Congenital Central Hypoventilation Syndrome
A Neurocristopathy with Disordered Respiratory Control and Autonomic Regulation

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KEYWORDS
- PHOX2B • Autonomic • Respiratory • CCHS • Hirschsprung • Neuroblastoma

KEY POINTS
- Congenital central hypoventilation syndrome (CCHS) is a rare neurocristopathy with disordered respiratory control and autonomic nervous system regulation.
- CCHS is caused by mutations in the PHOX2B gene, and the PHOX2B genotype/mutation anticipates the CCHS phenotype, including the severity of hypoventilation, risk of sinus pauses, and risk of associated disorders including Hirschsprung disease and neural crest tumors.
- It is important to maintain a high index of suspicion in cases of unexplained alveolar hypoventilation, delayed recovery of spontaneous breathing after sedation or anesthesia, or in the event of severe respiratory infection, and unexplained seizures or neurocognitive delay. This will improve identification and diagnosis of milder CCHS cases and later onset/presentation cases, allowing for successful intervention.
- Early intervention and conservative management are key to long-term outcome and neurocognitive development.
- Research is underway to better understand the underlying mechanisms and identify targets for treatment advances and drug interventions.

INTRODUCTION
Congenital central hypoventilation syndrome (CCHS) is a rare disorder of respiratory control with autonomic nervous system dysregulation (ANSD), and a result of maldevelopment of neural crest-derived cells (neurocristopathy). The first reported description of CCHS was in 1970 by

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Robert Mellins and colleagues.\textsuperscript{1} Despite a multitude of case reports, large series were not published until 1992.\textsuperscript{2} As of early 2014, laboratories from the United States, France, Italy, Japan, Germany, China, The Netherlands, and Australia have now collectively diagnosed approximately 1200 cases with \textit{PHOX2B} mutation-confirmed CCHS. However, the birth prevalence of CCHS is unknown, because demographically diverse, large, population-based studies have not been reported. Because the milder cases of CCHS and later-onset (LO) CCHS may go unrecognized or misdiagnosed, it is difficult to estimate the true frequency of CCHS in the general population at this time.

CCHS is characteristically diagnosed in the newborn period. However, individuals can also be diagnosed in childhood\textsuperscript{3–6} or adulthood,\textsuperscript{5,7–13} depending on the severity of symptoms and the inquisitiveness of the patient, family, and medical team. Impaired breathing regulation (respiratory control) is the hallmark of CCHS. Individuals with CCHS typically present with shallow breathing (alveolar hypoventilation) during sleep and, in more severely affected individuals, during wakefulness and sleep. These breathing complications occur despite the lungs and airways being anatomically and physiologically normal. Conditions associated with CCHS reflecting anatomic ANSD include Hirschsprung disease (HSCR) and tumors of neural crest origin, in addition to a spectrum of symptoms compatible with physiologic ANSD. CCHS is a life-long disease.

\textbf{PHOX2B Gene Mutations}

Individuals with CCHS have a mutation in \textit{PHOX2B}, a gene that plays an important role in the development of the ANS. The normal \textit{PHOX2B} gene has 20 repeats of the amino acid alanine. Approximately 90\% of individuals with CCHS are heterozygous for a \textit{PHOX2B} polyalanine repeat expansion mutation (PARM), with expansions to 24 to 33 alanine repeats on the affected allele,\textsuperscript{14} genotypes of 20/24 to 20/33 (normal genotype is 20/20; Fig. 1). The remaining 9\% to 10\% of

![Diagram of PHOX2B gene with location of all CCHS-associated mutations identified to date. Nearly all polyalanine repeat expansion mutations (PARMs) are located within the second polyalanine expansion region of exon 3 (shown in red). Nearly all NPARMs identified thus far have been found at the extreme 3' end of exon 2 or in exon 3. (Adapted from Weese-Mayer DE, Rand CM, Berry-Kravis EM, et al. Congenital central hypoventilation syndrome from past to future: model for translational and transitional autonomic medicine. Pediatr Pulmonol 2009;44:526; with permission.)](image-url)
individuals with CCHS and LO-CCHS have a different type of alteration in the \textit{PHOX2B} gene, referred to as non-PARM (NPARM). These mutations include missense, nonsense, frameshift, and stop codon mutations, mostly occurring in exon 2 and exon 3 of \textit{PHOX2B}. Fewer than 1% of individuals with CCHS/LO-CCHS or CCHS-like symptoms will have whole gene or exon deletions of \textit{PHOX2B} \cite{15}, and are phenotypically variable. Among PARMS, the 20/25, 20/26, and 20/27 genotypes, and among NPARMs, a 38-bp deletion at the site of the polyalanine repeat, remain the most frequently identified mutations. CCHS-related \textit{PHOX2B} mutations have not been found in thoroughly screened control populations. Although de novo germline mutations cause the majority of CCHS cases, an autosomal-dominant inheritance pattern exists for CCHS. This includes somatic mosaicism, identified in a subset (5%–25%) of parents of CCHS probands \cite{16–18} as well as inheritance from a fully affected parent (with CCHS).

