American Thoracic Society
MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

Idiopathic Congenital Central Hypoventilation Syndrome

Diagnosis and Management

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, FEBRUARY, 1999

OBJECTIVES

1. To improve general knowledge regarding idiopathic congenital central hypoventilation syndrome (CCHS), with recognition that because of the rarity of CCHS, many practitioners have not seen a case and therefore do not make the diagnosis in a timely manner.
2. To minimize time delays between onset of clinical symptoms and the diagnosis of CCHS, thereby decreasing initial health care costs and minimizing exposure to significant asphyxia and the development of cor pulmonale.
3. To familiarize practitioners with available diagnostic and treatment options, home health care options, and long-term outcomes. Because there may not be an intrinsic risk of neurodevelopmental sequelae due to CCHS, normal neurologic outcome should be achievable assuming that a timely diagnosis can be made and the infant managed appropriately so as to avoid acute and chronic asphyxia. Because mortality in CCHS appears to be primarily related to acute or chronic asphyxia, optimal long-term ventilatory and tracheostomy care (acute asphyxia) and prevention of cor pulmonale (due to chronic asphyxia) can minimize this risk.
4. To identify available referral options for state-of-the-art diagnosis and treatment, including resources for long-term evaluations. Access to a sleep laboratory that evaluates children is not sufficient. Infants with CCHS need to be evaluated in pediatric referral centers that have expertise in this category of abnormality both from the diagnostic and treatment perspectives, and have the interest and expertise to provide and/or coordinate the long-term follow-up.
5. To recognize the important concepts about respiratory control and state-related cardiorespiratory and autonomic function that can be learned from the care of children with CCHS.

BACKGROUND FROM WHICH TO INTERPRET THE STATEMENT

General Information

Idiopathic congenital central hypoventilation syndrome (CCHS) is a rare entity with approximately 100 published cases, typically in case report format. Current records indicate roughly 160-180 living children with CCHS worldwide, but these numbers are considered to be an underestimate. CCHS is diagnosed in the absence of primary neuromuscular, lung, or cardiac disease, or an identifiable brainstem lesion. It is characterized by generally adequate ventilation while the patient is awake but alveolar hypoventilation with typically normal respiratory rates and shallow breathing (diminished tidal volume) during sleep (1). Although not unique to CCHS, these patients will occasionally demonstrate apneic pauses after discontinuation of mechanical ventilation and before initiation of spontaneous breathing. More severely affected children hypoventilate both while awake and asleep. While asleep, children with CCHS experience progressive hypercapnia and hypoxemia (1-18). Their ventilation is better in rapid eye movement sleep than in non-rapid eye movement sleep (2). They have absent or negligible ventilatory sensitivity to hypercarbia and absent or variable ventilatory sensitivity to hypoxemia during sleep (1-16). They lack an arousal response to the endogenous challenges of isolated hypercarbia, hypoxemia, and to the combined stimulus of hypercarbia and hypoxemia (1). Awake ventilatory responsiveness to hypercarbia and hypoxemia is generally absent (l-3, 19), as is the perception of asphyxia (i.e., behavioral awareness of hypercarbia and hypoxemia), even when awake minute ventilation is adequate. Conditions associated with CCHS include Hirschsprung disease (1, 6, 7, 15, 17, 20–25), ganglioneuroma (26), neuroblastoma (15), ganglioneuroblastoma (1, 7, 8), lack of heart rate variability (1, 7, 27, 28), and eye abnormalities (1, 29), including diminished pupillary light response. Feeding difficulty with esophageal dysmotility in infancy, breath-holding spells, poor temperature regulation with the basal body temperature typically < 37" C, and sporadic profuse sweating episodes with cool extremities have been described anecdotally. Children with CCHS lack perception of dyspnea but maintain conscious control of breathing (30) (i.e., ability to "take a big breath" when asked). During exercise these children may be at risk of hypercarbia and hypoxemia, although the degree of exercise and the severity of the CCHS likely impact on the response for each child (31-33). Perception of anxiety is also decreased among children with CCHS (34). To the best of our knowledge CCHS is a lifelong diagnosis, with several patients entering early adulthood. Also to the best of our knowledge, these patients demonstrate continuing abnormalities in control of breathing and need for lifelong ventilatory support.

