly during nonrapid eye movement (NREM) sleep.[1–5] Over 1,000 cases have been reported worldwide and are expected to be higher due to the availability of genetic testing. The estimated incidence is one in 150,000–200,000 live births in France and Japan.[6,7] In 2003, the *PHOX2B* gene was identified as the disease-defining gene for CCHS and has prompted clinical genetic testing, making the diagnosis exact and early treatment feasible.[8,9] In this review, we discuss the clinical presentation, genetics of CCHS, and how the genotype affects the presentation, management, and outcome of CCHS patients.

## Clinical presentation

Most CCHS patients present in the neonatal period with apnea or hypercapnia requiring assisted ventilation.[1,5,6,10] Typically, these newborns will present with central apneas and cyanosis resulting in the need for assisted ventilation either invasively or noninvasively.[1,4–7] The hypoventilation is significantly worse during sleep, particularly during quiet, NREM sleep where breathing is critically dependent on the metabolic/automatic control of breathing.[2,3] However, hypoventilation may persist during active, rapid eye movement sleep and into wakefulness, albeit usually to a milder degree.[1–3] These infants do not increase their respiratory rate or tidal breathing and do not mani-

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fest respiratory distress, despite significant hypercapnia and hypoxemia. Once placed on ventilatory support, they fail to be weaned off assisted ventilation. As they mature, some infants may develop a normal pattern of adequate breathing while awake, allowing them to be off assisted ventilation for periods of time during wakefulness.[1,2,4,6,11–14]

Children and adults may present with unexplained apneas, significant hypoventilation without significant changes in their breathing pattern, or respiratory failure following either respiratory infection[15–18] or after undergoing sedation/anesthesia.[19–22] They have inadequate ventilatory responses to both hypercapnia and hypoxemia[23] and do not experience discomfort or dyspnea in response to either hypercapnia or hypoxia.[24] Therefore, they do not exhibit signs of respiratory distress in spite of significant hypoventilation. Furthermore, it is not unusual for some patients to report unusual ability to voluntarily hold their breaths for long periods as well as extraordinary capabilities for underwater swimming.[21] Some may present with seizures due to undetected hypoxemia and/or hypercapnia.[21,22,25] In light of unrecognized chronic respiratory failure, some patients may present with associated polycythemia.[21,26,27] Others may exhibit diaphoresis, edema, and signs of right heart failure leading to a mistaken diagnosis of congenital heart disease. In older children and adults, pulmonary hypertension and cor pulmonale are the results from unrecognized and untreated hypoxemia and hypoventilation and may be the presenting signs.[17,21,28,29]

CCHS is not just a disorder of respiratory control. Affected patients may have associated conditions due to ANS dysfunction including tumors of neural crest origin (neuroblastoma, ganglioneuroma, and ganglioneuroblastoma)[6,30–32] gastrointestinal manifestations such as esophageal dysmotility,[14,33] constipation,[14] aganglionic megacolon Hirschsprung's disease (HSCR),[1,6,14,34] and other signs and symptoms attributed to abnormal development of neural crest cells such as cardiovascular,[25,35–39] ophthalmologic,[14,40–43] endocrinologic,[44–48] and temperature regulation abnormalities.[49] CCHS patients may have dizziness and syncopal episodes due to cardiac rhythm or blood pressure control abnormalities. Hyperinsulinism and hypoglycemia may also predispose to seizures.[48] A summary of clinical manifestations of CCHS are listed in Table 1.[1,50]

**Table 1** Clinical manifestations of CCHS

| Organ System | Clinical manifestations |
|---|---|
| Ophthalmologic | Decreased/absent pupillary light response |
| | Anisocoria |
| | Strabismus |
| | Lack of convergent gaze |
| | Marcus Gunn jaw winking |
| Respiratory | Alveolar hypoventilation |
| | Absent perception of dyspnea |
| Cardiovascular | Bradycardia |
| | Prolonged sinus pauses (>3 seconds) |
| | Transient asystole |
| | Decreased heart rate variability |
| | Low normal daytime blood pressure |
| | Orthostatic hypotension |
| | Nondipping blood pressure circadian pattern |
| | Decreased BP response to exercise |
| | Syncope |
| GI | Hirschsprung's disease (20%) |
| | Constipation |
| | Esophageal dysmotility |
| Endocrine | Hyperinsulinism |
| | Hypoglycemia |
| | Hyperglycemia |
| Neuro | Decreased anxiety |
| | Decreased pain perception |
| | Seizures |
| | Neurocognitive deficits |
| Skin | Sporadic profuse sweating |
| Tumors | Neuroblastoma |
| | Ganglioneuroma |
| | Ganglioneuroblastoma |
| Others | Decreased baseline body temperature |
| | Poor heat tolerance |

