

CLINICAL ASPECTS OF CONGENITAL CENTRAL HYPOVENTILATION SYNDROME (ONDINE'S CURSE): A REVIEW

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ABSTRACT

CCHS, or Congenital Central Hypoventilation Syndrome, is a disorder of the central nervous system where, most dramatically, the automatic control of breathing is absent or impaired. A CCHS child's respiratory response to low blood oxygen saturation (hypoxia) or to CO₂ retention (hypercapnia) is typically sluggish during awake hours and absent, to varying degrees, during sleep, serious illness, and/or stress. Congenital central hypoventilation syndrome should be considered in children with episodic or sustained hypoventilation and hypoxemia in the first months of life without obvious cardiopulmonary or neuromuscular disease. Most patients breathe normally while awake but hypoventilate during sleep. Ondine's or Undine's curse is a very rare medical condition characterized by respiratory arrest during sleep. This rare form of apnea may require a patient to be on a ventilator to ensure that the patient is able to breathe while sleeping. Many cases are congenital, with symptoms emerging shortly after birth, although the condition can also be acquired as a result of severe trauma to the brain, as seen in traumatic brain injuries, strokes, and some types of brain tumours. One problem with Ondine's curse is that it is so rare that a doctor may not recognize it immediately, which can result in delays in care. In the present article, we have concentrated on congenital central hypoventilation syndrome; its sign, symptoms, clinical indications, causes, pathophysiology, frequency, mortality, morbidity, diagnosis, prognosis, treatments, as well as consultations required. The aim of present article is to provide in depth knowledge about various clinical aspects of Congenital Central Hypoventilation Syndrome.

Keywords: Ondine's Curse, Undine's Curse, congenital central hypoventilation syndrome, CCHS, primary alveolar hypoventilation, respiratory arrest.

INTRODUCTON

Ondine's Curse is a respiratory disorder that is fatal if untreated. Persons afflicted with Ondine's curse classically suffer from respiratory arrest during sleep. Persons who have CCHS get it at birth, or develop it due to severe neurological trauma/damage to the brainstem. The diagnosis may be delayed because of variations in the severity of the manifestations or lack of awareness in the medical community, particularly in milder cases¹. This very rare and serious form of central sleep apnea involves an inborn failure of autonomic control of breathing. About 1 in 200,000 live born children have the condition. In 2006, there were only about 200 known cases worldwide. In all cases, episodes of apnea occur in sleep, but in a few patients, at the most severe end of the spectrum, apnea also occurs while awake. A person's gender or race is not a determining factor when dealing with susceptibility to CCHS. Males and females are both affected equally and a person's ethnicity, as of this point, has not been coincided a variable to the disease. The term Ondine curse gained wide acceptance to denote congenital central hypoventilation syndrome in infants and children. The term has recently fallen out of favour. Children with congenital central hypoventilation syndrome have progressive hypercapnia and hypoxemia when asleep, particularly during light and deep sleep and, to a lesser extent, during rapid eye movement (REM) sleep. Unfortunately, patients with congenital central

hypoventilation syndrome also lack an arousal response to hypoxemia and hypercapnia. However, ventilation can be adequate while the patient is awake.

Sign, symptoms and clinical indications of Ondine's curse

Ondine's Curse is associated with respiratory arrests during sleep and, with incomplete penetrance, neuroblastoma (tumours of the sympathetic ganglia), Hirschsprung disease (partial agenesis of the enteric nervous system), dysphagia (difficulty swallowing), anomalies of the pupilla, etc. The clinical presentation of patients with congenital central hypoventilation syndrome may vary and depends on the severity of the hypoventilation disorder. Some infants do not breathe at birth and require assisted ventilation in the newborn nursery. Most infants with congenital central hypoventilation syndrome who present in this manner do not spontaneously breathe during the first few months of life but may mature and have a pattern of adequate breathing during wakefulness over time; however, apnea or central hypoventilation persists during sleep. This apparent improvement over the first few months of life is believed to result from normal maturation of the respiratory system (e.g., improved respiratory mechanics, postnatal development and compensation) and does not represent a true change in the basic deficit in respiratory control. Other infants may present at a later age, with cyanosis, edema, and signs of right heart failure as the



first indications of congenital central hypoventilation syndrome. These symptoms in infants have often been mistaken for those of cyanotic congenital heart disease; however, cardiac catheterization reveals only pulmonary hypertension.

