Chapter 17
Congenital Central Hypoventilation Syndrome (CCHS)

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Case

This case is a former late preterm male infant born at 36 weeks and 5 days gestational age to a 36-year-old mother via *in vitro* fertilization. Pregnancy was complicated by maternal cholestasis of pregnancy, advanced maternal age, and fetal renal pelviectasis. At delivery, infant had presumed secondary apnea after crying vigorously and becoming apneic at 1 minute of life. After 30 seconds of bag-mask ventilation and suctioning, he was vigorous, but remained dusky requiring supplemental

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oxygen. He was admitted into the Neonatal Intensive Care Unit for presumed respiratory distress syndrome related to prematurity. The infant required high-flow nasal cannula support with low oxygen supplementation (up to 30% F_iO_2). At day two of life, he had one prolonged apnea event (at least 30 seconds duration) with a peripheral pulse oximetry-measured oxygen saturation (SpO_2) nadir of 40%, then subsequent bradycardia (heart rate (HR) less than 60 bpm) that necessitated chest compressions for 30 seconds and positive pressure bag-mask ventilation for 2 minutes, with "prompt" recovery. Infant was also given a loading dose of caffeine and had video electroencephalogram (with no documented seizure activity).

Besides his cardiorespiratory history, the infant's course was notable for lack of stool output within the first 48 hours of life and feeding intolerance. With the initiation of enteral feeding, he developed emesis and abdominal distension; moderate dilation of bowel loops were reported on radiographic evaluation. The infant underwent abdominal decompression with a Replogle tube and had a lower gastrointestinal tract contrast enema study to evaluate for stool retention or obstruction. The contrast study revealed a normal caliber rectosigmoid colon, no mucous plug, and the passage of a moderate amount of stool during the study. Rectal irrigations were initiated with minimal stool output and the infant was transferred to a pediatric hospital for the evaluation of possible Hirschsprung disease.

The infant remained on low-flow nasal cannula upon hospital transfer at one week of age. Upon arrival, his exam was notable for small but reactive pupils, comfortable breathing with intermittent mild desaturations (SpO_2 nadir 90%), mild abdominal distention with bowel sounds present, and low-normal central tone. His vital signs showed a broad range of HR, often higher than normal for age, with limited HR variability by beat-to-beat measure. His blood pressures were normal for age and he maintained normal core temperatures without supplemental heat.

Central venous access was obtained upon arrival at the quaternary care center, with the aim to provide nutrition while establishing enteral feeds. Two days after initiating enteral feeds, the patient developed abdominal distension that escalated with feeding advancement over the next 48 hours. A suction rectal biopsy confirmed the absence of ganglion cells, and the diagnosis of Hirschsprung disease. A laparoscopic leveling colostomy with mucous fistula was performed at the level of the descending colon/sigmoid colon junction. A gastrostomy tube was also placed, and postoperative rectal irrigations were resumed with enteral feedings. Attempts at oral feeding led to desaturation events (SpO_2 nadir 75%), likely due to poor coordination of suck/swallow and breathing patterns. A swallow study confirmed esophageal dysmotility. A genetic microarray was ordered to evaluate for genetic aberrations that might account for the infant's unique constellation of symptoms.

Serial evaluations of the infant's respiratory status throughout the admission indicated cardiorespiratory instability. Specifically, after initial hospital transfer on 1 LPM nasal cannula, the low level of support was removed and the infant exhibited frequent self-resolving desaturation events (SpO_2 nadir 75%) awake and asleep. The nasal cannula was resumed, and a polysomnography evaluation at term (40 weeks 6 days gestational age) was obtained due to the persistent nature of desaturations. The study was notable for 77 central hypopnea events per hour (Apnea-Hypopnea Index 79/h; normal for age is 15/h) and periodic breathing occupying approximately

50% of total sleep time (normal for age is 5%). The average desaturation index was 34/h and the lowest SpO_2 was 81%, though results were confounded by supplemental oxygen titration throughout the entirety of the study, helping to artificially maintain saturations greater than 90%. With the severity of the polysomnography results during 7.5 hours of overnight sleep, the infant was swiftly intubated and mechanically ventilated (SIMV pressure control, pressure support mode) as additional physiologic testing in keeping with the American Thoracic Society Statement on Congenital Central Hypoventilation Syndrome (CCHS) was completed.

