Hypoventilation Syndromes of Infancy, Childhood, and Adulthood

Congenital Central Hypoventilation Syndrome (CCHS), Later-Onset CCHS, and Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation

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KEYWORDS
- Autonomic dysregulation • Hypothalamic dysregulation • Hypoventilation • PHOX2B

KEY POINTS
- Congenital central hypoventilation syndrome (CCHS) (including later-onset CCHS) and rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) are rare neurocristopathies with shared features including alveolar hypoventilation, disordered respiratory control, variable autonomic nervous system dysregulation (ANSD), tumors of neural crest origin, and risk of sudden death.
- Mutations in the \( \text{PHOX2B} \) gene are causative in all known cases of CCHS. The \( \text{PHOX2B} \) genotype is predictive of many features of the CCHS phenotype, including severity of hypoventilation, risk of cardiac sinus pauses, Hirschsprung disease, neural crest tumors, and symptoms of ANSD.
- For ROHHAD, research is under way to determine the etiology of the disease.
- Early consideration of CCHS and stepwise \( \text{PHOX2B} \) testing in cases with unexplained alveolar hypoventilation or delayed recovery of spontaneous breathing after sedation, anesthesia, or a severe respiratory infection will enhance diagnosis of milder CCHS cases and LO-CCHS, decreasing morbidity and mortality in these instances.
- Heightened clinical suspicion in cases of rapid-onset obesity with hypoventilation, especially in the event of a tumor of neural crest origin, will allow for early identification of ROHHAD patients. Coupled with conservative management, this strategy will optimize the long-term outcome and neurocognitive development for children with ROHHAD.
- For CCHS, LO-CCHS, and ROHHAD, targets for treatment and drug intervention are being evaluated as progress is made in understanding the underlying mechanisms and phenotypic manifestations of these disorders.

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INTRODUCTION: NATURE OF THE PROBLEM

Congenital central hypoventilation syndrome (CCHS) and rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) are rare disorders of hypoventilation. CCHS typically presents in the newborn period and ROHHAD in childhood, although later identification of CCHS is becoming increasingly more common, and these cases are now termed later-onset CCHS (LO-CCHS). Each of these syndromes causes apparent alveolar hypoventilation with disordered respiratory control during sleep and often during wakefulness, in addition to a varied and complex assortment of phenotypic manifestations (Table 1). Both disorders are included within the rubric of Respiratory and Autonomic Disorders of Infancy, Childhood and Adulthood (RADICA), and both are examples of neurocristopathies.

CCHS
Etiology
CCHS was first described by Mellins and colleagues1 as a case report in 1970. Early study of CCHS was focused on the respiratory control deficit in these patients. Symptoms of diffuse autonomic nervous system (ANS) dysregulation (ANSD) became evident as larger patient populations were reviewed, leading to the introduction of the ANSD acronym and a focus on central hypoventilation in the context of ANSD.2 In 2003, heterozygous mutations within the PHOX2B gene were discovered to be responsible for the CCHS phenotype.3,4 The PHOX2B gene encodes a highly conserved transcription factor known to play an integral role in the embryologic expression of neural crest cells involved in development of the ANS.5 PHOX2B variations in CCHS cases include polyalanine repeat expansion mutations (PARMs; ~90% of cases) in exon 3, as well as non-PARMs (NPARMs) with missense, frameshift, nonsense, and stop-codon mutations (8%–10% of cases) throughout the coding region, and whole or partial gene deletions (<1% of cases; Fig. 1).5 The type and location of the mutation within the PHOX2B gene influences the magnitude of cellular disruption.7,8 Accordingly, the type of PHOX2B mutation has been shown to be prognostic of phenotypic severity in CCHS, for both the hypoventilation and some features of ANSD (Fig. 2). However, a recent study of a 3-generation family with a CCHS-affected individual in each generation, all of whom were shown to have the same PHOX2B NPARM mutation, revealed distinct CCHS phenotypes in each case, indicating variable expressivity even within a single family sharing an identical NPARM.9 Whole or partial gene deletions tend to produce a less severe phenotype, although the relative severity of these large-scale deletions cannot be statistically assessed because of the limited number of patients identified to date.10

An autosomal dominant pattern of inheritance has been ascertained for CCHS through observation of somatic mosaicism in parents in addition to direct inheritance from an affected CCHS parent to child.4 Whereas up to 25% of CCHS cases are inherited from a parent with somatic mosaicism, de novo germline mutations are responsible for most cases of CCHS.8 As of early 2014, approximately 1200 cases of CCHS have been diagnosed since the first case report in 1970, including patients from at least 50 countries. The true prevalence of CCHS remains unknown, and estimation proves difficult because of undiagnosed mild or later-onset cases.