**Abbreviations:** CCHS, congenital central hypoventilation syndrome; BP, blood pressure; GI, gastrointestinal.

## *PHOX2B* gene mutation

CCHS is caused by a defect in the *PHOX2B* gene that is located in chromosome 4p12.[1,8,9] *PHOX2B* is a protein comprised 314 amino acids with two short and stable polyalanine repeats of 9 and 20 residues in the C terminus. It encodes a highly conserved homeodomain transcription factor that is essential in the development of the respiratory control neurons and ANS.[51,52] Majority (90%) of CCHS patients are heterozygous for an in-frame triplet duplication within the sequence stretch coding for 20 alanine amino acids in exon 3, resulting in polyalanine repeat mutations (PARMs) having an additional 4–13 alanine residues. Thus, the normal 20-alanine tract is expanded to 24–33 alanine repeats, with resultant genotypes of 20/24–20/33 PARMs.[1] The normal *PHOX2B* gene has 20 alanine repeats (20/20 genotype). The most common genotypes in CCHS are 20/25, 20/26, and 20/27 PARMs.[1] Ten percent of CCHS patients are heterozygous for non-PARMs (NPARMs) in exon 1, 2, or 3. These mutations include missense, nonsense, frame shift, and stop codon mutations. Most of the NPARMs are located in exon 2 and exon 3.[1] The *PHOX2B* exon or whole gene deletion accounts for <1% of cases and is associated with variable phenotypes.[31]

## *PHOX2B* and respiratory control

A series of physiologic studies suggest that the abnormality in CCHS is located in the area of the brainstem involved in the integration of both central and peripheral chemoreceptor inputs. The central chemoreceptors are found in the midline raphe, retrotrapezoid nucleus (RTN), ventrolateral quadrant of the medulla, nucleus tractus solitarius (NTS), and the locus ceruleus (LC). The central chemoreceptors sense changes in pH and $P_{CO_2}$. The peripheral chemoreceptors are located in the aortic and carotid bodies and sense changes in Po2, as well as to a lesser degree pH and $P_{CO_2}$. The chemoreceptors send inputs to the ventilatory controllers (central pattern generator) in the pons and medulla that then relay commands to the ventilatory muscles to perform breathing. Paton et al[23] showed that children with CCHS have absent ventilatory responses to both hypercapnia and hypoxia even while awake, suggesting abnormal central and peripheral chemoreceptor function or abnormality in the brainstem integration of chemoreceptor inputs. Marcus et al[53] tested the hypoxic and hypercapnic arousal responses of CCHS children and showed that under very controlled conditions, most CCHS patients have arousal responses, although blunted, to hypercapnia, thus demonstrating intact central chemoreceptor input. Gozal et al[54] then tested the ventilatory responses to acute hypoxia, hyperoxia, and hypercapnia in CCHS children who were able to sustain adequate ventilation during wakefulness and found that CCHS patients have ventilatory depression with hyperoxia while awake, thus showing that peripheral chemoreceptor function was also present and intact. Taken together, these studies point to a primary physiologic abnormality in the integration of chemoreceptor inputs rather than abnormalities in the chemoreceptors themselves.

*PHOX2B* is present throughout the peripheral and central nervous systems. *PHOX2B* is expressed by a chain of neurons involved in cardiovascular, respiratory, and digestive control and persists in most brainstem structures after birth including the hypercapnia-sensitive neurons of the RTN and the neurons of the nucleus of the solitary tract that mediate peripheral chemoreceptor function.[51,52,55–57] Studies support the key role of brainstem RTN in the control of breathing. RTN neurons are thought to function as central chemoreceptors regulating alveolar ventilation as well as site of integration of excitatory inputs from the peripheral chemoreceptors, raphe, and hypothalamus as well as from neighboring astrocytes that modulate respiratory drive.[58,59] In mice, *phox2b* function is fundamental to the development of the RTN.[60] Mice with *phox2b* mutation causing the severe form of CCHS are born without RTN neurons and die at birth from respiratory failure.[61] These mouse models of CCHS with *phox2b* mutations indicate how the lack of *PHOX2B* expression and RTN neuron agenesis are vital in the control of breathing and autonomic regulation.[58] Although an RTN-like structure has been identified in humans, there is currently no evidence that this is lacking in CCHS patients.[62]