At the onset of this evaluation and in discussions with the Molecular Diagnostics Laboratory about the patient's phenotype, preliminary analysis of the suggested microarray detected a heterozygous 369 kilobyte deletion on Chromosome 4p13 that included the full *PHOX2B* gene (4p12) and one neighboring gene on one allele. Consequently, the infant was evaluated for congenital neural crest tumors by chest radiograph evaluating along the sympathetic chain and abdominal/pelvis ultrasonography to evaluate for adrenal tumors, as well as urine catecholamines (to identify a neuroblastoma). Furthermore, 72-hour Holter recording to identify prolonged cardiac sinoatrial pauses was performed but with longest R-R interval 1.0 seconds. Because of the nature of the infant's *PHOX2B* mutation and recognition of an autosomal dominant inheritance pattern to CCHS and *PHOX2B* mutations, the proband's parents were tested with the Multiplex Ligation-dependent Probe Amplification (MLPA) dependent Probe Amplification (MLPA) *PHOX2B* test. It was determined the whole gene *PHOX2B* deletion was paternally inherited; linearly related relatives of the father and the proband are undergoing genetic testing to identify the generation source of the unique *PHOX2B* mutation with overt variable phenotype penetrance.

Discussion

Diagnostics

The paired-like homeobox gene 2B (*PHOX2B*), located on chromosome 4p, at 4p12, is the disease-defining gene for CCHS [1, 2]. CCHS-related *PHOX2B* mutations are heterozygous and diagnosis is confirmed by stepwise (also termed sequential) *PHOX2B* genetic testing (initially, the screening test, then if negative, sequencing test, and lastly if the prior tests are negative, deletion/duplication MLPA test). The *PHOX2B* allele has 20 alanines in exon 3 (normal genotype 20/20 indicating the number of alanines on each allele). This *PHOX2B* homeobox gene encodes a highly conserved transcription factor that determines neuron cell fate among sympathetic, parasympathetic, and enteric neurons of the autonomic nervous system. Additionally, *PHOX2B* has a key role in control of breathing by contributing to the formation of the retrotrapezoid nucleus which lies on the rostral surface of the medulla and contributes to central chemosensitivity [3].

A *PHOX2B* mutation is inherited in an autosomal-dominant fashion through germinal mutation or germline mosaicism (collectively 5–35% of infants) or as a *de*

novo mutation. Genetic testing for the most common *PHOX2B* genotypes is clinically available as a screening test and detects all polyalanine repeat expansion mutations (PARMs) (genotypes 20/24–20/33) (accounting for 90–92% of the CCHS cases) and large non-PARM (NPARM) deletions (primarily 35 and 38 base pair deletions), affecting the 20 alanine repeat regions of exon 3. Additionally, the screening test is the only clinically available test that will identify low level somatic mosaicism in the subset of parents who are affected. If the *PHOX2B* screening test is negative but the phenotype is convincing for CCHS, *PHOX2B* sequencing analysis is performed to identify smaller NPARMs (missense, nonsense, frameshift, or stop codon mutations); NPARMs will collectively account for 8–10% of CCHS cases. If the *PHOX2B* screening and sequencing tests are negative, deletion/duplication testing with MLPA is the next step to identify loss of the *PHOX2B* gene as well as potentially neighboring genes [4]. This was the case for the infant described above, he is heterozygous for a mutation involving the entire *PHOX2B* gene and a neighboring gene on one allele.