Overview of major features
Central hypoventilation Alveolar hypoventilation, without a primary neuromuscular, respiratory, or cardiac basis or a brainstem lesion that can account for the full CCHS phenotype, remains the most prominent indication of the disorder. Patients with CCHS have diminished tidal volumes with limited respiratory rate variability. This feature is most evident during non–rapid eye movement (REM) sleep but also can be observed during REM sleep and wakefulness.11–13 As a result, patients become hypoxemic and hypercarbic, and lack the physiologic and behavioral responsiveness to such challenges (absent adjustments of respiration and/or arousal during sleep). Tissue injury arising from intermittent hypoxia in central nervous system areas responsible for cardiac and respiratory control has been reported, potentially exacerbating control of breathing deficits, among other ANS irregularities.

Neurocognitive function Impaired neurocognitive function has been reported in a subset of patients with CCHS.13,15–18 Whether the noted neurocognitive deficits arise solely from intermittent hypoxia, a primary neurologic issue intrinsic to CCHS, or a combination of both remains unknown. Recent evidence has suggested altered cerebral autoregulation in CCHS,19 which could contribute to the observed neurologic deficit in conjunction with experienced hypoxemia in the disorder.

Hirschsprung disease and gastrointestinal dysfunction A subset of CCHS patients are born with Hirschsprung disease (HSCR), defined as an absence of ganglion cells from variable lengths of distal bowel. These patients typically present shortly after birth with failure to pass meconium,
Table 1
Overview of common and differentiating features in congenital central hypoventilation syndrome (CCHS), later-onset CCHS (LO-CCHS), and rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD)

<table>
<thead>
<tr>
<th>Phenotypic Features (%)</th>
<th>Alveolar Hypoventilation</th>
<th>ANSD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Neural Crest Tumors</th>
<th>Hirschsprung Disease</th>
<th>Hypothalamic Dysregulation</th>
<th>Rapid-Onset Obesity</th>
<th>Etiology</th>
<th>Onset/Clinical Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCHS</td>
<td>100</td>
<td>100</td>
<td>NPARM: ≥50</td>
<td>NPARM: &gt;80</td>
<td>&lt;5</td>
<td>0</td>
<td>PHOX2B gene mutations</td>
<td>Newborn</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PARM: &lt;1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LO-CCHS</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>≤5</td>
<td>0</td>
<td>0</td>
<td>PHOX2B gene mutations</td>
<td>Infancy-adulthood</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td></td>
<td>100</td>
<td>100</td>
<td>Unknown</td>
<td>1.5–11 y</td>
</tr>
<tr>
<td>ROHHAD</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>Unknown</td>
<td>1.5–11 y</td>
</tr>
</tbody>
</table>

Abbreviations: ANSD, autonomic nervous system dysregulation; NPARM, non–polyalanine repeat expansion mutation; PARM, polyalanine repeat expansion mutation.

<sup>a</sup> Features of ANSD vary greatly between CCHS/LO-CCHS and ROHHAD.
abdominal distention, and vomiting, although a subset will be diagnosed after the neonatal period presenting with severe constipation. New murine models indicate that PHOX2B dysfunction can lead to decreased bowel ganglion cell density,20 a condition that would not be termed HSCR but would likely lead to variable gastrointestinal dysfunction. Indeed, a recent abstract reported that non-HSCR CCHS patients are more likely than healthy controls to experience constipation, dysphagia, diarrhea, and bloating.21

**Neural crest cell–derived tumors** Solid extracranial tumors of neural crest origin have been described in CCHS. These tumors may occur anywhere along the sympathetic chain, including

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**Fig. 1.** CCHS-associated PHOX2B gene mutations. 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. (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.)