*Phox2b* is required in the differentiation of all noradrenergic centers in the brain, including the LC.[63] The LC fails to form in homozygous phox2b-deficient mice.[63] Nobuta et al[64] found neuronal losses within the LC in two lethal neonatal postmortem cases with a confirmed *PHOX2B* PARM or NPARM mutation. Mouse models also showed failure of the LC development and perinatal respiratory lethality, indicating that LC neuronal development is hindered with early onset mutant PHOX2B expression in CCHS.[64] Phox2B is likewise expressed in the NTS that conveys excitatory input from the carotid bodies (whose development are also controlled by phox2b) to the RTN.[55,57,58] Tomycz et al[65] reported novel brain findings in a full term infant with Haddad syndrome who died at 27 days of life with hypoplasia of the LC, delayed maturation of the arcuate nucleus (a putative homolog of the ventral medullary neurons in animals), and aberrant fascicles in the NTS. These abnormalities suggest that CCHS occurs in a network of sites critical to chemoreception.[65] Using functional MRI, Ogren et al[66] found muted and time-lagged responses to Valsalva maneuver in CCHS patients compared to controls, suggesting that the autonomic disturbances in CCHS most likely result from an impaired network of brain structures mediating sympathetic and parasympathetic control and not just alterations to isolated brainstem nuclei.

### Diagnosis and evaluation

All patients suspected of CCHS must be confirmed with the *PHOX2B* gene mutation analyses.[1] There are three PHOX2B testing methods currently available in establishing the diagnosis: 1) PHOX2B targeted mutation analysis (PHOX2B screening test; fragment length analysis),[1,67] 2) PHOX2B sequencing test,[1,67] and 3) deletion/duplication analysis.[31] PHOX2B-targeted mutation analysis involves PCR amplification of the 20 repeat polyalanine expansion region of exon 3 and determines the polyalanine repeat length. It identifies all PARMS and most NPARMs (large deletions and some out of frame deletions or duplications). These tests identify pathogenic variants in ~95% of individuals with CCHS. The PHOX2B-targeted mutation analysis has a very low limit of detection of mosaicism (1%).[68] Thus, it is considered the most appropriate test in the identification of low level mosaicism for both PARM and NPARM,[1,67–69] in seemingly asymptomatic

and mildly symptomatic individuals. The PHOX2B sequencing test identifies all PARMs and all known NPARMs. However, PHOX2B sequencing test has a limit of detection of 20%[68] and, thus, may not detect low-level mosaicism.[68,69] *PHOX2B* deletion/duplication testing identifies deletions of exon 3 or of the whole *PHOX2B* with other nearby genes; variants could be missed in the screening or sequencing tests.[31,67] Testing methods may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification, and chromosomal microarray that includes this gene/chromosome.[67] Deletion/duplication analysis may identify <1% of patients with CCHS.[31,67] When clinical suspicion is high, a combination of the screening, sequencing test, and deletion/duplication analysis may be required in cases in which one test fails to identify the disease-causing mutation.[67] Regardless of the method of testing used, patient and parents should undergo genetic counseling. While awaiting the *PHOX2B* gene testing results, an evaluation to rule out primary pulmonary, cardiac, neurologic, neuromuscular, and metabolic causes of hypoventilation may be undertaken. Suggested tests are listed in Table 2.[1]

Once a diagnosis is established, CCHS patients with symptoms or those at risk (depending on genotype) should be screened for associated autonomic dysfunction.[1] Tests to consider include 1) barium enema or rectal biopsy to assess HSCR, 2) cardiac rhythm monitoring to evaluate arrhythmias, and 3) chest and abdominal imaging to assess neural crest tumors.[1] Traditionally, 72-hour Holter monitoring has been used in the assessment of cardiac rhythm disturbances, but recent advent of the Zio patch monitoring that allows longer evaluation[70,71] has been used at our center. Patients should be referred for comprehensive ophthalmology evaluation to identify abnormalities and provide intervention to prevent learning interference.[1,11,12] CCHS patients have been found to demonstrate developmental delay and neurocognitive deficits as early as preschool age indicating need for neurocognitive evaluation.[14,72–76]