With clinical suspicion for the CCHS phenotype, genetic testing is used to confirm *PHOX2B*-CCHS-specific mutations. Since 1970, over 100 CCHS-causing *PHOX2B* mutations have been identified with ~2,000 cases confirmed and an estimated incidence of 1/200,000 live births; thus, CCHS is grossly underdiagnosed [3]. With established pediatric diagnoses, parental testing of children with CCHS is recommended to determine if mosaicism exists in either parent. Identification is essential for family planning and to address potential health risks of mosaic parents. In the presented case, the sibling and extended family members were then tested with the *PHOX2B* deletion/duplication MLPA test. Preimplantation genetics is a consideration for CCHS probands as well as mosaic parents. For pregnancies in which the fetus is known to have a *PHOX2B* mutation, and termination of the pregnancy is not a consideration, the infant can be delivered in a quaternary care medical center to ensure a smooth perinatal transition.

Phenotype

CCHS-related facial features include a boxy-shaped face, with a flattened profile and an overturned lateral one-third of the upper lip vermillion border such that it is flesh colored instead of pink, with the facies most easily identifiable among the more common heterozygous *PHOX2B* PARMs (Fig. 17.1) [4]. Children with the NPARMs additionally may have epicanthal folds and reduced movement of the lower one-third of the face. Strabismus, anisocoria, and altered pupillary responses to light stimulus are relatively common in CCHS.

Clinically, the hallmark feature of CCHS is central hypoventilation with markedly attenuated peripheral and central chemoreceptor responsiveness awake and asleep. Patients often have inappropriately elevated respiratory rates through infancy and persistently monotonous respiratory rates with diminutive tidal volumes and occasionally apnea. Children with severe CCHS phenotypes will demonstrate profound hypoventilation during quiet and exertional activity awake as well as during