Mutations in \textit{PHOX2B} result in altered development and regulation of the ANS, primarily by abnormal development in progenitors of early embryonic cells that form the neural crest (hence the term neurocristopathy \cite{19}). Individuals with the NPARMs are typically more severely affected than individuals with the PARMs, and individuals with a greater number of alanine repeats are typically more severely affected than those with fewer (especially among the most common PARMs). The small number of identified cases with whole-gene or exon deletions makes prediction of phenotype difficult in these cases, but thus far disease seems to be less severe in these cases. Typically, dysfunction of \textit{PHOX2B} during development is enough to cause manifestation of disease from the neonatal period; however, the less severe mutations may be “unmasked” by challenges to the respiratory system, such as respiratory infection or exposure to sedation, which can lead to fully manifest disease symptoms.

Genotype–Phenotype Correlations

The symptoms and severity of CCHS vary from one individual to another (Fig. 2).\textsuperscript{20} This variation is becoming clearer as these patients are studied by \textit{PHOX2B} genotype/mutation, such that repeat length and PARM versus NPARM are related to disease severity. A rapidly expanding understanding of the risks specific to the particular \textit{PHOX2B} mutation is allowing physicians and parents to anticipate risks for continuous ventilation, pauses in the heart rhythm, HSCR, neural crest tumors, and potential factors that influence autonomic regulation in individuals with CCHS.

Ventilatory dependence

In individuals with PARMs, the need for continuous ventilatory dependence has a direct relationship with the length of the alanine expansions.\textsuperscript{3,17,21} Specifically, individuals with the 20/25 genotype rarely require 24-hour ventilatory support; individuals with the 20/26 genotype have variable awake needs, depending on the level of activity; and

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
System & Physiologic Sign/Symptom & Pathologic Condition \\
\hline
Ophthalmologic & • decreased/absent pupillary light response & \\
 & • anisocoria & \\
 & • esotropia/esotropia & \\
 & • lack of convergent gaze & \\
Respiratory & • absent perception of dyspnea & \\
 & • alveolar hypoventilation & \\
Cardiovascular & • altered peripheral perfusion & \\
 & • decreased heart rate variability & \\
 & • prolonged sinus pauses & \\
 & • vasovagal syncope & \\
Gastrointestinal & • esophageal dysmotility & HSCR \\
 & • constipation & \\
Neuro & • decreased anxiety & neural crest tumor \\
 & • decreased pain perception & -sympathetic chain \\
 & & -adrenals \\
Sudomotor & • profuse sweating & temperature dysregulation (hypothermia) \\
\hline
\end{tabular}
\end{table}

Fig. 2. Signs and symptoms of CCHS-related ANS dysregulation. (From Weese-Mayer DE, Patwari PP, Rand CM, et al. Congenital central hypoventilation syndrome (CCHS) and \textit{PHOX2B} mutations. Primer on the autonomic nervous system. 3rd edition. Oxford: Elsevier; 2012; with permission.)
individuals with genotypes from 20/27 to 20/33 very often require continuous ventilatory support. LO-CCHS cases with the 20/24 or 20/25 genotype have the mildest hypoventilation, presenting primarily after exposure to respiratory depressants or severe respiratory infection, and may often be managed with nocturnal ventilatory support only. In contrast with the PARMs, most individuals with NPARMs require continuous ventilatory support. In contrast with the PARMs, most individuals with NPARMs require continuous ventilatory support (Fig. 3).21