Infants with less severe CCHS may present with tachycardia, diaphoresis, and/or cyanosis during sleep. Presumably, if the diagnosis is not made, right heart failure develops as a consequence of repeated hypoxemic episodes during sleep. Still others may present with unexplained apnea or an apparent life-threatening event, or some may even die and be categorized as having sudden infant death syndrome (SIDS). Thus, the wide spectrum of severity in clinical manifestations dictates the age at which recognition of congenital central hypoventilation syndrome takes place. Increased awareness of this unusual clinical entity and a comprehensive evaluation of every patient are critical for early diagnosis and appropriate intervention. Sleep-dependent hypoventilation in the absence of neuromuscular, heart, or lung disease is the hallmark of congenital central hypoventilation syndrome. The severity of hypoventilation varies considerably. In severe cases, hypoventilation is also present during wakefulness. Late-onset central hypoventilation syndrome has also been described. Patients with congenital central hypoventilation syndrome have an absent or blunted ventilatory response to sustained hypercapnia. They also have a depressed ventilatory response to sustained hypoxia.

Patients with congenital central hypoventilation syndrome have disorders of central hypoventilation syndrome does not differ from controls, the relative increase above the mean heart rate at rest and with exercise is attenuated and heart rate variability is decreased. Children with congenital central hypoventilation syndrome exhibit an increased frequency of arrhythmia, primarily sinus bradycardia and transient asystole, with documented pauses as long as 6.5 seconds in congenital central hypoventilation syndrome compared with 1.4 seconds in controls. Children with congenital central hypoventilation syndrome exhibit lower blood pressure values during wakefulness and higher blood pressure values during sleep, indicating attenuation of the normal sleep-related blood pressure decrement. The enteric nervous system may also be abnormal; about 15-20% of patients with congenital central hypoventilation syndrome also have Hirschsprung disease. Mild intellectual or cognitive deficits are also common². Neural crest-derived tumours such as neuroblastoma are autonomic nervous system (ANS) control, with abnormalities in heart rate, blood pressure, and pupil diameter control. Although baseline heart rate in persons with congenital present in about 5% of patients with congenital central hypoventilation syndrome. The *PHOX2B* gene is speculated to be the first gene for which germ line mutations can be shown to predispose to neuroblastoma³. In 1978, the co-occurrence of

Hirschsprung disease and central hypoventilation was named Haddad syndrome and was later expanded to include neuroblastoma, a triad currently known as the neurocristopathy syndrome⁴.

Physical symptoms

Unless Hirschsprung disease is present, no major diagnostic findings are present upon physical examination; in most cases, only subtle manifestations are present. Infants may be hypotonic, display thermal lability, and have occasional and sudden hypotensive events that are unexplainable based on the surrounding circumstances. These manifestations usually improve over time.

Gastroesophageal reflux and decreased intestinal motility with constipation are often present in younger patients. Ocular findings (e.g., abnormal pupils that are miotic, anisocoric, or abnormally responsive to light) can be found in 70% of cases. Abnormal irides (60% of cases); strabismus (50% of cases); and, on occasion, lack of tears during crying, can also be found. Thus, referring children with congenital central hypoventilation syndrome for a thorough ophthalmologic evaluation is important. In congenital central hypoventilation syndrome, ventilation is most severely affected during quiet sleep, the state in which automatic neural control is predominant. Ventilatory patterns are also abnormal during active sleep and even during wakefulness, although to a milder degree. The severity of respiratory dysfunction may range from relatively mild hypoventilation during quiet sleep with fairly good alveolar ventilation during wakefulness to complete apnea during sleep with severe hypoventilation during wakefulness. Other signs indicative of brainstem dysfunction, such as poor swallowing, may be present but are not essential to diagnose of congenital central hypoventilation syndrome. Congenital central hypoventilation syndrome is diagnosed in individuals with the following:-

- ❖ Hypoventilation with absent or negligible ventilatory sensitivity to hypercarbia and absent or variable ventilatory sensitivity to hypoxemia.
- ❖ Generally adequate ventilation while awake, but hypoventilation with normal respiratory rate and shallow breathing (diminished tidal volume) during sleep.
- ❖ Hypoventilation both while awake and asleep
- ❖ Absent perception of asphyxia (i.e., absent behavioural awareness of hypercarbia and hypoxemia) and absent arousal
- ❖ No evidence of primary neuromuscular, lung, or cardiac disease or identifiable brain stem lesion that might account for the constellation of symptoms

A *PHOX2B* mutation is required to confirm the diagnosis of congenital central hypoventilation syndrome.