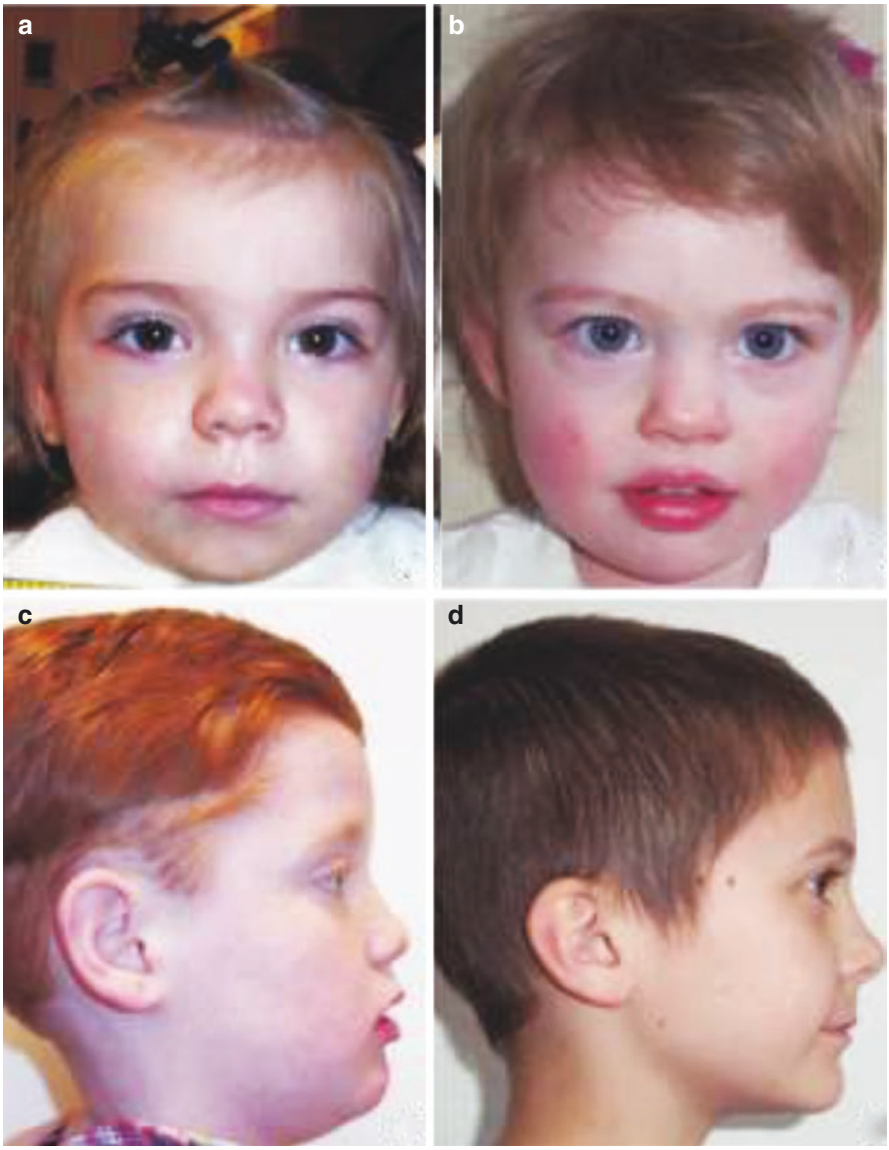


Fig. 17.1 Photographs of children with CCHS (**a** (20/25 genotype) and **c** (20/27)) and control subjects (**b**,**d**) matched for age, gender, and ethnicity. Children with CCHS have characteristic facial features including a boxy-shaped face that is shorter and flatter than matched controls, and the "lip trait" consisting of inflection of the lateral 1/3 of the upper vermillion border so it is flesh-colored instead of pink. (Reproduced with permission, Todd et al. 2006)

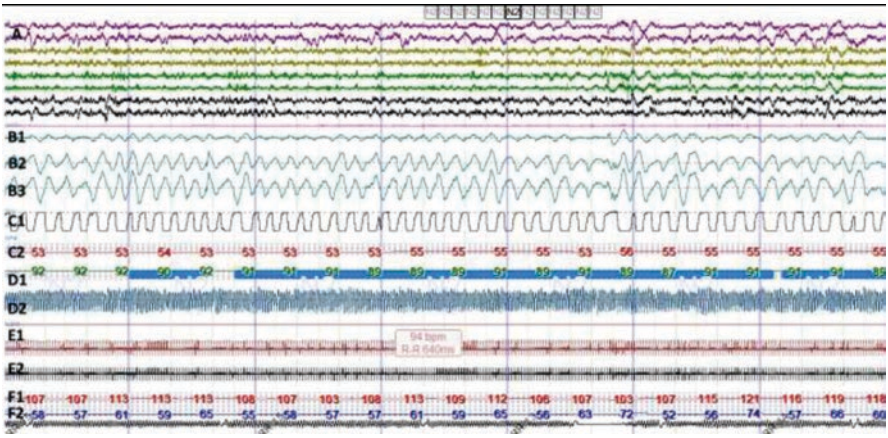


Fig. 17.2 Polysomnogram of patient with CCHS (20/27 genotype) during non-REM sleep and transiently without respiratory support to perform an intra-sleep spontaneous breathing trial. The montage in descending order consists of EEG and EOG tracings (A), respiratory inductance plethysmography bands (RIP; thoracic, abdominal, summation) (B1,B2,B3), end-tidal carbon dioxide waveforms and values (mmHg) (C1,C2), peripheral pulse oximeter value (%) and waveform (D1,D2), electrocardiogram (E1,E2), and finger probe blood pressure (systolic F1, diastolic F2) with the beat-to-beat waveform. Each epoch consists of 30 seconds denoted by the thickened vertical lines. The child demonstrated a central hypopnea without overt change in depth or rate of breathing despite the related hypercarbia and subsequent desaturations. Note the thoracic RIP band amplitude is diminished, while the continuous end-tidal carbon dioxide waveform shows regular breaths, without overt paradoxical inward movement of the chest on inspiration

sleep, though minute ventilation during rapid eye movement (REM) sleep tends to be "more normal" than in non-REM sleep primarily due to added spontaneous breaths. As in this infant, patients with CCHS typically have severely diminished chemoreceptor sensitivity and lack corrective efforts for normal gas exchange such as maintaining a regular respiratory rate and adjusting tidal volumes in the event of hypercarbia and hypoxemia (Fig. 17.2). Patients with CCHS consistently lack overt behavioral and perceived responses to hypercarbia and hypoxia such as dyspnea, complaint of headache, or sense of anxiety despite the physiologic challenges during awake activities of daily living. Additionally, children with CCHS do not awaken in response to hypercarbia and hypoxemia [5].