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**Fig. 2.** Rate of phenotypic manifestations in CCHS cases with PARMs in PHOX2B compared with those cases with NPARMs in PHOX2B. CCHS cases included were compiled from cases reported in the literature through 2009 including reports from groups in the United States, Italy, France, Japan, Germany, China, Australia, and the Netherlands, in addition to data reported by the authors, where adequate clinical information was available. Neural crest tumor data were derived from cases whereby information was available and the child had survived at least the first year of life. All PARM cases with tumors had large (29–33 repeat; genotypes 20/29–20/33) expansion mutations. (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;44:530; with permission.)
paraspinal masses of the chest and abdomen, and the adrenal gland. Tumors in NPARMs are typically neuroblastomas, whereas those in the PARMs are near exclusively ganglioneuromas and ganglioneuroblastomas.22,23

**Cardiac rhythm abnormalities** Reduced heart-rate variability, decreased respiratory sinus arrhythmia, and cardiac asystoles have been noted in CCHS. Gronli and colleagues24 reported an association between the longest sinus pause on Holter monitoring and the most common PARM genotypes 20/25–20/27. Specifically, sinus pauses of 3 seconds or longer were least frequent in children with genotype 20/25 (0%), intermediate in children with the 20/26 genotype (19%), and longest in children with the 20/27 genotype (83%). Though not identified with the 20/25 genotype in childhood, instances of prolonged sinus pauses reported in cases of LO-CCHS with the 20/25 genotype may suggest an effect of long-standing intermittent hypoxia on this aspect of the CCHS phenotype.25

**Autonomic nervous system dysregulation** In addition to prolonged sinus pauses, additional symptoms of ANSD have been described in CCHS, including diminished gut motility in the absence of HSCR, attenuated temperature regulation including lowered body temperature and cool extremities, and eye irregularities including pupillary response to light and strabismus, among others.24,26–28

**Diagnosis**

CCHS is characteristically diagnosed in the newborn period with cyanosis and hypercarbia resulting from diminished tidal volumes and resultant hypoventilation, always in the absence of respiratory distress. Some patients demonstrate a shallow depth of breathing only during sleep, whereas others with more severe phenotypes will exhibit hypoventilation during both sleep and wakefulness. Individuals with CCHS will lack the physiologic and behavioral responsiveness to hypoxemia/hypercarbia19 and will not automatically adjust spontaneous ventilation or awaken from sleep. Breathing in non-REM sleep will be synchronous with the mechanical ventilator, but spontaneous breaths will be increased in REM sleep.11

Many patients presenting with LO-CCHS are identified only after exposure to an environmental trigger. LO-CCHS should be considered in patients who exhibit cyanosis, alveolar hypoventilation, or seizures after receiving sedation or anesthesia, or following a severe respiratory infection, or those who fail traditional sleep apnea therapy. Once CCHS or LO-CCHS is suspected, the stepwise genetic testing suggested herein should be followed to confirm a mutation within the PHOX2B gene (Fig. 3). While awaiting results of PHOX2B genetic testing, it is important for clinicians to rule out other causes of alveolar hypoventilation. Chest radiography, computed tomography (CT), magnetic resonance imaging (MRI), echocardiography,

![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.](image-url)
neurologic evaluation, and/or (potentially) muscle biopsy should be performed to rule out other disorders that might account for the hypoventilation and CCHS phenotype.

Following a \textit{PHOX2B} mutation–confirmed diagnosis of CCHS, the American Thoracic Society (ATS) 2010 Statement on CCHS recommends parental genetic testing (Fig. 4).\textsuperscript{5} Given the autosomal dominant inheritance pattern exhibited by the disorder, such \textit{PHOX2B} genetic testing is invaluable for anticipating the risk of recurrence in subsequent offspring (by identifying somatic mosaicism in a parent of CCHS probands) and identifying any asymptomatic parents with LO-CCHS. Spontaneous miscarriages have been reported in the literature in both affected and unaffected parents.\textsuperscript{9} In rare cases germline mutations may be carried by a parent and would not be detectable by current testing methods,\textsuperscript{29} hence the recommendation for prenatal testing with each pregnancy.

\textbf{ROHHAD}

\textbf{Etiology}

The condition now referred to as ROHHAD was first described in 1965 by Fishman and colleagues.\textsuperscript{30} In 2000, Katz and colleagues\textsuperscript{31} described an additional new case and summarized 10 prior cases in the literature of what was then termed “late-onset central hypoventilation with hypothalamic dysfunction.” The acronym ROHHAD was introduced by Ize-Ludlow and colleagues\textsuperscript{32} in 2007, with the aim of describing the phenotypic features in the order of typical timing of presentation and highlighting the rapid-onset weight gain (20–30 lb [9–13.6 kg] over a 3–6-month period) as a harbinger of the syndrome.