Hirschsprung disease and tumors of neural crest origin
Some individuals with CCHS have anatomic/structural malformations including HSCR and tumors of neural crest origin. Overall, 16% to 20% of individuals with CCHS have HSCR, with a higher prevalence among individuals with NPARMs than those with PARMs. HSCR is reported in 87% to 100% of NPARMs, in contrast with 13% to 20% of PARMs. Notably, a high occurrence of HSCR in individuals with the 20/27 genotype has been described and anecdotally in approximately 30% of individuals with the 20/27 to 20/33 genotype. Extracranial solid tumors of neural crest origin have also been reported in CCHS and associated with PHOX2B genotype. The tumors include neuroblastomas, ganglioneuromas, and ganglioneuroblastomas. These are found in locations with sympathetic nervous tissue, such as the chest and abdomen in paraspinal ganglia or the adrenal glands. Neural crest tumors in individuals with the NPARMs are typically neuroblastomas, in contrast with the ganglioneuromas and ganglioneuroblastomas in individuals with the longest PARMs (20/30–20/33). However, in 1 case a child with the 20/33 genotype presented with a neuroblastoma.

ANSD
An increased number of symptoms of ANSD has been reported in association with PHOX2B genotype in individuals with CCHS. These symptoms can include heart rhythm abnormalities, such as prolonged asystoles (>3 seconds) necessitating a cardiac pacemaker, altered gut motility even in the absence of HSCR (often presenting as severe constipation), altered temperature regulation (as indicated by low body temperatures), decreased pain perception, decreased anxiety, and eye abnormalities that include strabismus, convergence insufficiency, and decreased pupil response to light.

LO-CCHS
A growing number of individuals are now being identified who present in later infancy, childhood, or even adulthood and are referred to as LO-CCHS. LO-CCHS seems to reflect the variable penetrance of the PHOX2B genotypes 20/24 and 20/25 or rarely an NPARM. Some of these affected individuals will not be identified until

**PHOX2B Testing for Individual with Central Alveolar Hypoventilation**

![Diagram of PHOX2B testing](image)

**Fig. 3.** Algorithm to determine when and what type of PHOX2B genetic testing should be performed in various clinical scenarios in which CCHS and LO-CCHS are suspected or confirmed. (Adapted from Weese-Mayer DE, Patwari PP, Rand CM, et al. Congenital central hypoventilation syndrome (CCHS) and PHOX2B mutations. Primer on the autonomic nervous system. 3rd edition. Oxford: Elsevier; 2012; with permission.)
after receiving sedation, anesthesia, or antiseizure medications. Children with CCHS—both those identified in infancy and those identified later—are now surviving into adulthood, giving new insights into the long-term sequelae of treated and untreated CCHS/ANSD. As more children and adults who were not identified in earlier life are diagnosed with CCHS at an advanced age, and documentation of sinus pauses in individuals with the LO-CCHS 20/25 genotype are reported, a more clear understanding of the importance of aggressive, conservative intervention at the youngest age possible is emerging.

EVALUATION AND PROCEDURE

Diagnosis

The classic presentation of an infant with CCHS includes cyanosis and hypercarbia, resulting from very shallow breathing during sleep (nap and night), but alertness and adequate breathing during wakefulness—and no description of respiratory distress. If on a ventilator, the infant is described as breathing synchronously with the ventilator when asleep but adding extra breaths during wakefulness or in rapid eye movement sleep. These individuals do not properly increase breathing or awaken in response to abnormal oxygen and carbon dioxide levels. This same lack of normal responsivity to low oxygen and elevated carbon dioxide occurs during wakefulness as well, even when clinical evaluation suggests awake breathing is generally “adequate.” LO-CCHS should be considered in the event of centrally mediated alveolar hypoventilation, cyanosis, or seizures after (1) anesthetics or central nervous system depressants, (2) severe pulmonary infection, or (3) obstructive sleep apnea intervention.

Once the diagnosis of CCHS/LO-CCHS is considered, blood should be sent for the clinical PHOX2B testing. The American Thoracic Society Statement on CCHS (published in 2010) advises that the PHOX2B Screening Test be the first step in making the genetic diagnosis of CCHS (see Fig. 3). This test diagnoses all of the PARMs, somatic mosaicism, polyalanine repeat contraction mutations, and the exon frameshift NPARMs. Another name for the PHOX2B Screening Test is fragment analysis (see http://www.genetests.org/by-disorder/?disid=217354). If the PHOX2B screening test is normal and the subject has the clinical presentation of CCHS, then the sequel PHOX2B sequencing test should be performed to identify the subset of patients with small NPARMs. Although the PHOX2B sequencing test detects the PARMs and NPARMs, it is typically more costly and it does not detect mosaicism. Because PHOX2B mutations can be inherited from a mosaic parent, the sequencing test is rarely useful in parents of children with CCHS (Fig. 4).