Causes

PHOX2B is the main disease-causing gene for congenital central hypoventilation syndrome, an autosomal dominant disorder with incomplete penetrance. Secondary central hypoventilation syndrome may result from other conditions or occurrences (e.g., brainstem tumour or other space-occupying lesions, vascular malformations, CNS infection, stroke, neurosurgical procedures to the brain stem). Correlations with genotype and phenotype have been described in patients with congenital central hypoventilation syndrome. An association with the number of *PHOX2B* repeats and the number of ANS dysfunction symptoms and the severity of respiratory disorders have been reported.

Patients with congenital central hypoventilation syndrome who develop malignant neural crest-derived tumours have either a missense or a frame shift heterozygous mutation in the *PHOX2B* gene. Therefore, a subset of patients with congenital central hypoventilation syndrome who are at risk for developing malignant tumours may be identified. Ondine's curse is exhibited typically as a congenital disorder, but in rare circumstances, can also result from severe brain or spinal trauma (such as after an automobile accident, stroke, or as a complication of neurosurgery). Long and Allen⁵ reported the abnormal brainstem auditory-evoked responses in an alcoholic woman who recovered from Ondine's curse. These investigators hypothesized that their patient's brainstem was poisoned, but not destroyed, by her chronic alcoholism. Medical investigation of patients with this syndrome has led to a deeper understanding of how the body and brain regulate breathing on a molecular level. *PHOX2B* can be associated with this condition⁶⁻⁸.

Pathophysiology

Remarkable progress has been made in the last couple of years in determining the genetic basis of congenital central hypoventilation syndrome and in recognizing that this disordered respiratory control syndrome actually represents a more global phenomenon of autonomic nervous system (ANS) dysregulation. A genetic defect for congenital central hypoventilation syndrome has been speculated because of its occurrence in certain families, suggesting a codominant Mendelian inheritance of a major gene. The disease-causing gene for congenital central hypoventilation syndrome is the paired like homeobox gene *PHOX2B*. Therefore, a mutation in the *PHOX2B* gene is required for the diagnosis of congenital central hypoventilation syndrome. Approximately 90% of individuals with the congenital central hypoventilation syndrome phenotype are heterozygous for a polyalanine repeat expansion mutation (PARM); the normal allele has 20 alanines, and the affected allele has 24-33 alanines.

The remaining 10% have a non-PARM mutation such as missense, nonsense, or frame shift⁹. *HOX2B* is located on chromosome 4p12 and was initially identified in mice

deficient in *PHOX2B* that died in utero with absent ANS circuits. The specific mutation appears to be a polyalanine repeat expansion in the second polyalanine repeat sequence in exon 3 of *PHOX2B*. *PHOX2B* gene codes for a transcriptional factor responsible in regulating expression of genes involved with development of the autonomic nervous system, such as dopamine- β -hydroxylase, *PHOX2A* and *TLX-2*. Some studies have shown that increased polyalanine repeat expansion mutation has been associated with decreased transcription of these genes. Over 90% of patients with congenital central hypoventilation syndrome have an increased polyalanine repeat expansion sequence in the *PHOX2B* gene, ranging from 24-33 alanines. Normally, this region of the gene contains a 20-alanine repeat sequence. The most common polyalanine repeat expansion sequences among patients with congenital central hypoventilation syndrome are 25, 26, and 27. Studies have shown a relationship between the number of expansion and the need for continuous ventilatory support.

Individuals with 25-polyalanine repeat expansion mutation rarely require 24-hour ventilatory support, those with 26-polyalanine repeat expansion mutation have a variable need for ventilatory support during the awake time periods based on their activity levels, and those with 27-33-polyalanine repeat expansion mutations require 24-hour ventilatory support.

Individuals with nonpolyalanine repeat expansion mutations also tend to require 24-hour ventilatory support. Mild and late onset congenital central hypoventilation syndrome has been associated with 24-polyalanine and 25-polyalanine repeat expansion mutations¹⁰. Certain polyalanine repeat expansion mutations, such as 24 and 25, have an autosomal dominant inheritance with incomplete penetrance¹¹. Therefore, the degree to which family members of individuals with congenital central hypoventilation syndrome may have evidence of respiratory control dysfunction remains uncertain. One report of 3 asymptomatic parents of children affected with congenital central hypoventilation syndrome and found to carry the same *PHOX2B* expansion mutations showed one parent with significant sleep anomalies and two without¹². However, many family members have some derangement in ANS function. Vertical transmission has been reported in at least 5 women, and symptoms of ANS dysfunction in families are prevalent. Approximately 20% of all reported congenital central hypoventilation syndrome cases are accompanied by Hirschsprung disease. The association of these 2 relatively rare clinical entities suggests a possible common pathogenetic basis. A disturbance of cardiac autonomic regulation in congenital central hypoventilation syndrome, may indicate the possibility of *PHOX2B* genotype in relation to the severity of dysregulation, predict the need for cardiac pacemaker, and offer the clinician the potential to avert sudden death¹³.



