REVIEW

Cardiovascular Abnormalities and Arrhythmias in Patients with Ondine's Curse (Congenital Central Hypoventilation) Syndrome

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MOVAHED, M. R., ET AL.: Cardiovascular Abnormalities and Arrhythmias in Patients with Ondine's Curse (Congenital Central Hypoventilation) Syndrome: A Review. *Patients with congenital central hypoventilation syndrome (CCHS) (Ondine's curse syndrome) have impaired autonomic control of ventilation with intact voluntary control of respiration. Autonomic dysfunction and cardiac abnormalities are common in CCHS. Bradyarrhythmias are life-threatening and often require pacemaker insertion. We presented a case of a patient with CCHS suffering from long sinus pauses requiring cardiac pacemaker insertion. Patients with CCHS are at risk for pulmonary hypertension and cor pulmonale secondary to chronic hypoxia. Diaphragmatic pacing has been beneficial in some patients with CCHS. In this article, we review concomitant cardiac abnormalities and the occurrence of bradyarrhythmias in patients with CCHS. (PACE 2005; 28:1226–1230)*

bradyarrhythmias, Ondine's curse, congenital central hypoventilation syndrome, cardiac abnormalities, pacemaker

Definition and Underlying Pathophysiology

Congenital central hypoventilation syndrome (CCHS) is a heterogeneous disorder presenting with impaired autonomic control of ventilation. Ondine was a female water sprite who fell in love with a knight and married him. Once he became unfaithful to her, he was condemned to stay awake in order to breathe. If he fell asleep, he would forget to breathe and die. This legend remarkably matches the CCHS, thus giving the name of Ondine's curse to this disorder. It usually presents with adequate ventilation while awake and diminished respiratory effort during sleep.[1–3] The incidence of this disorder is thought to be approximately 1 in 50,000 live births.[4] Children with this condition lack perception of dyspnea, but voluntary control of breathing is intact.[5] During exercise they are at risk for hypoxia and hypercapnea.[6] Most severely affected children have hypoventilation both during sleep and while awake. Autonomic dysfunction is the underlying pathophysiological abnormality in these patients. It is diagnosed in the absence of primary neuromuscular, cardiac, lung or brain abnormalities. There are many other organ system abnormalities associated with this syndrome, including the cardiovascular system which is the focus of this review. CCHS is generally thought to be secondary to insensitivity of the central chemoreceptors to carbon dioxide or abnormal central integration of chemoreceptor input. However, these children respond to hypercapnea with arousal suggesting that some chemoreceptor function is intact. The most probable mechanism of CCHS is a brainstem lesion in the area where input from chemoreceptors are integrated.[3] Most of these patients require mechanical ventilation early in childhood and some benefit from diaphragmatic pacing.[7–11] Few patients have late onset of the disease. Noninvasive ventilation has been successful in some patients.[12–14] The course of this disease is variable. Some patients survive into adulthood, but frequently need multiple hospitalizations and lifelong ventilatory support.[15–17] There are familial cases reported and genetic abnormalities have been found in patients with CCHS.[18–25] Genetic abnormalities involve mutation in a polyalanine tract of PHOX2b.[26–29]

Associated conditions are related to dysfunction of autonomic nervous system with involvement of ganglia. There are many primary concomitant illnesses with this syndrome such as gastroesophageal reflux, seizure disorder, Hirschsprung's disease, neuroblastoma, ophthalmologic abnormalities and developmental delay. Autonomic dysfunction is widespread and includes sporadic profuse sweating episodes, esophageal dysmotility, diminished pupillary light response, poor

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temperature regulation, lack of fever with infections, and abnormal tearing.

Cardiovascular abnormalities are present in many patients with CCHS and are thought to be secondary to chronic hypoxia or autonomic dysfunction. Autonomic dysfunction results in diminished heart rate variability, recurrent syncope, cardiac arrhythmias and asystole, requiring pacemaker insertion.[30] Secondary disorders are related to hypoxia such as pulmonary hypertension and cor pulmonale.[30–34] A comprehensive list of the associated disorders is reported by Vanderlaan et al.,[30] listing 59 comorbid conditions in patients with CCHS. It is important to realize that the clinical presentation of CCHS is quite variable and dependent on the severity of the disorder.[35] Some infants may require assisted ventilation initially but may mature to a level of adequate breathing during wakefulness, which is thought to be secondary to maturation of respiratory systems.[36] Others may present at a later age with hypoxia, cyanosis, and right heart failure as the first symptoms of CCHS and some may present with unexplained apnea and life-threatening event.[35]

Table I.