**Table 2** Suggested tests to assess other causes of hypoventilation

| Systems | Test |
|---|---|
| Respiratory | Chest X-ray |
| | CT chest |
| | Pulmonary function test |
| | Fluoroscopy or ultrasound of the diaphragm |
| Cardiologic | Echocardiogram |
| | EKG |
| Neurologic | Brain MRI |
| Inborn errors of metabolism/ mitochondrial disease | Metabolic screening |
| | Muscle biopsy |

**Abbreviations:** CT, computed tomography; EKG, Electrocardiography.

### Genotype–phenotype relationship

The *PHOX2B* gene mutation not only confirms the diagnosis of CCHS but also aids in predicting the respiratory compromise and associated ANS dysfunction.

### Alveolar hypoventilation

Alveolar hypoventilation is the hallmark of CCHS. The severity of respiratory failure and the need for ventilatory support can be anticipated by a patient's genotype.[1] In general, those with shorter PARMS (20/24–20/25) have more subtle symptoms and later onset with some surviving to adulthood without the need for ventilatory assistance.[21] They usually require assisted ventilation only during sleep. Some are asymptomatic until there is an associated triggering event (ie, exposure to respiratory illness, sedation, or anesthesia) that puts them in respiratory compromise. These clinical presentations indicate incomplete penetrance and variable expressivity for 20/24 and 20/25 PARMs. In these short-sized PARMs, the cellular defects are found to be relatively milder and may not always reach the threshold for clinical disease (presymptomatic) or may have a mild phenotypic consequence.[21] However, the presence of genetic modifiers or environmental cofactors acting in conjunction with *PHOX2B* impairment may allow the symptoms to manifest.[21,22]

CCHS patients with larger PARMs typically present in the newborn period. Those with 20/26 PARMs generally require ventilatory support during sleep and possibly during wakefulness depending on activity. CCHS patients with 20/27–20/33 PARMs are typically symptomatic at birth and require full-time ventilatory support.[1] With maturation of the respiratory system, some of these patients have been able to breathe adequately off the ventilator while awake and require ventilatory support only during sleep.[77] This improvement indicates normal maturation of the respiratory system and not a change in the basic disorder. Larger PARMs are generally not associated with variable penetrance or adult onset presentations since increasing the PARMs has been found to have more severe cellular impairments.[78–82]

NPARM *PHOX2B* genotype is also generally associated with more severe phenotype with patients typically requiring full-time ventilatory support.[1] However, NPARM mutations have variable expressivity and incomplete penetrance.[13,83,84] Some patients have been shown to present with

central apneas without hypoventilation,[85] mild hypoxemia,[85] or need for assisted ventilation only during sleep[13,84] while others are asymptomatic and are identified only by genetic testing through an affected family member.[13,83,85] Cain et al[84] described two patients with nonsense pathogenic variant in exon 1 of the PHOX2B producing an N terminally truncated protein presenting with milder phenotype (need for ventilatory support only during sleep and without HSCR or peripheral neuroblastic tumors). Lombardo et al reported a family with novel heterozygous mutation, c.234C>G, and variable phenotype. Two siblings had sleep hypoxemia, anisocoria, HSCR, and characteristic facial features (one sibling did also have a congenital heart disease), while their mother had sleep apnea, anisocoria, and a congenital heart disease but without HSCR or malignancy.[85] In 2017, Kasi et al[13] reported a three-generation family with four individuals possessing a novel *PHOX2B* NPARM (c.245C>T) with variable phenotypes. Two of the family members were ventilator dependent only during sleep, with one of them requiring a cardiac pacemaker. One of the adult family members was noted to have elevated $HCO_3$ on routine blood testing and reports the history of extraordinary ability to hold her breath as a child. The other adult family member was asymptomatic. This report confirms previously reported variable expression of NPARM even within families.[9] More recently, Di Lascio et al conducted a comprehensive review of all the frame shift mutations in CCHS reported in the literature and in their own cohort. They found that all the patients with frame 3 mutations (resulting from the insertion of two or more triplets + two nucleotides and the deletion of one or more triplets + one nucleotide) were present with isolated CCHS. In contrast, frame 2 mutations (resulting from the insertion of one or more triplets + one nucleotide and the deletion of two or more triplets + two nucleotides) were seen in the majority of syndromic CCHS.[86]

### Autonomic dysfunction

ANS dysfunction has also been found to correlate with *PHOX2B* gene mutations.