Genetic Testing for Both Parents of Individual with PHOX2B Mutation-Confirmed Congenital Central Hypoventilation Syndrome

![Algorithm to determine when and what type of PHOX2B genetic testing should be performed in parents of CCHS proband.](http://www.example.com/fig4)

Finally, in cases where both the PHOX2B screening and sequel sequencing tests are negative but clinical suspicion remains high, the PHOX2B MLPA test for copy number variations should be performed. While awaiting results of the clinically available PHOX2B testing, other causes of hypoventilation should be ruled out to expedite proper intervention and facilitate treatment strategies for home care. Primary lung disease, ventilatory muscle weakness, and cardiac disease should be ruled out with the following tests: Chest x-ray and potentially computed tomography of the chest, comprehensive neurologic evaluation and potentially muscle biopsy, and echocardiogram. Causative gross anatomic brain/brainstem lesions should be ruled out with magnetic resonance imaging and/or computed tomography of the brain and brainstem. Likewise, inborn errors of metabolism should be considered and a metabolic screen should be performed.

**Treatment**

**Hypoventilation**

Alveolar hypoventilation is the hallmark of CCHS, and its most apparent and potentially debilitating phenotypic feature. Characteristically, the diminution of tidal volume with resultant effect on minute ventilation is most apparent in non-rapid eye movement sleep in CCHS, but it is also abnormal during rapid eye movement sleep and wakefulness, although usually to a lesser degree. The spectrum of sleep-disordered breathing may range in severity from hypoventilation during NREM sleep with adequate ventilation during wakefulness, to complete apnea during sleep and severe hypoventilation during wakefulness. As mentioned, the CCHS phenotype relative to ventilatory needs is in large part PHOX2B genotype/mutation dependent. Typically, children with the 20/27 to 20/33 genotype and the NPARMs will require 24-hour mechanical ventilation, especially with exertion and during sleep. Children with the 20/24 and 20/25 genotypes, and a small subset of NPARMs, rarely require 24-hour ventilation, unless they have had suboptimal ventilatory management for prolonged periods in early childhood. The awake ventilatory needs of the children with the 20/26 phenotype varies with activity level. It remains unclear if awake spontaneous breathing improves with puberty, so ventilatory needs should be determined from physiologic testing, not assumptions about developmental stages.

**HSCR**

For those individuals with constipation symptoms, a barium enema or manometry, and potentially a full-thickness rectal biopsy should be performed to diagnose HSCR. HSCR, a rare gastrointestinal disorder characterized by aganglionosis of the distal hindgut, often presents in individuals with CCHS. Symptoms of HSCR appear soon after birth and may include constipation, abdominal distention, and vomiting. Older infants may have anorexia, failure to thrive, and severe constipation. Short segment HSCR may be diagnosed in older children and adults. Treatment of HSCR usually consists of surgery to remove the nonfunctional segment of aganglionic bowel and relieve obstruction. Typically, a temporary bowel opening of the colon in the abdominal wall (colostomy) is usually performed first. The second operation consists of removing the aganglionic colon and rectum and reconnecting the normal bowel to the anus. In some centers with extensive expertise in HSCR, these procedures can be performed in one operation.

**Neuroblastoma**

Thus far, tumors of neural crest origin have been identified in children with NPARM (typically neuroblastoma) and in children with 20/30 and 20/33 genotype PARMs (typically ganglioneuroma and ganglioneuroblastoma, though neuroblastoma remains a possibility). The American Thoracic Society Statement on CCHS suggests screening for tumors of neural crest origin in all NPARM cases and in children with the 20/28 to 20/33 PHOX2B genotypes. Among infants at greatest risk of a tumor of neural crest origin, chest x-ray/abdominal ultrasonography in infancy and later chest and abdomen magnetic resonance imaging or computed tomography is of value. An iodine metaiodobenzylguanidine scan, used to find tumors of neural crest-specific origin, might be performed in the patients at greatest risk for neuroblastoma. Neuroblastomas are removed surgically, followed by chemotherapy in some cases. Treatment for other tumors originating from the neural crest depends on the type and location of the tumor.

