Presentation and treatment of monozygotic twins with congenital central hypoventilation syndrome

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Congenital central hypoventilation syndrome is a rare genetic disorder characterized by hypoventilation during sleep secondary to a blunted response to hypercapnia and hypoxia. The current case report describes developmentally normal four-year-old monozygotic twin boys who presented in infancy with variable presentations and clinical severity of congenital central hypoventilation syndrome. Both were managed with noninvasive positive pressure ventilation.

Key Words: *Congenital hypoventilation syndrome; Pediatric; Twins*

La présentation et le traitement de jumeaux monozygotes ayant un syndrome d'hypoventilation centrale congénitale

Le syndrome d'hypoventilation centrale congénitale est un trouble génétique rare caractérisé par de l'hypoventilation pendant le sommeil, secondaire à une réponse émoussée à l'hypercapnie et à l'hypoxie. Le présent rapport de cas décrit des jumeaux monozygotes de 4 ans de sexe masculin, normaux sur le plan du développement qui, pendant la première enfance, avaient un syndrome d'hypoventilation centrale congénitale de présentations et de gravité clinique variables. Tous deux ont été traités au moyen d'une ventilation à pression positive non effractive.

Congenital central hypoventilation syndrome (CCHS) is characterized by ventilatory insensitivity to hypercapnia and hypoxemia during sleep and/or wakefulness (1). It is most pronounced during nonrapid eye movement (NREM) sleep during which breathing is primarily controlled by the autonomic nervous system (ANS) (2). ANS dysfunction is a hallmark of CCHS, and clinical manifestations of the disease may include diminished heart rate variability and transient abrupt asystoles, decreased pupillary light response, esophageal dysmotility, breath-holding spells, reduced basal body temperature, sporadic profuse sweating, lack of perception of dyspnea, altered perception of anxiety, and a lack of physiological responsiveness to exercise and environmental stressors (3-16). Additionally, CCHS may also be associated with neural crest tumours and Hirschsprung's disease.

Mutations in the *PHOX2B* gene, located on chromosome 4, cause CCHS (17). More than 90% of CCHS patients have polyalanine repeat mutations (24 to 33 repeats) in the *PHOX2B* gene; a genotype-phenotype correlation exists between the size of the *PHOX2B* expanded allele and the severity of symptoms (17-19). The remaining 10% of patients with CCHS are heterozygous for a nonpolyalanine repeat mutation and are at greater risk for neurocristopathies and Hirschsprung's disease (19,20).

We describe a case involving monozygotic twins with CCHS who presented differently despite harbouring identical genetic mutations. They were managed conservatively with noninvasive positive pressure ventilation (NIPPV).

CASE PRESENTATION

Monozygotic male twins were born at term. At 4 h of life, twin A developed apnea, and continuous positive airway pressure therapy was initiated and stopped 36 h later. A car seat test was performed before discharge from the hospital. During this test, a baby is placed in a car seat at a 45° angle with a cardiorespiratory monitor and an oxygen saturation monitor. Colour, heart rate, respiratory rate (RR) and oxygen saturation are measured over 90 min. Supraventricular tachycardia developed in twin A on day of life (DOL) 10 during the car seat test and converted with adenosine. He was discharged home on DOL 11.

Twin B was intubated at birth for carbon dioxide (CO_2) retention. He was extubated on DOL 4 and discharged home on DOL 8. At two months of age, he presented with poor feeding, lethargy and cyanotic spells. While sleeping, his oxygen (O_2) saturation was 50% with no respiratory distress. Arterial blood gas measurements on room air were the following: pH of 7.14, PCO_2 of 122 mmHg and bicarbonate level of 34 mmol/L. He was intubated for CO_2 retention. While intubated, infectious, cardiac, neurological and metabolic etiologies were ruled out. He was ventilated for five days. Postextubation, a polysomnogram (PSG) was performed and revealed severe hypoventilation. The RR was 24 breaths/min to 40 breaths/min, with irregular and shallow respirations, the percentage time of sleep with an O_2 saturation (SaO_2) of lower than 90% was 12.9%, and the percentage of sleep time with transcutaneous CO_2 ($TcCO_2$) higher than 50 mmHg was greater than 90%. The patient's central apnea index was 107.7/h in NREM sleep, while his obstructive apnea/hypopnea index was 11.1/h in NREM sleep (all hypopneas). Both indexes were zero in REM sleep.