## HSCR

HSCR is reported to occur in about 20% of CCHS patients. It is most prevalent in patients with NPARM mutations[1,87] and, to a lesser degree, patients with PARM 20/27. However, there is a report of patients with PARM 20/24 genotype with severe CCHS phenotype and HSCR.[88] HSCR typically presents in the neonatal period. Males and females are equally affected and most frequently with the long colonic segment involvement.[6] Di Lascio et al[86] also found that all the syndromic phenotypes associated with frame 3 mutations included HSCR; syndromic CCHS was more frequently accompanied by HSCR than by neuroblastoma.

## Sinus pauses

CCHS children with 20/27 PARM and, to a lesser extent, 20/26 PARM, are at risk for life-threatening sinus pauses of >3 seconds requiring cardiac pacemaker placement.[1,37] In one series, children with *PHOX2B* 20/25 PARM did not manifest sinus pauses of >3 seconds.[37] However, there is a report of a 22-year-old adult with *PHOX2B* 20/25 PARM with sinus pauses of up to 8.4 seconds during wakefulness occurring during a minor respiratory tract infection.[21] We also recently reported a patient with NPARM who at 21 years developed bradycardia during sleep, in addition to palpitations and dizziness with exercise.[13] Bradycardia and sinus pauses were documented on Holter monitoring, and the patient subsequently had cardiac pacemaker implantation.[13] These findings indicate that CCHS patients with 20/25 PARM and NPARMs require monitoring for arrhythmias as they become older.

### Tumors of neural crest origin

The overall risk of developing tumors of neural crest origin is <2%, with the risk higher in those with NPARMs and longer PARM (20/28–20/33) genotypes.[1,86,87,89] In one series, neuroblastoma was found more in those with frame shift and missense PHOX2B mutations, suggesting that both mutations may predispose to neuroblastoma, as opposed to PARM.[32] Furthermore, those with frame 2 mutations may be at increased predisposition to develop neuroblastoma tumors of sympathetic nervous system.[86]

## Ophthalmologic

Patwari et al[42] demonstrated that pupillary abnormalities were more frequent in patients with 20/26 and 20/27 PARMs than those with 20/25 PARM. A recent study revealed the presence of strabismus, pupillary, and iris abnormalities in CCHS adults.[43] In this cohort, the prevalence of pupillary and iris abnormalities was less compared to children, indicating their potential role as systemic disease severity marker.[43]

### Neurocognitive

Sub-optimal school performance and/or neurodevelopmental impairment have been reported in CCHS patients,[72–76] and these deficits have recently been reported to appear as early as preschool age and school age.[72,73] In a recent study, Bayley scores were essentially normal in patients with 20/25 PARM and lower in the other PARM groups.[73] Furthermore, the

study revealed that CCHS phenotype severity as indicated by cyanotic breath holding spells, need for 24-hour ventilator dependence, prolonged sinus pauses and seizures was associated with the severity of the neurocognitive delay.[73]

### Management

The goal of treatment is to ensure adequate ventilation at all times, both while awake and during sleep to prevent morbidities secondary to untreated hypoxemia or hypercapnia and anticipatory management of associated autonomic dysfunction.[1,4,11,12] At our center, we recommend maintaining $PetCO_2$ ~35 mmHg and $SpO_2$ ≥95%.[11,12] It is essential to recognize that oxygen alone relieves the hypoxemia and cyanosis but would not address hypoventilation. For those who are asymptomatic, it is important to remember that they are at risk for respiratory decompensation with stress, infections, or when undergoing procedures requiring sedation or anesthesia. CCHS patients lack the perception of dyspnea and do not manifest respiratory distress; thus, oxygen saturation monitoring with pulse oximetry should be a part of their monitoring, even though they appear nondistressed. Similarly, $CO_2$ should be monitored (end tidal or transcutaneous), because these patients do not increase their minute ventilation even with significant hypercapnia.[1,11,12]

