

Review Article

Congenital Central Hypoventilation Syndrome: A Comprehensive Review and Future Challenges

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Congenital central hypoventilation syndrome is a disorder predisposed by a paired-like homeobox PHOX2B gene. A mutation in the PHOX2B gene is a requisite when diagnosing congenital central hypoventilation syndrome. This mutation is identified in 93–100% of diagnosed patients. The mutation regarding this disorder affects the sensors, the central controller, and the integration of the signals within the central nervous system. This, inter alia, leads to insufficient ventilation and a decrease in PaO₂, as well as an increase in PaCO₂. Affected children are at risk during and after the neonatal period. They suffer from hypoventilation periods which may be present whilst sleeping only or in more severe cases when both asleep and awake. It is important for clinicians to perform an early diagnosis of congenital central hypoventilation in order to prevent the deleterious effects of hypoxaemia, hypercapnia, and acidosis on the neurocognitive and cardiovascular functions. Patients need long-term management and appropriate ventilatory support for improving the qualities of their lives. This paper provides a detailed review of congenital central hypoventilation syndrome, a congenital disorder that is genetic in origin. We describe the genetic basis, the wider clinical picture, and those challenges during the diagnosis and management of patients with this condition.

1. Introduction

Congenital central hypoventilation syndrome (CCHS) or primary alveolar hypoventilation is a very rare worldwide disorder. Laboratories from the United States, France, Chile, Italy, Japan, Germany, China, Taiwan, The Netherlands, the UK, and Australia have now collectively diagnosed nearly 1000 cases by PHOX2B mutation-confirmed CCHS [1]. It is estimated that the actual prevalence is much higher due to the extreme clinical variability [2–4]. The male to female ratio is estimated to be 1:1 [5]. This syndrome is defined as a failure to automatically control breathing and is present since birth. Patients have absent or sluggish ventilatory sensitivities to hypercapnia and hypoxaemia when asleep and/or awake. When asleep especially, children with CCHS experience progressive hypercapnia and hypoxaemia and lack of the arousal responses and sensations of dyspnoea. It is a syndrome portraying inadequate respiratory responses to hypoxia and hypercapnia in the absence of a primary pulmonary, cardiac, metabolic, or neuromuscular disease or

an identifiable brainstem lesion [6]. It was first described in 1970 by Mellins and colleagues, and since then its relation to PHOX2B gene mutations has been described together with its association with disorders of neural crest origin like Hirschsprung's disease [7–10]. The literary misnomer “Ondine's curse” has been used in prior literature and is based on a mythical story where a mortal knight Hans betrays Ondine the mermaid. Poseidon, God of the Sea and father of Ondine, cursed Hans in such a way that his bodily functions would fail unless he was conscious of them. As a consequence Hans died of forgetting to breathe. This misnomer “Ondine's curse” should not be routinely used to refer to people with CCHS.

2. Genetic Abnormalities

The disease-defining gene for CCHS is the paired-like homeobox 2B gene (PHOX2B) [11–14]. Mutations in the PHOX2B gene have been identified in 93–100% of patients with CCHS

[15]. The PHOX2B gene codes a transcription factor and is important for normal autonomic nervous system development since autonomic nervous system neurons either fail to form or degenerate. This predisposes a range of autonomic aberrations in addition to the loss of ventilatory drive during sleep, resulting in reduced CO₂ and O₂ sensitivity [16]. Two types of mutations in this gene have been described: polyalanine repeat mutations (PARMs) have a variable clinical presentation and the disease's severity correlates with allele size and nonpolyalanine repeat mutations (NPARMS) which are usually associated with a more severe presentation including Hirschsprung's disease and an increased tumor risk [4, 17, 18]. Milder forms of CCHS are due to smaller PARMs and have also been described [19–21]. The more prevalent polyalanine expansion is a 7-alanine expansion [22, 23]. Expansions range from 15 to 39 nucleotide insertions and, as already mentioned, a genotype-phenotype correlation exists between the size of the expanded allele and the severities of the symptoms [24–26]. Unequal crossover has been speculated as the expanding mechanism [27]. These mutations mostly occur *de novo* during gametogenesis although in some cases there is a possibility of inheritance from parents with somatic mosaicism or constitutive mutation. The disease has an autosomal dominant mode of inheritance (with incomplete penetrance) [4, 28]. CCHS more commonly presents itself in neonates and later onset cases have occurred up to the age of 10 years [29]. So far there have been at least five cases of adult onset PHOX2B mutation associated with central hypoventilation syndrome [30].