While significant advancements have been made in understanding the clinical presentation of the disorder, the etiology and pathogenesis of ROHHAD remain unknown. One current hypothesis that has been explored is an autoimmune or paraneoplastic basis for ROHHAD.\textsuperscript{33–35} However, such investigation has been limited to a handful of patients at varied stages of an evolving phenotype, making it difficult to determine the specific effect of the intervention. Likewise, no long-term follow-up has been provided in these reports. Though an intriguing concept, the hypothesis does not account for continued evolution of the ROHHAD phenotype after surgical neural crest tumor resection or for ROHHAD manifestations in the multitude of patients who never develop tumors of neural crest origin.

In recognition of the consistency in features of the ROHHAD phenotype, studies have been undertaken in attempts to identify the underlying genetic etiology. Such studies, limited by extremely

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\textbf{Fig. 4.} Algorithm to determine when and what type of \textit{PHOX2B} genetic testing should be performed in parents of CCHS proband. \textsuperscript{a} The \textit{PHOX2B} Sequencing Test does not identify low-level mosaicism.\textsuperscript{42} (From Weese-Mayer DE, Patwari PP, Rand CM, et al. Congenital central hypoventilation syndrome (CCHS) and \textit{PHOX2B} mutations. In: Robertson D, Biaggioni I, Burnstock G, et al, editors. Primer on the autonomic nervous system. 3rd edition. Oxford: Elsevier; 2012:448; with permission.)
small sample sizes, have thus far failed to identify any genetic variants related to the disorder.\textsuperscript{32,36,37} Identification of a case of monozygotic twins discordant for the ROHHAD phenotype raises the possibility of a more multifactorial or epigenetic basis for ROHHAD.\textsuperscript{38} Further research is needed to examine these concepts and to determine the underlying cause of ROHHAD.

**Overview of major features**

**Central hypoventilation** Individuals with ROHHAD have an evolving phenotype, especially in terms of the hypoventilation (Table 2). Initially they may have mild obstructive sleep apnea. Then, after surgical intervention with adenotonsillectomy, the child’s hypoventilation during sleep becomes more apparent. With advancing age, and often abruptly, the hypoventilation during sleep becomes severe enough to require artificial ventilation. In a subset of cases the children will advance to a need for continuous artificial ventilation as life support. Studies of formal control of breathing have not yet been published, although clinical care suggests attenuated physiologic response to hypercarbia/hypoxia and a lack of behavioral awareness of the compromise.

**Hypothalamic dysfunction** Rapid-onset obesity, with weight gain of 20 to 30 lb over a 3- to 6-month period, is the most prominent feature of the ROHHAD-related hypothalamic dysfunction. Subsequent hypothalamic defects can be encountered months or years after the initial symptom onset.

**Neural crest cell–derived tumors** Tumors of neural crest origin, typically ganglioneuromas or ganglioneuroblastomas in the chest or abdomen, can develop at any age in ROHHAD. However, most tumors are identified in the early stages of ROHHAD.

**Autonomic nervous system dysregulation** Individuals with ROHHAD experience symptoms of ANSD. These symptoms will be variably expressed and can develop throughout the clinical course.\textsuperscript{32}

**Diagnosis**

Diagnosis of ROHHAD is ascertained through an evaluation of the clinical presentation and progression of symptoms in suspected cases. Criteria for diagnosis include:

1. Rapid-onset obesity and the development of alveolar hypoventilation after the age of 1.5 years
2. Evidence of hypothalamic dysfunction as defined by 1 or more of the following findings: rapid-onset obesity, hyperprolactinemia, central hypothyroidism, disordered water balance, failed growth hormone stimulation test, corticotropin deficiency, or altered onset of puberty