### Modes of ventilatory support

Since CCHS patients generally have minimal lung disease, different modalities are available for ventilatory support. These include 1) positive pressure ventilation via tracheostomy,[1,11,12,90] 2) noninvasive positive pressure ventilation (NPPV),[11,12,91–96] and 3) diaphragm pacing (DP).[1,11,12,77,97,98] Negative pressure ventilation[99] had been used in the past, but these ventilators are not easily portable, thus limiting its current use. At our center, patients' previously utilizing this technique has been transitioned to NPPV. There is no consensus on the choice of ventilatory support. However, it is crucial for the mode of ventilation to be individualized to meet patient's needs, goals of treatment, and quality of life. At our center, we perform annual overnight polysomnographies to adjust ventilator settings, regardless of mode, to achieve target $PetCO_2$ ~35 mmHg and $SpO_2$ ≥95%. In our experience, patients ventilated to meet these targets have more reserve for acute respiratory infections or changes in pulmonary mechanics and are less likely to develop pulmonary hypertension.[4,11,12]

## Portable positive pressure ventilator via tracheostomy

This is the most common form of ventilatory support in CCHS patients.[1,6,14,90] It is particularly recommended in infants and younger children for several reasons. CCHS infants and younger children have longer sleep periods therefore require more hours of being on ventilatory support per day. In this age group, the components of the respiratory system are still unstable, thus minor respiratory infections may result in significant respiratory depression with complete apneas during both sleep and wakefulness. To achieve the target $SpO_2$ and $PetCO_2$, we recommend the pressure control/assist control mode. We also prefer a relatively smaller uncuffed tracheostomy tube to allow a leak to facilitate speaking and prevent pressure on the airway and development of tracheomalacia.[4,11,12]

## Noninvasive positive pressure ventilation

CCHS patients can be ventilated by noninvasive positive pressure ventilation via mask (nasal or face) or nasal prongs using bilevel positive airway pressure[1,91–93] or average volume assured pressure support ventilation mode.[94,96] Continuous positive airway pressure (CPAP) should not be used in CCHS patients as they do not spontaneously increase their breathing frequency in response to hypercapnia or hypoxemia. Ideal candidates for NPPV are stable older children who require ventilatory support only during sleep.[1,12] Although there are reports of younger children ventilated solely noninvasively,[93,95,100] the American Thoracic Society recommends noninvasive ventilation in older stable patients.[1] Because CCHS patients do not increase their respiratory rate or tidal breaths with hypoxemia or hypercapnia, only spontaneous/timed or timed mode with mandatory rate can guarantee breath delivery.[11,12,91] Similar to CPAP, spontaneous mode is not recommended. At our center, we ventilate our patients using the timed mode only, with pressures adjusted to deliver inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) difference that is adequate to provide optimal tidal volume.[11,12] Long-term use of noninvasive ventilation by nasal mask can be associated with midface hypoplasia and dental malocclusion. Therefore, patients must alternate different interfaces and must be monitored with consideration for referral to a craniofacial team for the monitoring of facial growth as well as dental malocclusion.[1]

## DP

DP is an attractive treatment option for CCHS patients because it can provide daytime ventilatory support without being tethered to the home mechanical ventilator for those who are 24-hour ventilator dependent. It can be the sole ventilatory support for those who are only ventilator dependent during sleep, possibly permitting tracheal decannulation.[1,77,98]

With DP, the child uses her own diaphragm as the respiratory pump. A DP system involves the following four components: 1) monopolar electrodes that are surgically implanted bilaterally on the phrenic nerves, 2) receivers that are surgically implanted on the abdomen or chest bilaterally, 3) antennae that are placed over the receivers, and 4) an external battery operated portable transmitter that generates electrical energy similar to radio frequency. The electrical energy generated by the external transmitter is transmitted via external antennae that are placed over the receivers. The receivers then convert the energy to electrical currents that are then conducted to the phrenic nerve, stimulating contraction of the diaphragms.[1,98]

The ideal candidate for DP should have normal diaphragm function, intact phrenic nerve, little or no lung disease, and healthy weight. Overweight and obese patients are not ideal candidates for successful DP because the high amount of adipose tissue increases the distance between the antennae and receivers of the diaphragm pacers, resulting in an increased variability in the signal inputs to the receiver.[1,77,98]