3. Nervous System Abnormalities

PHOX2B codes a transcriptional factor responsible for regulating the expressions of genes involved during the development of the autonomic nervous system like TLX-2 and dopamine- β -hydroxylase. Increased polyalanine repeat expansion mutation in PHOX2B is associated with decreased transcription of these genes because of a missing transcriptional factor. This results in altered axonal projections, cellular injury, or impaired interactions between central nervous sites that regulate autonomic actions. Patients with CCHS have multiple disturbances of autonomic dysfunction with both sympathetic and parasympathetic components. The loss of ventilatory drive during sleep and reduced ventilatory sensitivity indicate dysfunctions of brainstem autonomic nuclei [31]. The broader range of symptoms indicates more widespread alterations. Functional MRI changes have been described in those areas that control the autonomic and chemosensory functions and which could be deficient in this condition [32–38]. Multiple brain sites in CCHS patients, including frontal, prefrontal, insular, and cingulate cortices, putamen and caudate nuclei, ventral, parietal, and temporal cortices, and cerebellar cortices, could have significantly reduced gray matter volume over time [31]. These reports on functional MRI changes must be interpreted with caution as they likely reflect bias due to small sample size, reported in the pre-PHOX2B era, without documentation of specific PHOX2B confirmation of CCHS in all subjects and data

presentation inclusive of subjects with CCHS and with other causes of hypoventilation.

Therefore, we cannot state that the injuries arise from the mutant PHOX2B gene. However, the reason for MRI changes might be more complex because the affected children are also exposed to intermittent hypoxia especially during sleep but occasionally in the day during periods of inactivity or elevated temperature. Such hypoxic exposures aggravate neural injuries [38–41]. In addition, impaired autonomic development affects brain perfusion due to impaired blood-flow regulation and this may also contribute to injury progression [31, 42–44]. Therefore, abnormal sympathetic patterns, together with increased and variable carbon monoxide levels, could be the reason for sustained cerebral vasculature changes [45].

Regardless of the etiology of patients with CCHS, have clinically apparent abnormalities in the autonomic regulation of blood pressure, cardiac rhythm, pain and anxiety perception, papillary reactivity, temperature regulation, gut motility, urinary retention, and more [46–51], many of these functions are regulated within the rostral brain areas, especially within limbic structures. Fluid regulation and thermoregulation are controlled in anterior hypothalamus. The anterior cingulate cortex regulates the voluntary initiation of urination. The next important abnormality arising from the central nervous system's dysfunction is the loss of perception regarding suffocation [52, 53]. Patients with CCHS do not feel drives of inspiration at low O₂ and high CO₂. The perception of dyspnea is regulated by the limbic areas including the amygdale, insular, and cingulate cortexes [54–56].

The mutations in PHOX2B are also expressed in the dorsal rhombencephalon, a region that gives rise to facial structures [57]. The typical CCHS face has been characterized as having a broad, flat, rectangular appearance. This face has a characteristic box-like appearance. There is also a distinctive pattern to the upper lip with the lateral edges of the vermilion line having inferior turning.

4. Ventilatory Disturbances

Poor integration of signals within brainstems explains the ventilatory disturbances in CCHS. The more significant respiratory disruption in children with CCHS is hypoventilation during sleep with preserved breathing frequency, reduced tidal volume, and minute ventilation [58]. It is also possible to have hypoventilation when awake. During REM sleep there is a significant cortical control of breathing and therefore the typical pattern of breathing is not as apparent as during NREM sleep when chemical control of breathing maintains respiration. Hypercapnia and hypoxaemia do not lead to arousal and awakening from sleep [59]. It is interesting that patients respond to exogenous hypercapnia during arousal. This indicates at least some functioning chemoreceptor activity [60]. Children with CCHS can hold their breath for a long period of time with no urge to breathe afterwards [61]. Another important characteristic of children with CCHS is their response to exercise when an abnormal increase in minute ventilation is seen up to the lactate threshold

but beyond this level it tends to lag, thus resulting in carbon dioxide retention and hypoxaemia. This response is accompanied by a lower increase in heart rate [62–64].