**Neurocognitive function**

Suboptimal school performance and/or decreased intellectual function have been observed in CCHS patients. It is unclear whether this is owing to hypoxemia from inadequate ventilatory support or a direct result of the primary neurologic problem associated with CCHS. As children with CCHS are more consistently identified in the newborn period, and as management for these complex and vulnerable children becomes more standardized, improved neurocognitive performance is anticipated with an increased understanding of the distinction between sequelae of hypoxemia (owing to hypoventilation or asystoles) and innate
disease specific to CCHS. There is also new evidence that CCHS patients may have altered cerebral autoregulation, a condition that may contribute to neurocognitive decline related to recurrent hypoxemia/hypercarbia. Comprehensive neurocognitive testing performed annually in a controlled setting assesses the child’s progress relative to intervention, management, and compliance and may identify new areas for intervention. Aggressive educational intervention coupled with careful ventilatory and cardiovascular management is essential.

**Cardiac function**

Cardiac rhythm abnormalities include decreased beat-to-beat heart rate variability, reduced respiratory sinus arrhythmia, and transient abrupt asystoles. Seventy-two–hour Holter monitoring performed annually may identify aberrant cardiac rhythms, typically sinus pauses that necessitate bipolar cardiac pacemaker implantation (ie, any pauses of ≥3 seconds) and the frequency of shorter pauses (ie, <3 seconds) that may have physiologic and neurocognitive impact.

**Cor pulmonale**

Children with CCHS are at risk for progressive pulmonary hypertension and cor pulmonale, as a result of recurrent hypoxemia owing to inadequate ventilator settings or tracheostomy caliber, unrecognized hypoventilation during spontaneous breathing while awake, excessive exercise with resultant physiologic compromise, or suboptimal compliance with artificial ventilation. As a result, echocardiograms, hematocrits, and reticulocyte counts should be performed at least annually to identify potential cor pulmonale and polycythemia.

**Ophthalmology**

CCHS patients frequently exhibit ophthalmologic abnormalities reflecting the role of PHOX2B in the development of cranial nerves controlling pupillary function. Comprehensive ophthalmologic testing and pupillometry determines the nature of the ophthalmologic involvement and allows for intervention strategies to avoid interference with learning.

**Other**

Anecdotal reports of poor heat tolerance and profuse sweating have been described, although not studied comprehensively. Very limited formal assessment of the ANS has been reported, and none analyzed by PHOX2B genotype. Comprehensive autonomic testing as clinically indicated to assess ANS dysfunction may include head up tilt testing, heart rate–deep breathing, Valsalva maneuver, thermoregulatory chamber sweat testing, quantitative sudomotor sweat testing, pupillometry, and more.

**AFTER CARE**

Care for individuals with CCHS is ideally provided through centers with extensive expertise in CCHS, working in close partnership with parents and regional pediatric pulmonologists and pediatricians, to provide consistent, state-of-the-art management and guidance, and to provide thorough, up-to-date education regarding CCHS. The concept of centers is based on an understanding that management of children with CCHS is more time intensive and complex than the care of other ventilator-dependent children. Multidisciplinary care must typically be organized to include pediatricians, internists, pulmonologists, cardiologists, intensivists, ENT physicians, surgeons, gastroenterologists, neurologists, ophthalmologists, psychologists, psychiatrists, respiratory therapists, nurses, social workers, speech and language therapists, special education teachers, and more. And because of the nature of the PHOX2B mutations, and the range of phenotype based on these mutations, experience with even 15 to 30 patients does not provide the scope of experience necessary for understanding the needs of children with CCHS. The model of centers with extensive expertise in CCHS working in partnership with regional experts in pediatric pulmonology and pediatricians improves the consistency of management and likely outcome for individuals with CCHS. It also extends education about CCHS in all communities with CCHS patients, thereby improving identification of new patients.