At our center, diaphragm pacer electrodes are surgically implanted on the phrenic nerves thoracoscopically.[101,102] After surgery, the diaphragm pacers are not used immediately; as a result, patients' go back on their presurgery mode of ventilatory support. We wait 6–8 weeks to initiate pacing in order to allow healing. We begin pacing for 1–1 1/2 hours and gradually increase time on pacers by 30–60 minutes each week to train the diaphragms and prevent fatigue.[11,12,98] We believe that the phrenic nerve electrodes stimulate those fibers, which happen to touch the electrodes by chance, and that those fibers are often not the same fibers that are stimulated during spontaneous breathing. Second, the electrical impulse profile of the diaphragm pacers may be different from natural phrenic nerve impulses. For these two reasons, training the diaphragm is necessary to accept longer periods of pacing without fatigue. It takes an average of 6.6 months to establish full DP.[77]

DP permits tracheostomy decannulation in stable older CCHS patients who require ventilatory support only during sleep. To be considered for DP without tracheostomy, a CCHS patient should meet the following requirements: 1) ventilator dependence only during sleep, 2) not requiring daytime naps, 3) stable medical course with infrequent hospitalizations, 4) not requiring full-time ventilatory support during acute respiratory illnesses, and 5) acceptance that DP is not a secure method of ventilation and intubations maybe necessary for serious illnesses.[77] A disadvantage of DP without tracheostomy is the risk of obstructive sleep apnea, which can occur due to the diaphragm contraction without concomitant upper airway muscle contraction.[1,77,103] Wang et al[103] reported that obstructive sleep apnea (OSA) if present during DP without tracheostomy, it can be alleviated by decreasing the DP amplitude settings to decrease the force of inspiration with each diaphragmatic contraction.

Because of the risk of diaphragm fatigue, we recommend that DP only be used for up to 14–16 hours a day.[1,11,12,98] Therefore, during an acute illness, a patient must have an alternative form of ventilatory support when additional time is required on assisted ventilation beyond 14–16 hours is necessary. In these circumstances, a patient can be connected back to the home ventilator if the tracheostomy tube is still in place. If a patient has been decannulated, ventilatory support by NPPV is provided.

## Genetic counseling for CCHS

*PHOX2B* gene mutation in CCHS has an autosomal pattern of inheritance[1,13,104] with variable penetrance. Although most cases occur de novo, it is necessary to test the parents of the affected patient even if they do not report symptoms. Bachetti et al[69] re-examined parents of CCHS patients without any mutation detected via PHOX2B sequencing test, by using an improved molecular protocol, "FAM" method, and found low levels of mosaicism and increased recurrence risk of 25%. The short sized PARMs (ie, 20/24 and 20/25) and some NPARMs have incomplete penetrance, and therefore, affected individuals may be asymptomatic until they are older or experience a trigger that puts them in respiratory compromise.

Genetic counseling is imperative for individuals diagnosed with CCHS and their families as there is a 50% chance of recurrence with each child. Thus, if a parent is affected, there is also a 50% risk of CCHS to the patient's siblings.

Prenatal testing is recommended in all mothers with CCHS.[1,105] Prenatal testing will allow parents' optimal information with which to make an informed decision and aid the obstetrician and the pregnant mother plan for smooth delivery. Rajendran et al[105] reported a case of CCHS diagnosed in utero at 18 weeks gestation by *PHOX2B* gene analysis in fetal amniocytes. The fetus was not noted to initiate breathing or tachypnea in response to modest hypercapnia resulting from transient maternal breath holding. At birth, the infant was unable to establish adequate spontaneous breathing despite normal Apgar scores and thus was subsequently intubated and mechanically ventilated at the age of 1 hour.[105] This case underscores the importance of prenatal testing. Knowledge of the anticipated infants' status prepares the medical and

nursing teams to optimally plan for the infant's care in the delivery room and neonatal intensive care unit.[1]

## Conclusion

In the past 50 years, there has been a tremendous advancement in our knowledge of CCHS. Although CCHS is a rare disease, the discovery of the disease defining gene, *PHOX2B*, has increased early identification of CCHS patients, defined their clinical presentations, and brought new insights in the ability to provide optimal care tailored to their needs. The *PHOX2B* gene mutation analysis not only confirms the diagnosis of CCHS but also aids in predicting the outcome and management of CCHS. The capacity for early identification of CCHS via genetic testing methods allows the clinicians to provide early intervention to prevent morbidity and mortality and improve the patient's and family's quality of life.

## Disclosure

The authors report no conflicts of interest in this work.

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