Given Twin B's admission, twin A was evaluated at his mother's request. A PSG showed an RR of 26 breaths/min to 30 breaths/min, the percentage of sleep time with an SaO_2 of lower than 90% was 5.2%, and the percentage of sleep time with a $TcCO_2$ of higher than than 50 mmHg was 84%. Twin A's central apnea index was 44.7 events/h and his obstructive apnea/hypopnea index was 3.4 events/h in NREM sleep. Both indexes were zero in REM sleep. His arousal and awakening index was 17.2.

A diagnosis of CCHS was suspected and disclosed to the parents. Given the young age of the twins, tracheostomy and nocturnal ventilation were recommended. The family was opposed to invasive ventilation despite an explanation of the risks of untreated CCHS and NIPPV. Initiation of NIPPV on an outpatient basis failed; however, reinitiation during hospital admission was successful.

The twins were heterozygous for the 25 polyalanine repeat mutation in the *PHOX2B* gene, and monozygosity was confirmed.

The twins were reviewed biannually, and were most recently reviewed at five years of age. Twin A was maintained on NIPPV settings of inspiratory positive airway pressure of 14 cmH_2O and expiratory positive airway pressure of 6 cmH_2O with a backup rate of 16 breaths/min.

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His spontaneous respiratory rate during the PSG was between 16 breaths/min and 20 breaths/min. His echocardiogram and Holter monitoring were within normal limits.

Twin B was maintained on NIPPV settings of inspiratory positive airway pressure 10 cmH_2O and expiratory positive airway pressure of 4 cmH_2O with a backup rate of 16 breaths/min. His respiratory rate during the PSG was between 16 breaths/min and 20 breaths/min. On echocardiography, the right ventricular systolic pressure was elevated at presentation but normal at follow-up at five years of age. The twins have normal daytime capillary blood gases. Both twins have developed midface hypoplasia secondary to the NIPPV mask and are being conservatively followed up with plastic surgery. A cognitive developmental assessment at two years of age was within normal limits. The twins are currently attending senior kindergarten and there are no developmental concerns.

DISCUSSION

The first case of CCHS was reported by Mellins et al (21) in 1970. They described an infant boy who was cyanotic on nursery admission, during sleep and with feeding. The clinical spectrum of CCHS is diverse. Severe cases demonstrate profound hypoventilation both awake and while asleep, whereas less severely affected children appear to breathe normally while awake but demonstrate hypoventilation during sleep. Delayed diagnosis is, therefore, not uncommon in milder cases, with some patients not diagnosed until adulthood (17).

To our knowledge, the present report is the first to describe a case of CCHS in monozygotic male twins with the identical mutation (25 polyalanine repeats) yet different clinical presentations.

The twins differ in both their respiratory and nonrespiratory complications of CCHS. Twin B's respiratory compromise was more severe. He was noted to experience hypoventilation that required intubation both at birth and at two months of age, whereas Twin A came to medical attention only because his mother expressed concerns about shallow breathing after Twin B's PSG. Twin B's PSG was also more abnormal. Both twins have shown signs of improvement in their PSGs at five years of age compared with previous years, but Twin A now requires higher noninvasive ventilatory support settings than his brother. Regarding their nonrespiratory complications, one twin developed supraventricular tachycardia, reflecting ANS dysfunction, while the other has experienced elevated pulmonary pressures at presentation that have subsequently resolved at five years of age (14).

Therefore, the variable presentations and differing clinical severities suggest a role for an epigenetic environmental influence on the phenotypic presentation of CCHS given the twins' confirmed monozygosity. Similar findings have also been reported in monozygotic twins with Huntington's disease, Marfan syndrome and Moyamoya disease (22-24).

There remains significant variation in the management of patients diagnosed with CCHS during infancy. Tracheostomy and invasive ventilation are significantly more likely to be used in some parts of the world compared with NIPPV and vice versa. Certainly, noninvasive ventilation is increasingly being used, although the majority of patients are initially treated with invasive ventilation and subsequently weaned to noninvasive ventilation with increasing age. In a recent worldwide survey of 196 CCHS patients (25), 14.3% of the patients had never undergone a tracheostomy, with very few of the patients who presented in infancy being managed from the outset with NIPPV, as was the case for the twins described in the current report (25). Supplemental oxygen alone is insufficient for the management of hypoxemia and hypercarbia CCHS patients, and will not prevent the development of complications such as pulmonary hypertension. Furthermore, supplemental oxygen alone may exacerbate hypoventilation, given its potential to further suppress respiratory drive.