In-hospital, comprehensive, clinical, physiologic testing awake and asleep are essential to assess ventilatory needs during varying levels of activity and concentration and all stages of sleep, with spontaneous breathing and with artificial ventilation. Furthermore, tests of ventilatory responsivity to endogenous and exogenous physiologic challenges awake and asleep ascertain each child’s needs for optimal clinical management. This evaluation should be performed annually in CCHS patients 3 years and older, and biannually in the first 3 years of life. These clinical studies performed over the course of a several-day hospitalization in a center with extensive CCHS experience allows for a clear understanding of needs when breathing spontaneously as well as with artificial ventilation, with simulation of activities of daily living. These physiologic studies should include constant supervision by highly trained personnel and continuous audiovisual surveillance with continuous recording (at a minimum) of respiratory inductance...
plethysmography (chest, abdomen, sum), ECG, hemoglobin saturation, pulse waveform, end-tidal carbon dioxide, sleep state staging, blood pressure, and temperature. Other recommended testing for individuals with CCHS is provided in Table 1.

All individuals with CCHS require artificial ventilatory support. In infants, the safest way to deliver this is with a mechanical ventilator via a tracheostomy. Individuals with CCHS require a mechanical ventilator at home (with a backup ventilator, pulse oximeter, end-tidal carbon dioxide monitor, generator and preferably ventilator batteries) as well as experienced registered nursing care 24 hours a day. In select cases, other assistive breathing apparatus and/or techniques may be used, such as diaphragm pacing. Diaphragm pacing may be an option for CCHS patients, who are often ideal candidates (no or mild intrinsic lung disease, not obese with intact phrenic nerve–diaphragm axis integrity, and presence of a tracheostomy at least at the beginning of diaphragm pacing). Diaphragm pacing is an optimal form of ventilatory support during wakefulness because it allows freedom from mechanical ventilator use and participation in age-appropriate activities otherwise not possible.\(^2,45,46\) In general, conservative use of diaphragm pacing is provided in active children, with 12 to 15 hours per day typically recommended. In older children and adults, noninvasive (mask) ventilation may be considered. This technique is discouraged in infants and young children because of the risk of facial deformation from the mask and inadequate stability of mask ventilation at a time of rapidly progressing neurodevelopment. The goal is to optimize oxygenation and ventilation to optimize neurocognitive outcome. Diaphragm pacing is a consideration in older children and adults for support during sleep only, although tracheostomy removal cannot be ensured. CCHS is a life-long disease and affected individuals will, at a minimum, always require artificial ventilation during sleep. Ventilatory needs vary with the specific \(PHOX2B\) mutation. However, supplemental oxygen alone is not adequate for treating the child with CCHS.

With modern technology for artificial ventilation, most children with CCHS can have prolonged survival with a good quality of life. At present, the oldest neonatally identified patients with CCHS are graduating from college, marrying, and maintaining employment. It behooves the family and medical personnel to provide optimal ventilation and oxygenation to ensure maximization of neurocognitive potential.

**COMPLICATIONS**

**Alcohol and Drug Abuse**

With advancing technology and treatment options, CCHS patients are now surviving into adolescence.

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### Table 1

**Recommended testing to characterize the CCHS phenotype**

<table>
<thead>
<tr>
<th>PHOX2B Genotype</th>
<th>Annual In-Hospital Comprehensive Physiologic Testing (Awake and Asleep), Exogenous and Endogenous Gas Challenges, Autonomic Testing</th>
<th>Assessment for Hirschsprung Disease</th>
<th>Annual Neurocognitive Assessment</th>
<th>Annual 72-h Holter Recording and Echocardiogram</th>
<th>Annual Imaging to Assess for Tumors of Neural Crest Origin</th>
</tr>
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<tbody>
<tr>
<td>PARMs</td>
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<tr>
<td>20/24 and 20/25</td>
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<td>X</td>
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<td>X(^a)</td>
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<td>NPARMs</td>
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<td>X</td>
<td>X</td>
<td></td>
<td>X(^b)</td>
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</tbody>
</table>

**Abbreviations:** NPARM, nonpolyalanine repeat expansion mutation (missense, nonsense, frameshift); PARM, polyalanine repeat expansion mutation.

\(^a\) Annual chest and abdominal imaging to identify ganglioneuromas and ganglioneuroblastomas.

\(^b\) Abdominal imaging and urine catecholamines every 3 months in first 2 years, then every 6 months until 7 years of age to identify neuroblastomas.

and adult life. With this advancement comes the normal adolescent temptations of alcohol and drug abuse.\textsuperscript{47} The use of drugs and alcohol can further depress ventilatory drive awake and asleep in these patients to the point where continuous assisted ventilation is required; without such support, results can be fatal.\textsuperscript{47} Therefore, CCHS patients and families should receive counseling about the special dangers drugs and alcohol present before adolescence, and continuing through adult life.