5. Clinical Picture

Most cases first come to light during the newborn period. Some infants do not breathe at birth and require assisted ventilation. The onset of hypoventilation after the newborn period (28 days after birth) is classified as late-onset CCHS.

The hypoventilation during wakefulness in infants is masked by their higher baseline respiratory rate. Therefore the hypoventilation is more apparent during sleep because of lack of insufficient respiratory drive. Infants require ventilatory support because of the longer time spent asleep and sudden transitions from wake to sleep. As they grow older, their baseline respiratory rate intrinsically declines and hypoventilation during wakefulness also becomes apparent.

Some infants only show their first symptoms at a later age by displaying a rigorous clinical picture that includes cyanosis, right-sided heart failure, and edema. It seems that these symptoms in infants have often been mistaken for congenital heart disease. Infants with less severe CCHS can display diaphoresis, cyanosis during sleep, and tachycardia. Others may have unexplained apnea, even die, and be categorized as having sudden infant death syndrome (SIDS) [65, 66]. Patients also have symptoms related to the autonomic nervous system abnormalities described earlier. The enteric nervous system may also be abnormal due to the defective migration of neural crest cells. Therefore about 15–20% of patients with CCHS also have Hirschsprung's disease. CCHS with Hirschsprung's disease is also known as Haddad syndrome [67]. Tumors may arise because of defects in neural cell development. Germline mutations of the PHOX2B are predisposed to neuroblastoma, which is found in about 5% of patients with CCHS. A triad of CCHS, Hirschsprung's disease, and neuroblastoma is known as neurocristopathy syndrome [68]. Mild cognitive and intellectual deficits due to anomalies in brain perfusion are also common [69]. Totals of CCHS-related symptoms are collated in Table 1.

6. Diagnosis and Management

Diagnosis of CCHS is exclusive. Infants may display thermal lability, have occasional hypotensive events, and are hypotonic. Other signs may be present that indicate a brainstem dysfunction like poor swallowing. No major diagnostic findings are present unless it is Hirschsprung's disease. If Hirschsprung's disease is present it is detected as gastroesophageal reflux and decreased intestinal motility patterns. In 70% of cases, abnormal pupils can be found that are miotic, abnormally responsive, or anisocoric.

CCHS is diagnosed in patients with no evidence of primary neuromuscular, lung, or cardiac disease or identifiable brainstem lesions which might be responsible for the symptoms [70]. Usually parents report shallow breathing during sleep and this is the most prominent characteristic. Ventilation is the most severely affected during sleep or while

TABLE 1: Totals of CCHS-related symptoms. The symptoms emerge from different organ systems and could be overlooked by the clinicians.

| | |
|---------------------------|---|
| Respiratory symptoms | Nocturnal hypoventilation and possible daytime hypoventilation Ability to hold breath for a long period of time and absence of air hunger afterwards |
| Cardiovascular symptoms | Arrhythmias Reduced heart rate variability Vasovagal syncope Syncope Cold extremities Postural hypotension |
| Neurologic symptoms | Developmental delay Seizures (primarily during infancy) Motor and speech delay Learning disabilities Altered perception of pain |
| Gastrointestinal symptoms | Hirschsprung's disease-related symptoms: dysphagia, constipation, and gastroesophageal reflux |
| Ophthalmologic symptoms | Nonreactive/sluggish pupils Altered lacrimation and near response Anisocoria, miosis, and ptosis Strabismus |
| Temperature instability | Altered perspiring Absence of fever with infections |
| Malignancies | Tumors of neural crest origin |
| Psychological | Decreased anxiety |

both awake and asleep and with absent perception of asphyxia and absent arousal.