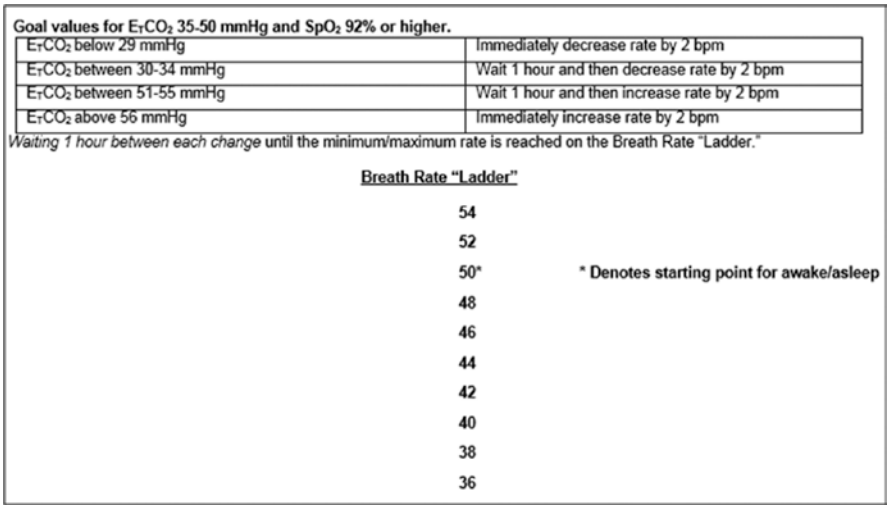
Further comorbidities of CCHS include Hirschsprung disease, esophageal and gastrointestinal dysmotility, and in the first year of life feeding intolerance as exemplified in the presented case. Patients with CCHS often demonstrate reduced HR variability, possibly due to a decrease in baroreflex sensitivity and sympathetic input, and prolonged cardiac sinoatrial pauses can occur. Children with CCHS are also at risk for neural crest tumors, most commonly neuroblastomas, ganglioneuromas, and ganglioneuroblastomas, although prevalence and type of tumor varies by *PHOX2B* genotype (neuroblastoma occurs in ~50% of children with NPARMs and ganglioneuroma and ganglioneuroblastoma occur in less than 5% of children with the longer PARMs (reports in 20/29, 20/30 and 20/33 genotypes). Patients with CCHS have reduced core and peripheral temperatures with attenuated circadian

variation, dampened temperature response to infection with rare febrile response, and elevated pain threshold [1]. Autopsy of two neonates with CCHS (one with a *PHOX2B* PARM (20/27) and one with an NPARM mutation (8 base pair deletion/frameshift)) revealed loss of noradrenergic nerve fibers in the cerebral nucleus locus coeruleus, thought to be associated with sympathetic activation. A murine model reproduced this finding in early onset *PHOX2B* NPARM mutations (8 base pair deletion; at less than 10.5 days embryologically) revealing a loss of functional locus coeruleus, abnormal adrenergic neurons, and absence of the retrotrapezoid nucleus, associated with chemoreceptor insensitivity [6].

Treatment and Surveillance

CCHS disease severity and morbidity varies by genetic mutation among the most common *PHOX2B* mutations. PARMs and NPARMs are well-described, while whole *PHOX2B* deletions resulting in potential haploinsufficiency (such as the case study above) and mosaicism have less defined phenotypes due in large part to their reduced incidence. In general, the longer PARM expansions, especially 20/27 and longer, and NPARMS have more severe phenotypes [7].