Existing Impediments to Optimal Diagnosis and Management

Owing to the rarity of CCHS, many practitioners have not seen a case and therefore do not make the diagnosis in a timely manner. Further, practitioners often provide ongoing care commensurate with that of a chronically ventilated child, without attending to the unique needs of the child with CCHS. Finally, limitations of financial resources imposed by health care providers often prevent these children from receiving optimal evaluation and long-term care in pediatric referral cen-

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ters that have expertise in CCHS both from the diagnostic and treatment perspectives, and have the interest and expertise to provide and/or coordinate the long-term follow-up. The introduction of a written Statement from the ATS has the potential for increasing the knowledge base of the practitioner, minimizing delays in diagnosis, standardizing the initial evaluation and subsequent management, and optimizing the outcome of these special children by tailoring their care to their individual needs.

RECOMMENDATIONS FOR DIAGNOSIS AND MANAGEMENT

Typical Presentation and Initial Evaluation

Children with CCHS typically present in the newborn period. Presenting symptoms include a period with duskiness or cyanosis on falling asleep; oxyhemoglobin saturation decreases while the carbon dioxide level rises, yet no increase in breathing frequency occurs, and the infant may not awaken. While some infants appear to have diminutive chest wall movement, others will "appear" apneic both awake and asleep. Studies should be performed to rule our primary neuromuscular, lung, or cardiac disease, or an identifiable brainstem lesions. Because CCHS is a mimicker of a great many treatable diseases, the possibility of a discrete congenital myopathy, myasthenia gravis, altered airway or intrathoracic anatomy, diaphragm dysfunction, congenital cardiac disease, a structural hindbrain or brainstem abnormality, or Mobius' syndrome should be considered. Specific metabolic diseases such as Leigh disease, pyruvate dehydrogenase deficiency, and discrete camitine deficiency should also be considered in the differential diagnosis. Confounding variables including asphyxia, infection, trauma, tumor, and infarction should be distinguished from the unique diagnosis of CCHS. The initial evaluation should include a detailed neurologic evaluation that may require a muscle biopsy, a chest X-ray, fluoroscopy of the diaphragm, bronchoscopy, an electrocardiogram, Holter recording, echocardiogram, and magnetic resonance imaging (MRI) of the brain/brainstem. Serum and urinary carnitine levels to rule out an inborn error in fatty acid metabolism should be obtained from a laboratory with known expertise in their assessment. The infant with camitine deficiency may require a muscle biopsy for diagnostic confirmation. A detailed ophthalmologic evaluation should be performed to assess for pupillary reactivity and optic disk anatomy. A rectal biopsy should be considered in the event of abdominal distention and delayed defecation to assess for Hirschsprung disease.

Each infant should have a detailed recording in a pediatric respiratory physiology laboratory to evaluate spontaneous breathing during sleep (nonrapid eye movement [non-REM] and REM) and wakefulness. The recording montage should include at a minimum tidal volume (pneumotachograph), movement (respiratory inductance plethysmography) of the chest and abdomen, hemoglobin saturation with pulse waveform, end tidal carbon dioxide, and electrocardiogram. Careful observation should be made of the infant's tidal volume and respiratory frequency response to the endogenous challenges of hypercarbia and hypoxemia, both while awake and asleep. Such endogenous challenges during spontaneous breathing awake and asleep may preclude the need for exogenous challenge testing. The distinction between need for artificial ventilatory support only while asleep, or while awake and asleep, should be made after several detailed evaluations in a controlled laboratory setting. As soon as a diagnosis of CCHS is confirmed a tracheostomy should be performed by a pediatric otolaryngologist. A transition to a home mechanical ventilator should be made to allow ample time for parental training before discharge. Arrangement for discharge to home with the primary mechanical ventilator and a back-up ventilator should be completed and requests for adequate home nursing care made. Often 24 h/d care with highly trained registered nurses is required to optimize patient management. Many children benefit from discharge with a pulse oximeter and an end tidal carbon dioxide monitor. These monitors often provide objective evidence of early deterioration of ventilation or "outgrowing" of ventilator settings, in both cases preventing clinical deterioration, risk of prolonged hospitalization, and risk of cor pulmonale. Because these patients do not demonstrate dyspnea in response to chronic hypoventilation or acute pulmonary infection, objective measures of physiologic compromise are necessary to assure early clinical intervention.

Rarely, a child will present with seemingly classic symptoms of CCHS later in infancy. In these cases, it is essential that a prior apparent life-threatening event that resulted in damage to their control of breathing be considered. There is speculation that untreated CCHS is compatible with life for 1 to 2 mo, but the infant would be susceptible to organ damage from the chronic exposure to hypoxemia and hypercarbia throughout that time. All available medical records should be reviewed to seek an etiology for the alveolar hypoventilation. It is remotely possible that an infant will have such subtle disease that the condition will go undetected until later in infancy. In retrospect, these rare infants may have demonstrated abnormalities in the newborn period that went unrecognized. If so, these infants likely have CCHS. For the purpose of clarity, those rare infants who have no identifiable etiology for the alveolar hypoventilation and who have previously documented normal breathing during sleep should be considered to have late onset central alveolar hypoventilation. Despite a differing diagnosis, these infants with alveolar hypoventilation and deficient responsiveness to hypoxemia and hypercarbia will likely benefit from management comparable to that of the child with CCHS. The key is to investigate each child's history and presentation to expeditiously offer the most accurate diagnosis and optimal management.