NIPPV in this age group is, however, not without its challenges. First, depending on severity, it may not be an effective form of ventilation for some CCHS patients. NIPPV is successful in patients with neuromuscular disease because these patients initiate a breath and abduct the vocal cords; NIPPV then augments the spontaneous breath, consequently decreasing the respiratory load on the weakened respiratory muscles. As a result of the decreased respiratory drive and subsequent hypoventilation in CCHS patients, NIPPV may be an inadequate method of ventilation for some patients if a sufficient number of spontaneous breaths are not initiated because positive pressure cannot be effectively delivered through closed vocal cords. Second, NIPPV is not a secure method of ventilation; it lacks the ability to provide guaranteed minute ventilation. As a result, families must be even more vigilant than with other children to ensure a CCHS child wears the NIPPV mask all night given the reduced arousal response secondary to hypercarbia and hypoxia. Furthermore, given the ANS dysfunction when CCHS children are unwell, fever and respiratory distress are absent (2). This reinforces the importance of objective monitoring of these children by pulse oximetry and end-tidal capnography in addition to having informed, aware caregivers (2). NIPPV in infancy often leads to midface hypoplasia as a consequence of mask pressure on the developing maxilla, as seen in our patients (2). Finally, there is evidence of neurocognitive defects in long-term survivors of CCHS (26). What remains unclear is whether this arises as a consequence of repeated episodes of sleep-related hypoxemia, which would argue for more aggressive ventilatory management, or whether it arises simply as a direct effect of the underlying genetic defect on cortical development (26).

Diaphragmatic pacing is also a potential ventilation strategy for some CCHS patients. Typically, the pacer system consists of an external transmitter on the skin overlying a surgically implanted subcutaneous receiver. The receiver delivers electrical pulses to an electrode placed beneath the thoracic phrenic nerve resulting in contraction of the diaphragm (27). Alternatively, the device can be surgically connected to the phrenic motor area in the diaphragm (28). Although uncommonly performed, diaphragmatic pacing is reported to be successful in pediatric patients with CCHS. In general, these patients all require tracheostomies to prevent upper airway obstruction caused by the absence of laryngeal and pharyngeal dilator muscle activation during paced breaths (27). In addition, patients are bilaterally – as opposed to unilaterally – paced to ensure adequate ventilation given the compliant chest walls and higher metabolic rates (27). The main advantage of diaphragmatic pacing is the opportunity for mobility; this mode of ventilation should be considered as patients become ambulatory (29). Therefore, diaphragmatic pacing is of particular benefit for patients requiring mechanical ventilation 24 h/day to ensure the opportunity to participate in normal, age-appropriate activities of childhood. The benefits are less apparent for patients, such as our twins who only require nocturnal support; therefore, mechanical ventilation or NIPPV remain first-line treatments for this subset of patients (27). The main risks of diaphragmatic pacing include an invasive surgical procedure for insertion of the pacer, breakage or malfunction of the device, and infection (30). In addition, there is a potential risk of phrenic nerve damage secondary to traction as well as diaphragm fatigue due to phrenic nerve burn out (27). Because the latter is of particular concern for young patients, diaphragm pacing is usually performed for up 12 h/day in the pediatric population (31).

SUMMARY

Invasive ventilation is the mainstay of management for CCHS infants and young children, but NIPPV and diaphragmatic pacing are potential noninvasive alternatives. However, NIPPV and diaphragmatic pacing can only be implemented with objective monitoring devices in the home, trained caregivers and regular follow-up with a multidisciplinary team to ensure the development of avoidable complications of CCHS. Although further short- and long-term studies are needed to definitively document the safety of noninvasive ventilation for these patients from infancy, the present case demonstrates that noninvasive ventilation is an alternative for some infants with CCHS, and that the spectrum of disease among CCHS patients is widespread even among monozygotic twins.

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