Frequency, mortality and morbidity

United States

Congenital central hypoventilation syndrome is a very rare disorder with an estimated prevalence of 1 case per 200,000 live births¹⁴. The introduction of clinically available molecular genetic testing for *PHOX2B* mutations has revealed that congenital central hypoventilation syndrome is not as rare as previously considered. Current estimates are likely an underestimate.

International

Nearly 1,000 children worldwide have *PHOX2B* mutation-confirmed congenital central hypoventilation syndrome. However, some feel that this number is likely underestimated. The clinical outcome of children with congenital central hypoventilation syndrome has markedly changed since the description of the disorder. In the past, most patients presented with neurocognitive deficits of varying severity, stunted growth, cor pulmonale, and/or seizure disorders; however, early diagnosis and institution of adequate ventilatory support to prevent recurrent hypoxemic episodes clearly offers the potential for improved growth and development and should be associated with normal longevity.

Mortality is primarily due to complications that stem from long-term mechanical ventilation or from the extent of bowel involvement when Hirschsprung disease is present. Nevertheless, stressing that the characteristic central hypoventilation during sleep is a life-long symptom is important. Neural crest tumours have also been associated with congenital central hypoventilation syndrome. Therefore, the prognosis depends on adequate treatment of the underlying tumour.

Diagnosis and Prognosis

Children with Congenital Central Hypoventilation Syndrome develop life-threatening episodes of apnea with cyanosis, usually in the first months of life. Medical evaluation excludes lesions of the brain, heart, and lungs but demonstrate impaired responses to build-up of carbon dioxide (hypercapnia) and decreases of oxygen in the circulation (hypoxia), the two strongest stimuli to increase breathing rate. Polysomnography shows that hypoventilation is most marked during slow-wave sleep. In the most severe cases, hypoventilation is present during other nonrapid eye movement sleep stages and even wakefulness. A subset of CCHS patients are at very high risk for developing malignant neural crest derived tumours, such as neuroblastoma. The sequence of *PHOX2B* reveals mutations in 91% of the cases¹⁵. As in many disorders that are very rare, an infant with this unusual form of sleep apnea suffers from the probability that their physician has most likely never seen another case and will not recognize the diagnosis. In some locations, such as France, optimal management of patients, once identified, has been aided by the creation of a national registry and the formation of a network of centers.

Overall, the prognosis of patients with congenital central hypoventilation syndrome is excellent if the diagnosis is prompt and medical management is appropriate; however, neurocognitive deficits of varying severity, stunted growth, cor pulmonale, and/or seizure disorders are frequent in older patients who may not have benefited from prompt recognition or intervention. Survival into adulthood is increasingly reported¹⁶. Although rare, cases of long-term untreated CCHS have been reported¹⁷.

Possible Treatments, Care and Management

Patients generally require tracheotomies and lifetime mechanical ventilation on a ventilator in order to survive. However, it has now been shown that Biphasic Cuirass Ventilation can effectively be used without the need for a tracheotomy. Most people with congenital Ondine's curse do not survive infancy, unless they receive ventilatory assistance during sleep. An alternative to a mechanical ventilator is Phrenic Nerve Pacing/diaphragm pacing¹⁸.

Medical Care

Congenital central hypoventilation syndrome (CCHS) is a lifelong condition. A multidisciplinary approach to provide for comprehensive care and support of every child is needed.

General measures

Infants with congenital central hypoventilation syndrome may have significant hypotonia and temporary feeding difficulties. In addition, moderate-to-severe gastroesophageal reflux is frequently present. Initiate early administration of prokinetic agents and antireflux medications in patients with hypotonia, temporary feeding difficulties, and gastroesophageal reflux; furthermore, begin nasogastric feeding to provide adequate nutrition. More radical approaches (e.g., percutaneous gastrostomy tube feeding insertion, antireflux surgical procedures, or both) may be necessary if these problems are severe or persistent.

Respiratory stimulants

Attempts to enhance the respiratory stability and promote eucapnia in patients with congenital central hypoventilation syndrome failed when pharmacologic approaches were used. Trials with doxapram in 2 infants and with the carotid body stimulant almitrine bismesylate in 13 patients did not show consistent improvements in spontaneous ventilatory or gas-exchange parameters. Therefore, respiratory stimulants have no current role in the treatment of congenital central hypoventilation syndrome.