Ventilatory Support Options

Several ventilatory support options are available for the infant and child with CCHS. Typically the infant who requires ventilatory support 24 h/d will have a tracheostomy and use a home mechanical ventilator in the pressure-plateau mode. As the infant becomes ambulatory the possibility of diaphragm pacing by phrenic nerve stimulation (35, 36) should be considered to allow for increased mobility and improved quality of life. The paced older infants and toddlers may use a Passy-Muir one-way speaking valve while awake, allowing for vocalization and use of the upper airway on exhalation. The paced child may also be assessed for capping of the tracheostomy tube during pacing while awake, thereby allowing for inspiration and exhalation via the upper airway. Nonetheless, these 24 h/d supported patients will still require a tracheostomy for the nighttime mechanical ventilation. Although not yet accomplished, the older child with an entirely normal airway may be able to rely on pacing while awake and on bilevel positive-pressure mask ventilation while asleep, thus eliminating the need for a tracheostomy. In the event of severe pneumonia requiring more aggressive ventilatory management, such a child would require interim endotracheal intubation to allow for adequate ventilation.

Those children who consistently require ventilatory support during sleep only (as opposed to sleep and wakefulness) and who are able to cooperate can be considered as candidates for noninvasive support with either bilevel positive-pressure mask ventilation or negative-pressure ventilation. If successful,

a tracheal decannulation can be considered, but with the recognition that in the event of overwhelming pneumonia the child may require interim endotracheal intubation. Conversely, the child who requires support only while asleep may require ventilatory assistance while awake and asleep during an intercurrent illness.

Regardless of the method of ventilatory support, the goal is to optimize oxygenation and ventilation for each child. Typically the recommendation is for hemoglobin saturation values $\geq$ 95%. The end tidal carbon dioxide range may be broad, with limits of 30–45 mm Hg, allowing for variation with sleep position. The rationale for achieving relative hyperventilation in the respiratory physiology laboratory is to ensure that when the child is later exposed to suboptimal conditions at home, end tidal carbon dioxide values will never be worse than in the normal range of 35–45 mm Hg. The goal for chronic care is thus to minimize exposure to hypoventilation, not to achieve hyperventilation. The value of long-term hyperventilation with low end tidal carbon dioxide values during sleep (25-35 mm Hg) versus "normal" values (35-45 mm Hg) has not been studied prospectively.

For each of the above-described modalities, the goal is to match the patient with the optimal technology for his/her life style needs. Although diaphragm pacing is not typically recommended for the young child who requires only nighttime support (the benefits do not outweigh the risks), for the older child this might be an appropriate consideration.

Long-term Comprehensive Management

Meticulous follow-up and coordination of care by the family in conjunction with the local pulmonologist and the physicians in a center with recognized expertise in CCHS are vital to achieve a successful outcome for each child. Ideally, infants and young children should be evaluated every l-2 mo by their local pulmonologist and pediatrician, and every 6 mo by a center with recognized expertise in CCHS. The local evaluations should include assessment of growth, speech, and mental and motor development. The evaluations every 6 mo should include an in-hospital evaluation with detailed recording during sleep and wakefulness in a respiratory physiology laboratory to monitor the adequacy of ventilation. Because many infants appear to "acquire" awake hypoventilation at 2-3 yr of age, when a natural decrease in respiratory frequency occurs, toddlers in this age group must be closely monitored to assure adequate ventilatory support. With advancing age physiologic assessment of oxygenation and ventilation during exercise and recovery from exercise should be performed on a routine basis. After $\sim$ 3 yr of age the child may undergo detailed center evaluation on an annual basis. An echocardiogram should be performed every 6 mo to evaluate for right-ventricular hypertrophy and pulmonary hypertension, occurring as the result of unrecognized hypoxemia. A Holter recording should be considered annually to assess for transient asystole (37), and especially in the event of dizziness or syncope. A bronchoscopy should be performed every 12-18 mo to assess for suprastomal granulation tissue and/or adenotonsillar hypertrophy, which may interfere with successful use of the Passy-Muir one-way speaking valve or mask nocturnal ventilation. Detailed developmental and ophthalmologic assessments should be performed every 12 mo to verify that the child is on track and/or to provide guidance for intervention. Pulmonary function testing should be performed as needed to identify and monitor the status of reactive airway disease.