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Percentage of ROHHAD cases\textsuperscript{a} with specific phenotypic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamic Dysfunction (%)</td>
<td>Respiratory Manifestations (%)</td>
</tr>
<tr>
<td>Rapid-onset obesity 100</td>
<td>Alveolar hypoventilation 100</td>
</tr>
<tr>
<td>Failed growth hormone stimulation test 60</td>
<td>Cardiorespiratory arrest 60</td>
</tr>
<tr>
<td>Hyperphagia 53</td>
<td>Reduced CO\textsubscript{2} ventilatory response 60</td>
</tr>
<tr>
<td>Hyperprolactinemia 47</td>
<td>Obstructive sleep apnea 53</td>
</tr>
<tr>
<td>Hypernatremia 47</td>
<td>Cyanotic episodes 27</td>
</tr>
<tr>
<td>Diabetes insipidus 33</td>
<td>Autonomic Dysregulation (%)</td>
</tr>
<tr>
<td>Hypothyroidism 33</td>
<td></td>
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<tr>
<td>Hypodipsia 27</td>
<td>Ophthalmologic manifestations 87</td>
</tr>
<tr>
<td>Adrenal insufficiency 27</td>
<td>Thermal dysregulation (hyper- or hypothermia) 73</td>
</tr>
<tr>
<td>Polyuria 27</td>
<td>Altered gastrointestinal dysmotility 67</td>
</tr>
<tr>
<td>Short stature 20</td>
<td>Altered perception of pain (often decreased) 53</td>
</tr>
<tr>
<td>Delayed puberty 13</td>
<td>Altered sweating 53</td>
</tr>
<tr>
<td>Hyponatremia 13</td>
<td>Cold hands and feet 40</td>
</tr>
<tr>
<td>Low IGF-1 and IGFBP-3 13</td>
<td>Bradycardia 33</td>
</tr>
<tr>
<td>Precocious puberty 13</td>
<td>Tumor of neural crest origin (ganglioneuroma and ganglioneuroblastoma) 33</td>
</tr>
</tbody>
</table>

*Abbreviations: IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein.

\textsuperscript{a} Percentages calculated from 15 cases with full phenotypic information available in Ize-Ludlow and colleagues.\textsuperscript{32} Data from Ize-Ludlow D, Gray J, Sperling MA, et al. Rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation presenting in childhood. Pediatrics 2007;120:182.*
3. Absence of a \textit{PHOX2B} mutation confirmed through genetic testing

Onset of obesity in ROHHAD typically precedes the central hypoventilation. As a result, differentiating ROHHAD from obesity-related hypoventilation can prove challenging for those with limited experience with such patients. ROHHAD remains a distinct clinical phenomenon, as evidenced by the persistence of central hypoventilation despite decreases in body mass in children with ROHHAD.

Even with heightened clinical suspicion, the variable constellation of symptoms in ROHHAD makes a conclusive diagnosis difficult, and necessitates a comprehensive physiologic evaluation. At a minimum, serial overnight polysomnography and awake physiologic recording should be performed to monitor signs of obstructive sleep apnea or central hypoventilation. It is further recommended to provide additional cardiac, endocrine, and oncologic evaluation from the outset of consideration of a ROHHAD diagnosis, with the aim of ensuring optimal outcomes for the patient. ATS recommendations for clinical evaluation in CCHS provide the current framework for ROHHAD testing.

**THERAPEUTIC OPTIONS**

Treatment of individuals with CCHS and ROHHAD ideally requires comprehensive testing and an integrated and multidisciplinary team with coordination among regional, national, and international providers (Tables 3 and 4). The diversity in \textit{PHOX2B} mutations and corresponding phenotypic diversity in CCHS, and the extreme rarity of ROHHAD, make it difficult to provide care that encompasses the many complex needs of individuals with CCHS or ROHHAD and, consequently, emphasizes the required involvement of centers with extensive experience with these disorders.

**CCHS**

**Central hypoventilation**

As the most prominent symptom, immediate recognition and provision of ventilatory support for the central hypoventilation in CCHS is imperative in optimizing the neurocognitive outcome for patients. All individuals with CCHS will require mechanical ventilation, but some children will only require support during sleep time (nap and night) whereas others will require round-the-clock artificial ventilation as life support. In infants and young children, ATS guidelines currently recommend positive pressure ventilation via tracheostomy. With the advent of \textit{PHOX2B} genetic testing, CCHS can be promptly diagnosed and a tracheostomy can be performed in the first weeks of life. The tracheostomy tube must be upsized with growth to ensure sufficient ventilation. Supportive ventilation with bilevel positive pressure via nasal or face mask and negative pressure ventilators can be considered in the older child. Diaphragm pacing is an excellent form of ventilatory support for the child requiring artificial ventilation awake and asleep, allowing for freedom from the mechanical ventilator when paced during wakefulness. In carefully selected patients, diaphragm pacing for sleep time may be a consideration, although removal of the tracheostomy tube is not guaranteed. Thoracoscopic implantation of the diaphragm pacemaker minimizes morbidity and mortality for the child with CCHS. Although more noninvasive means of ventilation such as mask ventilation have been described for use at all ages, current guidelines advise strongly against their use in children younger than 6 years because of the risk of facial deformity and unreliable ventilatory support during a time of significant neurodevelopment.