Invasive mechanical ventilatory support

To date, most centers that provide long-term home care for children with congenital central hypoventilation syndrome use positive-pressure ventilation through a permanent tracheotomy. The types of positive-pressure ventilators used in the home vary among centers and



have gradually evolved, reflecting the dynamic needs of the population of patients with congenital central hypoventilation syndrome and the technical developments in the field. Ventilators should be used in the spontaneous intermittent mandatory ventilation (SIMV) mode. Because an uncuffed tracheostomy should be used to minimize granuloma formation, ventilator settings should compensate for air leaks around the tracheostomy tube by increasing volume and peak airway pressure as necessary.

Pressure plateau ventilation is suggested to be a useful alternative in home mechanical ventilation of children with congenital central hypoventilation syndrome who are not receiving adequate ventilation with standard volume ventilation using demand compressor ventilators. More recently, transition from invasive mechanical ventilation to nasal mask ventilation has been reported in patients with congenital central hypoventilation syndrome who are older than 7-8 years and who were nocturnally dependent on the ventilator. One study showed that mask ventilation can be safely commenced at an early age in children affected with congenital central hypoventilation syndrome. It is not only effective but is the preferred mode of ventilatory support by parents and patients, and even children who are established on other modes of ventilatory support can also be successfully weaned on to mask ventilation within a short period¹⁹.

Diaphragm pacing

Daytime diaphragm pacing in children with congenital central hypoventilation syndrome provides greater mobility than mechanical ventilation²⁰.

Thus, candidates for diaphragm pacing are potentially ambulatory patients who require ventilatory support 24 h/d via tracheostomy and who do not exhibit significant ventilator-related lung damage. Diaphragm pacer settings must provide adequate alveolar ventilation and oxygenation during rest and daily activities. Long-term outcome appears good, especially quality of life²¹. Aside from cost, potential discomfort may be associated with surgical implantation and possible need for surgical revisions because of pacer malfunction. Diaphragm pacing requires increased level of fitness of the diaphragm. This is achieved by gradually increasing the length of time the child is paced. Most children can tolerate approximately 12-14 hours of pacing per day. Despite these limitations, most parental reports regarding diaphragm pacing are favourable. Development of a quadripolar electrode offers several advantages that primarily include greater durations of diaphragmatic pacer support at diminished risk of phrenic nerve damage, decreased diaphragmatic fatigue, and optimization of pacing requirements during exercise. Therefore, as equipment improves, the need to replace components is lessened. Deciding on the most appropriate type of ventilatory support requires referral to specialized centers with personnel experienced in diaphragm pacing.

Pharmacologically induced restoration of the defective ventilatory response to hypercapnia was reported in two patients with congenital central hypoventilation syndrome, which indicates that a very potent progestin such as desogestrel could reverse the *PHOX2B* mutation²².

Surgical Care

Surgical interventions include traditional procedures. Tracheostomy may be indicated for ventilatory support. Colostomy is sometimes required when Hirschsprung disease is present. When feeding problems arise, particularly during infancy, gastrostomy tube placement with or without antireflux procedures may be required. Usual postoperative follow-up care for these procedures is necessary but does not differ from the care needed by any other patient. Diaphragmatic pacing should be considered in appropriate patients.

Consultations

The diagnostic evaluation of patients with congenital central hypoventilation syndrome requires a multidisciplinary approach involving many specialists.

- **Neurologist:** Consultation with a paediatric neurologist is recommended in the evaluation of hypotonia or seizure activity (seizures can occur in some children with congenital central hypoventilation syndrome spontaneously or as a result of acute hypoxia). Nerve conduction studies, electromyography (EMG), muscle biopsy, auditory-evoked potentials, EEG, and imaging studies of the CNS may be necessary.
- **Cardiologist:** Evaluation by a cardiologist is suggested to exclude any cardiac involvement.
- **Gastroenterologist:** Evaluation by a gastroenterologist is suggested to rule out bowel hypo- motility, to evaluate for gastroesophageal reflux, and to assist in management of Hirschsprung disease.
- **Ear, nose, and throat (ENT) specialist:** Evaluation by an otolaryngologist is suggested for tracheostomy evaluation, surgery, and regular postoperative and long-term care.
- **Social worker, speech therapist, respiratory therapist, and other health care specialists:** Evaluation by these specialists is suggested to provide multidisciplinary care and follow up.
- **Child behaviour specialist:** Periodic developmental assessment by a child behaviour specialist is suggested.

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