Reported Cardiovascular Abnormalities in Congenital Central Hypoventilation Syndrome (CCHS) or Ondine's Curse Syndrome[18,30,50]

	Number of Patients in Percent
Recurrent fainting episodes	12–25%
Cardiac arrhythmias	22–39%
Cardiac pacer	4–6%
Cor pulmonale/pulmonary hypertension	17–78%
Blurred vision with standing	14%
Decrease heart rate variability	55%
Vasovagal syncope	13%
Cold finger and toes	14–43%
Dizziness	14%
Postural hypotension	7%
Paroxysmal hypertension	4%
Raynaud	4%
No nocturnal BP dipping	90%

Cardiac Abnormalities

Autonomic Dysfunction and Cardiac Arrhythmias

Autonomic dysfunction has been reported in many patients with CCHS. Autonomic regulation of respiratory and cardiac function occurs simultaneously. Abnormal hypothalamic function[28] as a regulator of respiratory and cardiac function can partially explain this connection. Many patients with autonomic dysfunction present with abnormal heart rate variability affecting the low- and high-frequency components.[37–43] Furthermore, abnormal heart rate beat-to-beat variability has been demonstrated in patients with this disorder.[38,39] An increased ratio of low-frequency to high-frequency band spectral power and transient asystolic episodes have been seen in these patients.[38,39] In a series of 56 patients with CCHS, the following disorders were noted: 31 patients with heart rate variability, 22 with dysrthmia, 13 with vasovagal syncope, 12 with loss of consciousness, 8 with cold fingers and toes, 8 with dizziness, 4 with postural hypotension, 2 with altered vascularity of the face, 2 with paroxysmal hypertension and 2 with Raynaud (see Table I).[18]

Some patients have attenuated heart rate response to exercise.[25,44] Interestingly, by using spectral analysis, the low-high frequency spectra ratios decreased in sleep, but was similar in both control and CCHS groups during wakefulness.[43] Silvestri et al. found significant baseline low heart rates in patients with CCHS and higher rates of long sinus pauses up to 6 seconds in patients with CCHS undergoing broncoscopy, in comparison to the control.[45] Although these episodes resolved spontaneously, it was severe enough to alarm the anesthesiologist. Close monitoring of these patients for bradyarrhythmias is recommended during bronchoscopy. Aberrant neural response to cold pressor challenges has been documented in CCHS patients affected by abnormal PHOX2B gene.[42] The percentage of time in respiratory sinus arrhythmia, which is a signal of normal regulation of autonomic nervous system, is significantly decreased in CCHS patients.[1] This phenomenon, together with decreased breath-to-breath variability during spontaneous breathing while asleep, is an indicator that the autonomic control of the cardiorespiratory system is impaired. This is thought to be a basic pathophysiology of this disorder.

Other concomitant disorders of autonomic dysfunction are severe constipation, profuse sweating, abnormal pupillary function, and decrease in body temperature. Furthermore, autonomic crisis has been described in patient with CCHS, with or without elevation of urinary catecholamines.[46] Abnormal findings of neuronal loss of the reticular, ambiguous nuclei, and dorsal motor nuclei of the vagus nerve support the structural abnormalities involving the autonomic nervous system.[47]

Autonomic dysfunction can present with neurally-mediated syncope[48] which is most likely secondary to baroreflex abnormalities. Baroreflex

sensitivity was reduced by one-third in comparison to matched control.[41] The autonomic dysfunction could progress to a more severe form of cardiac arrhythmias with overreaction to medications such as propofol causing complete heart block[49] or it can present with long sinus pauses and asystole.[45] Some patients will require pacemaker insertion. In a series of 32 patients with CCHS, the predominant arrhythmias were sinus bradycardia and transient asystole. Heart block and sick sinus syndrome occurred in two patients requiring permanent cardiac pacemaker insertion.[50] In a larger survey of 196 patients with CCHS, cardiac pacing was required in 4.1% of the patients.[30] However, underlying rhythm abnormalities leading to pacemaker insertion was not reported. Significant abnormalities in dopamine turnover is consistent with abnormal catecholaminergic neuronal activity.[15] We presented a case report of a patient with CCHS who required a cardiac pacemaker insertion in addition to a diaphragmatic pacemaker due to multiple episodes of long sinus pauses later in life. A summary of the described cardiovascular abnormalities of reported cases can be seen in Table I.