Once the diagnosis of CCHS is considered blood should be sent for the PHOX2B screening test [71]. While awaiting the results of the test other causes of hypoventilation should be ruled out. Chest X-ray and potential chest CT, comprehensive neurological evaluation, potential muscle biopsy, and echocardiogram should exclude as a primary lung disease, ventilatory muscle weakness and cardiac disease. Seventy-two hours of Holter monitoring may determine aberrant cardiac rhythm abnormalities including decreased beat-to-beat heart rate variability [72]. Causative gross anatomic brain/brainstem lesions should be ruled out following a CT or/and MRI scan [73]. Inborn errors of metabolism should also be considered and a metabolic screen should also be performed. For those infants with associated symptoms of constipation a potentially full thickness rectal biopsy should be performed to diagnose Hirschsprung's disease [74]. Comprehensive autonomic testing to assess autonomic nervous system function may include tilt testing, deep breathing, thermal stressors, pupillometry, and more. Comprehensive ophthalmologic testing should determine the nature of ophthalmologic involvement.

Patients with CCHS need ventilatory management. CCHS cannot be resolved spontaneously and does not

respond to pharmacologic therapy [1]. Therefore chronic ventilatory support is necessary for these patients. Positive pressure ventilators via tracheostomy, bilevel positive airway pressure, negative pressure ventilators, and diaphragm pacing should be considered [75–80]. In order to ensure optimal oxygenation and ventilation beginning in the first days of life and to provide optimal neurocognitive outcome, positive pressure ventilation via tracheostomy is recommended during the first crucial years of life. Portable positive pressure ventilator via tracheostomy is the most common method of providing home mechanical ventilation in CCHS [81]. In order to provide an optimal neurocognitive outcome, noninvasive ventilation for stable patients should not be a consideration in conservative management until 6 to 8 years of age at the earliest. Today electronic home positive pressure ventilators are commercially available and are relatively portable. A tracheostomy is required for access and as the patient grows the tracheostomy tube must be upsized. A second ventilator in the home may prevent emergency admission in the event of ventilator failure and a power generator should be provided in the event of a power failure. Every 12–24 months bronchoscopy should be performed to allow for early diagnosis of granulomas or other airway abnormalities.

Noninvasive intermittent positive pressure ventilation is delivered via a face mask using bilevel positive airway pressure [78]. Bilevel ventilators are smaller and easier to use; tracheostomy is not required, but they are not life-supporting machines. Moreover bilevel ventilation should not be used during the day as the mask may limit daily activities and social interaction. It is also important to emphasize that the mask may cause mid-face hypoplasia when introduced from infancy or early childhood [82]. Therefore a bilevel positive airway pressure via a face mask is not a primary method of support and may be introduced later in the life of a patient with CCHS.

Negative pressure ventilators apply a negative pressure outside the chest and abdomen with the help of a chest shell, wrap, or portable tank for expanding the chest. There are several limitations to this system including difficulty sleeping in the supine position, portability (not battery operated), skin irritation, and a sense of feeling chilled. Only a limited number of children after 6 to 8 years of age have been successfully transitioned from positive pressure ventilation via tracheostomy to negative pressure ventilation without tracheostomy [1].

Diaphragmatic pacing operates through a battery-operated external transmitter which generates a train of pulses which are transmitted via an external antenna [83]. The antenna crates a signal which is communicated to the subcutaneously implanted receivers bilaterally. The subcutaneous receivers provide an electrical current that transmits to the phrenic nerve electrodes. The electrical stimulation of the phrenic nerve causes diaphragmatic contraction. In general diaphragmatic pacing is provided in active children during daily activities. It allows freedom and is portable. At night positive pressure ventilation via tracheostomy is still recommended because diaphragmatic pacing without tracheostomy can result in upper airway

occlusion. Furthermore the system does not have any associated alarms and if the components fail, then the results for the patient can be devastating.