Annual, in-hospital physiologic monitoring and assessment of ventilatory needs should take place over a multiday hospitalization under the supervision of trained personnel. This testing should include evaluation of ventilatory needs during all stages of sleep, varying levels of exertion, and with and without mechanical ventilation. Testing should also assess the ventilatory response to physiologic challenges during wakefulness and sleep. At a minimum, continuous recording of respiratory inductance plethysmography, electrocardiography, hemoglobin saturation, pulse waveform, end-tidal carbon dioxide, sleep staging, blood pressure, and core body temperature should accompany the evaluation. The goal of such evaluation is to optimize ventilatory support and oxygenation during activities of daily living, with a focus on safety and positive developmental outcomes.

In cases of untreated LO-CCHS or in patients with insufficient oxygenation despite artificial ventilation, progression to right ventricular dilation, cor pulmonale, and polycythemia may occur. It is important, consequently, to perform annual echocardiograms to check for right ventricular hypertrophy/cor pulmonale and to monitor levels of hemoglobin, hematocrit, and reticulocyte counts to identify any early signs of polycythemia.

**Neurocognitive function**

It is expected that earlier identification and clinical intervention in CCHS cases, coupled with more standardized patient care, will lead to improved neurocognitive outcomes in CCHS. Neurocognitive testing should be performed annually.
Table 3
Recommended testing to characterize CCHS and ROHAD phenotypes

<table>
<thead>
<tr>
<th></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>
<th>Hypothalamic/Pituitary Axis Endocrine Testing</th>
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</thead>
<tbody>
<tr>
<td><strong>CCHS and LO-CCHS</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>PHOX2B</strong> Mutations</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>20/24–20/25 PARMs</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>20/26 PARMs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>x</td>
<td></td>
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<tr>
<td>20/27 PARMs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>20/28–20/33 PARMs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NPARNMs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>ROHAD</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviations: NPARM, non–polyalanine repeat expansion mutation; PARM, polyalanine repeat expansion mutation.

- Endocrine testing every 3–4 months from time of ROHAD diagnosis.
- Annual chest and abdominal imaging to identify ganglioneuromas and ganglioneuroblastomas.
- Chest and abdominal imaging and urine catecholamines every 3 months in first 2 years, then every 6 months until 7 years of age to identify neuroblastomas.
Hirschsprung disease
A rectal biopsy should be performed in all CCHS newborn patients presenting with failure to pass meconium, and barium enema or manometry in older patients with severe constipation, to identify or rule out HSCR. Treatment of HSCR involves surgical removal of the aganglionic segments of the colon, ideally in the first days or weeks of life, and intensive involvement by a team experienced in HSCR management.

Neural crest cell–derived tumors
Screening can include chest radiography or ultrasonography in infants, and chest and abdominal MRI or CT scans for older children and adults. A meta-iodobenzylguanidine scan can identify neuroblastomas in patients who are at highest risk for the development of such tumors (NPARMs). Tumors of neural crest origin are typically surgically resected, but the treatment plan is contingent on the type, size, location, and stage of the tumors.
**Cardiac rhythm abnormalities**

Patients with sinus pauses of 3 seconds or longer may require implantation of a cardiac pacemaker. Sudden death has been reported in CCHS for those with sinus pauses of 3 seconds or longer who have not received pacemakers.\(^{24}\)

**Autonomic nervous system dysregulation**

Improved characterization of ANSD can be achieved through more formal clinical assessment of ANS function including head-up tilt testing with cerebral regional blood flow, heart rate–deep breathing, Valsalva maneuver, thermoregulatory chamber sweat testing, and pupillometry, among other noninvasive tests. Most manifestations of ANSD can be managed on a per-symptom basis, and referred to appropriate specialists when necessary.