Long-term Outcome

Published data show prolonged survival of children with CCHS as well as overall good quality of life (1, 3, 38, 39). Long-term follow-up and neurodevelopmental outcome reveal a broad range of results, with a great deal of variability. Sadly, many children demonstrate findings that may be related to sequelae of intermittent hypoxemia. Thus it is difficult to determine whether neurodevelopmental outcome is related to a diffuse central nervous system process specific to CCHS or is secondary to intermittent hypoxemia. These studies of neurodevelopmental follow-up serve to emphasize the importance of early diagnosis, ongoing vigilant care in the day-to-day management of these special children with CCHS, and management in collaboration with a center with broad experience with CCHS.

Key to Successful Management of the Child with CCHS

Management of CCHS requires a cooperative and diligent effort on the part of the parents and other family members, home health care personnel, and referring physicians. With an increasing awareness of the disease entity, patients will be recognized and referred earlier than in the past. With earlier diagnosis and referral to centers with known expertise in the management and research of CCHS, vigilant management of ventilation, and rigorous efforts to support an age-appropriate and progressively independent life style, the outcome for these children is encouraging.

These patients are not like other children on home ventilators; they must be managed with extreme vigilance because of their lack of responsiveness to hypoxemia and hypercarbia. Likewise, these patients are not like unaffected children with adequate responses to exercise and infection. Special consideration must be made with regard to the management of normal childhood activities and infections. Guided by maximally conservative management, these children should be participating in noncontact sports with a moderate level of activity and frequent rest periods; they should not be swimming, even when the tracheostomy tube has been removed. Some physicians will allow children with CCHS to swim; however, constant supervision by the caregiver and counting by the child to limit the amount of time spent under water are mandatory. Recall that these children do not perceive the challenges of hypoxemia and hypercarbia even with adequate awake ventilation; they will likely swim farther and longer than their friends without sensing their physiologic compromise (hypoxemia, hypercarbia, and acidosis). Infection is another key area where children with CCHS will differ from children who do not have CCHS but are ventilator dependent. Children with CCHS do not typically increase their respiratory rate or have dyspnea in response to pneumonia. The absence of these symptoms does not preclude severe respiratory compromise. Likewise, they do not typically develop a fever in spite of an infection. These limitations emphasize the importance of (1) the objective measures of hemoglobin saturation and end tidal carbon dioxide by noninvasive monitoring in the home, (2) highly skilled and consistent caregivers in the home, and (3) the need for ongoing care by a center with known expertise in CCHS, allowing for close supervision of each child. Early intervention is clearly in the best interest of the child, the family, and the health care provider with the goals of optimal neurodevelopmental outcome balanced with a satisfactory quality of life.

In the event of an untimely death of a child with CCHS, it is imperative that an autopsy be performed according to guidelines provided by a standardized protocol available from the International Registry for CCHS. By maintaining a consistent centralized database of patient records and standardized autopsy results the enigma of CCHS will be resolved in a more expedient manner than through piecemeal investigation. Both

the standardized protocol for autopsy as well as medical records required to assure a diagnosis of CCHS are available on request.

GUIDE TO FUTURE DIRECTIONS IN THE STUDY OF CCHS

Evidence of a Diffuse Alteration in Autonomic Nervous System Function

Autonomic dysfunction leading to abnormalities of the autonomic regulation of cardiovascular and/or respiratory function has long been postulated in CCHS. A growing body of data lends support to this theory, the most compelling of which are cited below. Although clearly a research avenue, they are included in this ATS Statement because of their relevance to clinical management.

Decreased heart rate beat-to-beat variability, particularly at slower heart rates, has been demonstrated by Holter recording during sleep in subjects with CCHS. The ratios of low-frequency band to high-frequency band spectral power were increased during sleep in subjects with CCHS, as compared with all control subjects, in whom these ratios were consistently decreased during comparable sleep states, suggesting an imbalance in sympathetic/parasympathetic regulation in patients with CCHS (27). Cardiac arrhythmias have also been identified among patients with CCHS (37). In that study, the predominant arrhythmias were sinus bradycardia or transient asystole, with the longest asystole in a subject with CCHS lasting 6.50 s (versus 1.42 s in a control subject). The percentage of time in respiratory sinus arrhythmia was also decreased in CCHS versus control subjects. Although these findings may reflect intrinsic problems in cardiac function, they are most often considered manifestations of improper autonomic nervous system (ANS) control. The phenomenon of decreased breath-to-breath variability, producing a monotonous respiratory rhythm during spontaneous breathing while asleep, is also a well-accepted observation among children with CCHS and likely represents improper ANS control.