Recently a novel device has been introduced that can acquire real-time data from a pulse oximeter and display it on an android tablet [84]. This device collects data from a pulseoximeter and monitors blood oxygenation throughout the night. It was built to wake up a patient and the caregiver of a patient with CCHS during nighttime hypoventilation events if they occur. If the saturation falls below safety levels, the device starts to stimulate the patient in order to wake him/her up. This is achieved by means of an air fan, a vibrating pillow, and a buzzer. The components of this device are shown in Figure 1. An alarm activates and wakes up the supervisor in order to deal with the situation and then wakes up the patient if required. So far this system has only been tested on healthy volunteers and during the next step, which is still going on, it is to be introduced within the volunteering family of a CCHS patient. It is because this device continuously monitors the dynamics of blood saturation with oxygen, there is a small chance of a false alarm during the night. Furthermore the system works independently from the intrinsic alarm in the ventilatory machine and therefore provides a double security during the nighttime. Moreover the caregivers who usually go to sleep with the awareness that someone else's life depends on them have reported a reduction in anxiety and stress. Further planned testing will investigate the possibilities of customizing the system's configuration for different kinds of patients and their evolving situations.

Long-term management of patients with CCHS requires close monitoring of growth and development, careful periodic ophthalmologic evaluations, high suspicions of infections because of impaired ability to sense hypoxia, regular echocardiography, limitation of sporting to moderate activity and noncontact sports, screening for Hirschsprung's disease, monitoring after sedation and anesthesia, and advising abstinence from alcohol. Taken altogether, CCHS is a prototypical example of transitional and translational medicine. It represents the success of collaboration between clinicians and basic scientists.

The long-term outcome is variable. Children do not outgrow the need for ventilatory support during sleep and remain technologically dependent all of their lives. The first years of life are connected with the greatest need for medical attention.

7. Conclusion

CCHS is a rare and complex disorder that involves alterations in the mechanisms of ventilatory control and autonomic dysfunction. For many years the etiology of this disorder was misunderstood and genetic typization was unknown. Today we understand the etiology of this rare disorder and we can discover the relevant symptoms much earlier. The improved quality of life for these patients may be attributed to wider recognition of such a disorder, specialized centers for treating such children, and improved technology and monitoring throughout life.

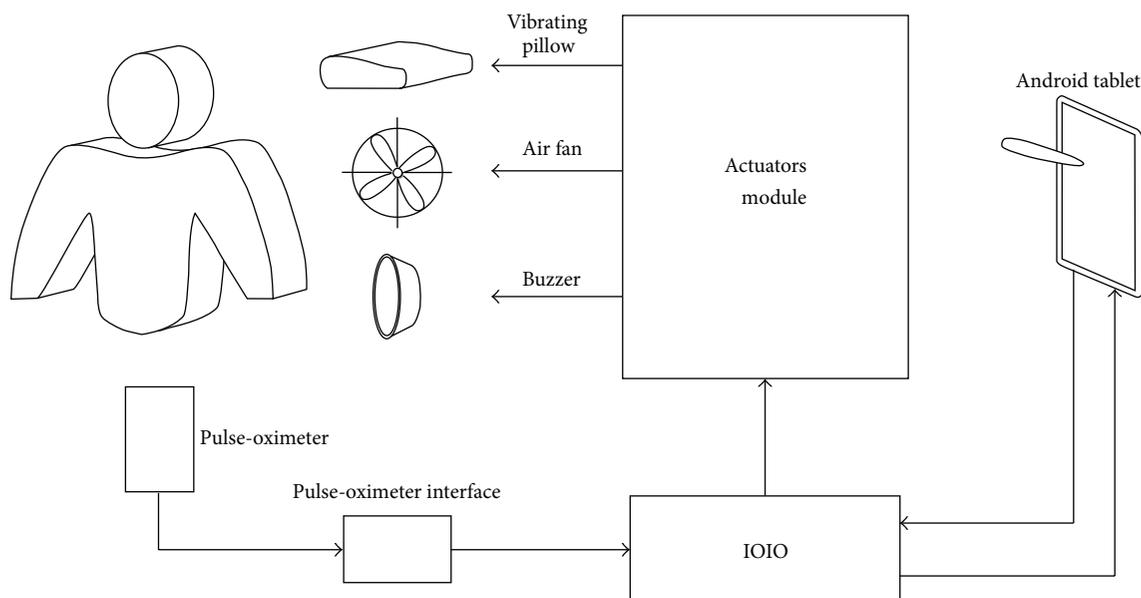


FIGURE 1: The device for nocturnal controlling of CCHS patients.

Conflict of Interests

The authors declare that there would be no conflict of interests regarding the publication of this paper.

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