CCHS is typically diagnosed in the newborn period except for a subset of cases diagnosed after one month of age and sometimes not until adulthood (later-onset CCHS, LO-CCHS). Since the *PHOX2B* genetic mutation informs regarding the CCHS phenotype, it is essential to identify the specific mutation to allow for anticipatory management. CCHS is a life-long condition *without* expectation to "wean" a child from life support. After diagnosis and at hospital discharge to home, infants should have a portable mechanical ventilator and a back-up portable ventilator, a tracheostomy to provide a secure airway ideally with a tight-to-the-shaft cuffed tracheostomy tube (to minimize air leak asleep but allow for voice awake), a pulse oximeter that shows waveform and saturation value, a capnography monitor that shows the exhaled carbon dioxide waveform and actual value, and an experienced registered nurse with expertise in caring for an infant/child who is ventilator-dependent with a control of breathing deficit (as the child with CCHS will not show typical indicators of illness). The ATS Statement on CCHS advocates for diligent at-home monitoring with pulse oximeter and end tidal. Ideally, nursing should provide continuous one-on-one care when the infant or child is awake and asleep, attending to the continuously used monitors, making ventilator changes as needed accordingly, and providing immediate intervention in acute situations to sustain life support [8]. Use of custom ventilator management with clear guidelines for the parents and home care providers to adjust respiratory support according to monitor values at home (called the custom "ventilator ladder") has reduced need for hospitalization. For example, patients on mechanical ventilation via tracheostomy have varied gas exchange between different levels of activity and while awake or during sleep. Nursing or family members can respond to elevated carbon dioxide levels by following a prescribed "ladder" ventilator plan and increasing the respiratory rate. The case's respiratory plan and ventilator ladder are displayed in Fig. 17.3.



Goal values for E_TCO_2 35-50 mmHg and SpO_2 92% or higher.

E_TCO_2 below 29 mmHg	Immediately decrease rate by 2 bpm
E_TCO_2 between 30-34 mmHg	Wait 1 hour and then decrease rate by 2 bpm
E_TCO_2 between 51-55 mmHg	Wait 1 hour and then increase rate by 2 bpm
E_TCO_2 above 56 mmHg	Immediately increase rate by 2 bpm

Waiting 1 hour between each change until the minimum/maximum rate is reached on the Breath Rate "Ladder."

Breath Rate "Ladder"

54
52
50* * Denotes starting point for awake/asleep
48
46
44
42
40
38
36

Fig. 17.3 Example of custom mechanical "ventilator ladder" prescription for patient with CCHS described in case. The ladder provides guidance for parents, home nursing, and care providers to adjust ventilator settings in varied conditions (asleep, awake in varied levels of exertion) according to the child's continuously monitored end-tidal capnography values. E_TCO_2 end-tidal carbon dioxide, mmHg millimeters of mercury, bpm breaths per minute

Independent of genotype, the ATS recommends positive pressure ventilation through a tracheostomy for the first several years of life to ensure optimal gas exchange for well-being, growth, and development [8]. Neurocognitive outcome in patients with CCHS is variable, with mean full scale IQ scores one standard deviation below the norm (mean score is 100 and standard deviation is 15 points) [9]. It is not clear if this variation and reduced mean scores are intrinsic to CCHS, due to alteration in cerebrovascular autoregulation, or due to recurrent physiologic compromise, even with conservative management [10]. Therefore, in infancy and early childhood, physiologic evaluation awake and asleep should be performed at a minimum every six months in varied activities of daily living, in a controlled testing environment. This is particularly important with advancing age, growth, milestone achievements, and changes in activity levels and metabolic demands with varying gas exchange. Furthermore, these comprehensive in-laboratory/in-hospital evaluations are paramount as children with CCHS do not demonstrate behavioral changes to being under-supported with resultant hypoxemia or hypercarbia. Hence, comprehensive evaluations monitoring patient's autonomic functions and gas exchange with various activities awake and asleep are necessary to provide guidance with aim to offer the highest quality of life within the patient's physiologic capacity.