In addition to the clinical features of alveolar hypoventilation, patients with CCHS often manifest a spectrum of clinical symptoms reflecting dysfunction of the ANS. These include Hirschsprung disease and/or severe constipation, feeding difficulty, decreased perception of discomfort, pupillary abnormalities, decreased perception of anxiety, profuse sweating, and decreased basal body temperature. In addition, "autonomic crises" with and without elevated urinary catecholamines have been described in children with CCHS (40).

Neuropathologic findings supporting ANS dysfunction (ANSD) in CCHS include a report of one infant with CCHS and neuronal loss of the reticular nuclei and nearby cranial nerve nuclei, including the nucleus ambiguus and the hypoglossal and dorsal motor nuclei of the vagus nerve (10). Cutz and coworkers (41) reported small carotid bodies with fewer glomus cells in two patients with CCHS, supporting the notion of deficient "hardware." Report of an absent arcuate nucleus in a child with CCHS (16) similarly supports what is likely a structural ANS defect. Although labeled as CCHS, the clinical detail provided about the subject of that case report (16) was not consistent with CCHS as described here.

Evidence of a Genetic Component in CCHS

Interest in the familiality of CCHS comes from two lines of reasoning. First, a genetic origin of CCHS has been hypothesized on the basis of published reports describing one case each of monozygotic female twins (9), female siblings (7), and male-female half-siblings (20). Particularly noteworthy is the observation that the monozygotic female twins are the only cases reported of familial recurrence without the association of Hirschsprung disease. Conversely, the female siblings and the male-female half-siblings of the other reports indicating familial recurrence had hypoventilation and Hirschsprung disease. In addition, several monozygotic twins have been observed, although not reported in the medical literature. The second line of reasoning comes from the observation that $\sim$ 16% of CCHS cases occur in association with Hirschsprung disease, a frequent congenital malformation characterized by the absence of parasympathetic intrinsic ganglion cells of the hindgut and regarded as a neurocristopathy (42). Several genetic mutations have already been identified among patients with Hirschsprung disease, including mutations in the receptor tyrosine kinase gene among 50% of familial cases and 15–20% of sporadic cases (43). In addition, endothelin signaling pathway mutations (including the endothelin B receptor gene and endothelin 3 gene) have been identified in $\sim$ 5% of cases of Hirschsprung disease (44-47). Finally, mutations in glial-derived neurotrophic factor, a ligand of the *ret* proto-oncogene (48), have also been reported in Hirschsprung disease (49, 50). As a result of the relationship of CCHS to Hirschsprung disease and the identification of specific gene mutations associated with Hirschsprung disease, it followed that these candidate genes, i.e., those encoding receptor tyrosine kinase, the endothelin B receptor, endothelin 3, and glial-derived neurotrophic factor, were evaluated among children with CCHS.

Several important studies that provide evidence of a genetic component in CCHS have been published. Briefly, segregation analysis among families of 50 probands with CCHS indicated that CCHS was familial (51). Further, an endothelin 3 mutation (exon 4) in one child with CCHS (no Hirschsprung disease) was identified (52). Although no abnormalities in receptor tyrosine kinase were found in 14 patients with CCHS (53), including 4 with associated Hirschsprung disease, mutations in the receptor tyrosine kinase have been identified by investigators in Japan (54) and France (55). Sakai and colleagues (54) identified a receptor tyrosine kinase mutation in one child with CCHS and Hirschsprung disease. Amiel and coworkers (55), investigators in France, studied seven children with CCHS, two of whom had associated Hirschsprung disease. A different mutation of the receptor tyrosine kinase gene was identified in one child with CCHS and total colonic aganglionosis, and a mutation of the glial-derived neurotrophic factor gene was identified in one child with CCHS and growth hormone deficiency.

Taken together, these data suggest a diffuse alteration in autonomic nervous system function in patients with CCHS. Further, those data identifying the three candidate genes (receptor tyrosine kinase, endothelin 3, and glial-derived neurotrophic factor) in patients with CCHS, and the variable expression of a respiratory control defect in receptor tyrosine kinase −/− homozygous mice exposed to increased carbon dioxide (56), support the consideration of a genetic origin of CCHS. Therefore, a detailed family history should be obtained for each proband with CCHS, with particular attention given to symptoms of autonomic nervous system dysfunction.

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