**ROHHAD**

**Central hypoventilation**

In approximately half of patients, ventilation is only required for use during sleep. Noninvasive positive airway pressure ventilation may be sufficient in such individuals. Another subset of the patient population will develop alveolar hypoventilation necessitating 24-hour mechanical ventilation via tracheostomy. Limited experience with diaphragm pacing in ROHHAD precludes specific recommendations.

Early identification and characterization of the respiratory deficit in individual patients remains a crucial facet of patient care in ROHHAD. In acknowledgment of the variable onset of symptomatic alveolar hypoventilation and the potential for its progressive nature in ROHHAD, routine assessment of ventilatory needs as part of a comprehensive examination of all affected systems is recommended to be provided every 4 to 6 months after initial onset of symptoms, and annually once they have stabilized. Respiratory evaluation should be inclusive of all parameters described herein for CCHS. Annual neurocognitive testing is further recommended to assess the intellectual function as a correlate to the efficacy of the clinical management of ventilatory needs, and provide an early indication of any neurologic decline.

**Hypothalamic dysfunction**

Obesity in ROHHAD is very difficult to manage, even with diet and exercise. Caution should be used during exercise, as individuals with ROHHAD are often fundamentally unable to meet increased respiratory demands arising from significantly increased levels of exertion. Given the variable presentation of the hypothalamic dysfunction in ROHHAD, care must be provided in conjunction with a pediatric endocrinologist to identify and treat hypothalamic abnormalities on a case-by-case basis and with advancing age. Special attention should be paid to hormonal levels, water balance, urine and plasma osmolarity, and any other issues arising from dysfunction in the hypothalamic/pituitary axis, all with advancing age.

**Neural crest cell–derived tumors**

Initial screening of patients through chest radiography and abdominal ultrasonography is recommended. Based on these results, more aggressive imaging including CT and MRI can be pursued to accurately identify the presence of ganglioneuromas and ganglioneuroblastomas. Tumors are typically surgically resected.

**Autonomic nervous system dysregulation**

ANSD within ROHHAD varies greatly as the phenotypic features seem to unfold with advancing age. Seventy-two hour Holter monitoring, electrocardiography, and echocardiography are recommended to check for any rhythm abnormalities or pathologic anatomy. Eye abnormalities such as pupillary dysfunction warrant regular ophthalmologic follow-up. Stool softeners can be used in the treatment of altered gut motility.

**Annual testing**

Successful management of these disorders requires regular follow-up and clinical assessment of the many manifestations of these diseases (see Table 3).

**CLINICAL OUTCOMES**

**CCHS**

If untreated, central hypoventilation can result in cardiorespiratory arrest, severe morbidity, and death. Increased recognition and diagnosis of CCHS, introduction of clinical PHOX2B testing, and modern techniques for home ventilation and monitoring with pulse oximetry and capnography have significantly improved the prognosis for affected individuals. With early clinical intervention and regular follow-up, individuals with CCHS are expected to achieve a high quality of life and a normal life span. Neonatally identified patients have graduated from high school and college, married, and maintained steady employment. Annual physiologic evaluation and screening for all features of the disease are integral to the success of patients with such disorders. Significant disability has been noted in individuals with CCHS who experienced long-term inconsistent or insufficient management of their condition, stressing the importance of regular evaluation and adjustment of management.
When undiagnosed or insufficiently managed, individuals with ROHHAD can progress to significant irreversible neurocognitive compromise or death. Diagnosis, however, only represents the first step in the ongoing care of affected individuals. Given the evolving nature of the disorder and its variable presentation of symptoms, frequent comprehensive evaluation of individuals with ROHHAD can allow for the anticipatory management of the unfolding phenotype and meet developing needs accordingly. Ongoing evaluation should be performed frequently in the early phases and then every 10 to 12 months thereafter. If treated expediently and adequately, individuals with ROHHAD can maintain a good quality of life with the potential to achieve above-average intellectual ability. The life span of individuals with ROHHAD is unknown, although anecdotal evidence for improved breathing during wakefulness with increasing age is certainly encouraging. Conversely, individuals who have not been identified promptly or who have had suboptimal ventilatory support are at increased risk of premature death.