Blood Pressure Abnormalities

Autonomic dysfunction causes blood pressure dysregulation in CCHS. Nocturnal dipping in systolic blood pressure is impaired with lower baseline blood pressure while awake and higher blood pressures during sleep with reduced nocturnal blood pressure dipping with high frequency in these patients.[51] Trang et al. measured continuous blood pressure in the supine, head-up tilt, and standing positions. Blood pressure levels were preserved at rest but failed to overshoot after standing in response to orthostatic stimulation. This suggests vagal dysfunction and baroreflex failure with relatively preserved vascular sympathetic function.[37] The baroreflex abnormalities and low baseline blood pressure could partially explain recurrent fainting spells that occurs in 25% of these patients.[36] Postural hypotension has been found to occur in 7% and paroxysmal hypertension in 4% of patients with CCHS.[18] This is consistent with dysregulation of blood pressure control (Table I).

Right Heart Failure and Cor Pulmonale

Many patients with CCHS can develop severe hypoventilation and hypoxia, especially during sleep. This could lead to pulmonary hypertension and cor pulmonale. Clinical presentation of CCHS is quite variable. Some children may present at a later age with hypoxia, cyanosis, and right heart failure as the first indications of CCHS.[35] Infants with less severe CCHS can present with tachycardia, diaphoresis, and cyanosis during sleep which could lead to pulmonary hypertension and cor pulmonale.[44,52] Weese-Mayer et al.[50] reported 78% incidence of cor pulmonale which can lead to right heart failure[35] and can be mistaken as cyanotic heart disease. In a large survey of 196 patients with CCHS, cor pulmonale was found in 16.8% of the patients. These studies suggest a high prevalence of this condition in patients with CCHS.[30] However, Oren et al. found that cardiac complications such as heart failure mostly occurred early in the course of this disease and resolved with correction of inadequate mechanical ventilation.[15] This suggests that early recognition and treatment of CCHS could reverse hypoxic-induced heart failure.

Comparison to Obstructive and Central Sleep Apnea

Sleep-related disorder of ventilation, the so-called obstructive or central sleep apnea, can occur in children and adults and resembles CCHS, which cause hypoxia during sleep. However, these sleep disorders are not congenital and are mostly secondary to airway obstruction during sleep or central apnea secondary to concomitant disorders involving heart or central nervous system. Obstructive sleep apnea (OSA) is one of the most common respiratory disorders affecting 1–2% of children[53–55] and 2–4% of adults.[56,57] In children, it is thought to be secondary to adenotonsilar hypertrophy, craniofacial malformation, anatomical narrowing of the upper airway, reduced airway tone, neuromuscular disorder, and obesity.[53] Adenotonsillectomy is curative in most patients.[58] Children at high risk for OSA are those with Down syndrome, achondroplasia, mucupolysaccharosis, premature infants, and spina bifida.[53] The apneas in this disorder is secondary to airway obstruction and should be differentiated from CCHS. Central sleep apnea (CSA) is an acquired sleep disorder that usually occurs in adults and is not a single disease but present as the final pathway in a large group of heterogeneous disorders. It is characterized by apneic events during sleep with no associated ventilatory effort.[59] It usually occurs in patients with congestive heart failure, nasal obstruction, neurological or inflammatory disorders affecting the brain stem, obesity, and idiopathic.[60] However, there is substantial overlap between OSA and CSA.[61] There is a clear relationship between sleep apnea and cardiovascular disease. These abnormalities include cor pulmonale and systemic and pulmonary hypertension. Cardiac arrhythmias are very common with a prevalence of 58% and include sinus arrest, AV blocks, tachyarrhythmias, and atrial fibrillation.[56,62–64] Increase sympathetic tone and cycle variation in blood pressure and heart rate are thought to be the reason for increase prevalence of coronary

artery disease, congestive heart failure, and stroke in this population.[56,62,65] Treatment with continuous positive airway pressure ventilation or correction of anatomical obstruction has been shown to decrease the risk of arrhythmias and cardiovascular disease.[58,66,67] On the other hand, cardiac pacing in OSA patients presenting with significant bradyarrhythmias has shown to reduce apnea episodes.[68–71]

Conclusion

There is a wide spectrum of severity in the clinical manifestation of CCHS. There are over 50 concomitant disorders that can occur with this syndrome. Most cardiovascular abnormalities are related to autonomic dysfunction and can present with life-threatening bradyarrhythmias and asystole. Pulmonary hypertension and right heart failure are common complications secondary to chronic hypoxia. Comprehensive evaluation of every patient with CCHS is important for early diagnosis and appropriate treatment of significant cardiac abnormalities. We agree with the American Thoracic Society[1] that 24-hour Holter monitoring should be performed every 12 months or with the occurrence of syncope or dizziness in order to detect long sinus pauses and asystole. Early recognition of significant bradyarrhythmias should prompt the clinician to consider permanent cardiac pacemaker insertion. CCHS should be differentiated from OSA, which is caused by airway obstruction during sleep.

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