**Pregnancy**

CCHS patients are increasingly having children of their own.\textsuperscript{48,49} Pregnancy presents potential risks both to the mother with CCHS and the fetus, which may also have a CCHS-associated PHOX2B mutation. In the mother with CCHS, the enlarging uterus increases respiratory load; already breathing at a lower minute ventilation and higher PCO\textsubscript{2} than other pregnant women,\textsuperscript{49} the central respiratory drive to meet these increased ventilatory demands is inadequate. As such, these pregnancies require frequent physiologic monitoring of the mother, evaluating adequacy of gas exchange both during spontaneous awake breathing, and while on assisted ventilation during sleep. Special care must be taken for a caesarian birth occurring in a pregnant woman with CCHS who relies on diaphragm pacing without a tracheostomy. In this situation, the obstetric staff should be prepared to use bilevel positive airway pressure ventilation after delivery, because diaphragm pacing is poorly tolerated after an abdominal incision.\textsuperscript{49} For offspring born to individuals with CCHS, prenatal PHOX2B testing allows for the anticipated infant with CCHS to be delivered in a tertiary care center with plans for immediate intubation and ventilation in the delivery room. Therefore, prenatal PHOX2B testing in any fetus with a CCHS-diagnosed parent (mother or father) or a parent with somatic mosaicism is recommended, even if termination of pregnancy is not anticipated, to optimally plan for the immediate newborn care of a CCHS infant. Plans should also be made to ensure that the mother with CCHS has adequate ventilator support during labor, postpartum, and during and after any general anesthesia which may be required.

**SUMMARY**

Our understanding of CCHS is expanding rapidly, but it remains a work in progress. Optimal diagnosis and management of CCHS patients requires further advances in our knowledge through research. Owing to the rarity of the disease, these advances require the participation of all CCHS patients and their families and physicians around the world. Because the biology of CCHS is not completely understood, it is hoped that families of the few CCHS patients who die will agree to autopsy, which can provide tissues to further identify and delineate biologic abnormalities. These tissues would include frozen and fixed brain, brainstem, carotid and aortic bodies, adrenal glands, autonomic plexus, sympathetic chain, and the entire intestine. The presentation, symptoms, severity, and relationship of these to PHOX2B genotype are complex issues in CCHS. To further our understanding of these issues in the hope of bettering the lives of CCHS patients, and to prepare for possible drug trials in CCHS in the future, an international CCHS registry has been developed. This registry is a secure online interface allowing CCHS families around the world to participate. Further information on this registry can be found on the Center for Autonomic Medicine in Pediatrics at the Ann & Robert H. Lurie Children’s Hospital of Chicago website (http://www.luriechildrens.org/en-us/care-services/conditions-treatments/autonomic-medicine/Pages/basics/basics.aspx), or by emailing CRand@LurieChildrens.org.

Recently, the first study in a large cohort of individuals with PHOX2B mutation-confirmed CCHS evaluating comprehensive chemosensory function was completed.\textsuperscript{38} The study was designed to determine whether residual chemosensory function exists in CCHS patients and if it is associated with PHOX2B genotype. The results suggest that CCHS patients maintain a weak residual awake ventilatory response to chemosensory challenge with hypoxia/hypercarbia, independent of PHOX2B genotype. However, the PHOX2B genotype was found to associate with graded dysfunction in cardiovascular regulation. This contrast in phenotype–genotype association suggests differential effects of PHOX2B dysfunction on different autonomic subsystems. Although these results also emphasize the continual risk of physiologic compromise from hypoxemia and hypercarbia to CCHS patients during activities of daily living, they also suggest partial preservation of central nervous system networks that could provide a fulcrum for potential pharmacologic interventions. A high index of suspicion, early detection, and aggressive, conservative intervention are critical to optimize neurocognitive outcome and quality of life for individuals with CCHS and LO-CCHS of all ages. If inadequately treated, affected individuals will likely suffer neurocognitive compromise and potentially sudden death. If treated conservatively and followed comprehensively, individuals with CCHS can have a good quality of life and an anticipated normal life span. As children with
CCHS are advancing into adulthood, the development of transitional medicine programs in the centers already caring for children with CCHS is essential.

REFERENCES