For the child with CCHS who is ventilator-dependent awake and asleep, phrenic nerve-diaphragm pacers are a consideration to allow for awake time mobility and improved quality of life [11]. For the child who requires respiratory support during sleep only, nasal or full face mask non-invasive ventilation might be a consideration,

although not until the child can take responsibility for replacing the mask such as after using the bathroom during the night and not until the child's facial features are adequately developed to prevent further facial flattening beyond the innate configuration of the CCHS face. Method of daytime and nighttime support varies by genotype and disease severity, patient age, airway structural maturity and integrity, the availability and quality of home health care, insurance coverage, the patient and family goals of care, and other factors. Most patients with short PARM mutations (20/24 and 20/25) have milder hypoventilation and require only nighttime support. With rare exceptions, patients with longer PARM and NPARM mutations require 24-h per day artificial respiratory support.

The aforementioned morbidities will need to be monitored as well. Semi-annually under 3 years of age and annually thereafter, a 72-h Holter monitoring to screen for cardiac sinoatrial pauses is recommended as the prevalence of 3 s or longer pauses is above 80% of patients with the 20/27 *PHOX2B* genotype. For patients with cardiac pauses ≥3 s, a bipolar cardiac pacemaker is typically recommended. Evaluation for neural crest tumors in patients with longer PARM mutations (20/28–20/33) is recommended every 6 months until age 3 years, then annually thereafter, including chest anteroposterior and lateral radiographs and abdominal/pelvic ultrasound to identify neural crest tumors (primarily ganglioneuroma and ganglioneuroblastoma). For patients with NPARMs, a chest X-ray and abdominal and pelvic ultrasound, potentially with urine catecholamines, should be performed initially every 3 months until age 3 years, and then every 6 months until at least age 7 (primarily evaluating for a neuroblastoma). Lastly, if the newborn has abdominal distension and failure to pass stool, consider biopsy for rectal ganglion nerve cells to evaluate for Hirschsprung disease with the risk of 20–30% occurrence in PARMs (20/26–20/33) and 50% or higher occurrence in patients with NPARMs [8].

Clinical Pearls

- Congenital central hypoventilation syndrome (CCHS) is caused by a mutation in the highly conserved *PHOX2B* gene, a gene essential to the embryologic development of the autonomic nervous system and intact control of breathing.
- CCHS-related *PHOX2B* mutations are heterozygous and include polyalanine repeat expansion mutations (PARMs) (90–92% of cases), non-PARMs (NPARMs) (8–10% of cases), and whole gene deletions (less than 1% of cases).
- The *PHOX2B* gene mutation and genotype allows for anticipatory management relative to disease severity and prevalence of morbidities.
- A principal feature of CCHS is diminished to absent central and peripheral chemoreceptor responsiveness awake and asleep, even in the children who seem to have adequate awake spontaneous breathing.

- On polysomnography, the patient with CCHS will demonstrate diminutive tidal volumes, monotonous respiratory rates (mildly elevated to normal for age), hypercarbia and hypoxemia without a physiologic or arousal response, and heart rate that is often elevated for age and with limited variability.
- Additional features of CCHS include cardiac sinoatrial pauses, Hirschsprung disease, esophageal and gastrointestinal dysmotility, and altered pupillary response to light. Although occurrence is rare overall, screening for neural crest tumors is imperative in children with longer PARMs and essential in patients with NPARMs in whom the tumor risk is close to 50%.
- For the first several years of life, the standard of care is continuous mechanical ventilation for 24 h a day via tracheostomy, except for the most mildly affected that will only require support asleep. Phrenic nerve diaphragm pacing for use during wakefulness in children who require continuous mechanical ventilation via tracheostomy is an effective means to improve quality of life.
- Patients are followed every 6 months until age 3 years and then annually thereafter with comprehensive in-hospital physiologic testing to ensure adequate oxygenation and ventilation during awake activities of daily living and sleep with adjustment of respiratory support as needed and to screen for anticipated comorbidities, with the ultimate goal of optimizing neurodevelopmental outcomes and quality of life.

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