COMPLICATIONS AND CONCERNS

CCHS

With advancements made in the early identification and improved management of the condition, individuals with CCHS are now surviving well into adulthood, bringing about a set of issues that merit concern and clinical consideration.

Alcohol and drug abuse

Use of depressants such as alcohol or other drugs can have potentially fatal consequences during wakefulness and sleep, particularly in the absence of artificial ventilation. Parents and patients should be counseled on the harms of their use. Similarly, caution should also be applied when administering prescribed medications with a respiratory depressant effect (including sedatives and anesthetics).

Pregnancy

Prenatal PHOX2B testing is recommended in any pregnancy in which the mother or father has been diagnosed with CCHS or a somatic mosaicism. Even when termination is not expected, prenatal testing can allow for adequate planning for the immediate care of a CCHS infant. Pregnancy poses specific risks to a mother with CCHS because the increased respiratory demand may exceed the ventilatory support. For women undergoing cesarean section who use diaphragm pacing, bilevel positive airway pressure ventilation or, potentially, intubation after delivery may be needed, as abdominal incisions may make diaphragm pacing too painful. During delivery and the postpartum period, all women with CCHS should be provided sufficient ventilatory support.

Breath-holding spells

As noted earlier, individuals with CCHS exhibit a loss of or an attenuated responsiveness to hypercarbia and hypoxemia. Concomitant with this loss of chemosensitivity in CCHS is the absence of "air hunger." Consequently, individuals with CCHS must not engage in risk-taking respiratory behaviors, including voluntary extended breath-holding spells or swimming.

ROHHAD

As ROHHAD is extremely rare and patients are only now surviving to adulthood, issues of alcohol or drug abuse and pregnancy have not yet been encountered. However, other psychosocial issues have been identified in the disorder.

Behavioral and mood disorders

Both behavioral and mood disorders have been reported in ROHHAD with mention of frequencies of approximately 31% and 16%, respectively, across 51 literature-reported cases in a recent case report. Increased anxiety, emotional lability, and psychosis have also been reported in a recent ROHHAD case report. Individuals exhibiting psychiatric symptoms should be referred to the appropriate health provider and treated accordingly. From the authors’ experience, the issues of behavior and mood were reported most typically in the earliest reports, and in the event of suboptimal artificial ventilation in more recent cases.

Developmental disorders

Developmental issues, as noted by low intelligence quotient (IQ) from neurocognitive testing, are most likely related to inadequate cardiorespiratory arrest intervention, as several patients with ROHHAD have above-average IQ. In addition, suboptimal ventilatory management may result in chronic intermittent hypoxia. Taken together, these risks underscore the value of early identification and clinical intervention to reduce the risk of neurocognitive decline.

Seizures

Seizures have been reported in a subset of individuals with ROHHAD. Seizures can occur secondary to hypoxemia resulting from inadequate ventilatory support, or hyponatremia or hypernatremia attributable to disordered hormonal secretion and the
accompanying electrolyte imbalances. Correction of these underlying causes, when appropriate, can help prevent additional seizures.

**SUMMARY**

Early clinical identification and intervention, along with regular surveillance of all clinical features as part of ongoing care, are paramount in ensuring that individuals with CCHS and ROHHAD maximize their neurocognitive potential and ability to lead stable, relatively normal lives. With the discovery of a genetic basis and the advent of diagnostic testing, significant strides have been made in the clinical management and understanding of CCHS/LO-CCHS. These advances highlight the potential value of an analogous discovery in ROHHAD, for which efforts are ongoing.

As disorders with phenotypic manifestations that span an array of medical systems and processes, CCHS/LO-CCHS and ROHHAD warrant specialized medical attention. Ideally this care should be provided at centers dedicated specifically to the care of individuals with these unique disorders, with continuous collaboration and coordination with regional providers. Such consolidation of principal care can allow for improved recognition and management of clinical symptoms of these disorders and, accordingly, improve outcomes for affected individuals.

To further aid with these efforts, registries have been established for both CCHS and ROHHAD. These secure online systems aim to consent and enroll all individuals internationally with CCHS and ROHHAD to systematically document their clinical development with advancing age. Such documentation allows for strengthened coordination and dissemination of novel developments related to the evolving understanding of the diagnosis and management of these disorders, and, accordingly, improve outcomes for affected individuals.

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**REFERENCES**


