CASE REPORT

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Noninvasive ventilation in a young infant with congenital central hypoventilation and 7-year follow-up

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ABSTRACT

Introduction: Congenital central hypoventilation syndrome (CCHS) is a rare disorder characterized by alveolar hypoventilation and autonomic system dysregulation secondary to mutations of the *PHOX2B* gene. Treatment consists of assisted ventilation using positive-pressure ventilators via tracheostomy, bi-level positive airway pressure (BPAP) via a noninvasive interface, negative-pressure ventilators, or diaphragm pacing. The long-term use of BPAP in younger children at home has been less frequently reported.

Case presentation: We present a case of a 2-month-old infant with CCHS who was successfully managed by BPAP without the need for tracheostomy and followed up for 7 years.

Conclusion: CCHS is a rare disease that manifests as nocturnal desaturation and carbon dioxide retention in early life. Noninvasive ventilation can be successfully used in young infants via an appropriate mask.

KEYWORDS
Congenital central hypoventilation syndrome, *PHOX2B* gene, Noninvasive ventilation

INTRODUCTION

Congenital central hypoventilation syndrome (CCHS) is a rare, lifelong condition characterized by abnormal control of breathing.[1] The main cause of this syndrome is mutations in the *PHOX2B* gene, which is located on chromosome 4p12. The main clinical manifestations of CCHS include adequate ventilation while awake

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but alveolar hypoventilation during sleep. The aim of treatment is to ensure adequate gas exchange by using assisted ventilation during sleep. Positive-pressure ventilation via tracheostomy is recommended by the American Thoracic Society for patients with CCHS in their first several years of life.[2] However, disadvantages include limited mobility while awake as well as parents' concerns about the lack of home health care services for tracheostomy and patients' quality of life. Bi-level positive airway pressure (BPAP) via mask has been applied in many cases and is less expensive and easier to use than home ventilators. We herein describe a 2-month-old girl who developed shallow breathing and cyanosis during sleep and was diagnosed with CCHS with *PHOX2B* mutation. The young infant was successfully treated with BPAP via mask and followed up for 7 years.

CASE REPORT

A 2-month-old female infant, born at term to non consanguineous parents by cesarean section without complications (birth weight of 3600 g), had an Apgar score of 9 at 1 minute and a score of 10 at 5 and 10 minutes. The infant was born when the mother was 39 years old, and the pregnancy was uneventful. The infant's older brother was 16 years old and healthy, and her father was 43 years old and healthy.

The newborn presented with recurrent cyanosis in the first hour of life. She was admitted to the neonatal intensive care unit of a local hospital because of shallow breathing and cyanosis during sleep. Her blood gas analysis in the hospital showed type II respiratory failure [arterial partial pressure of oxygen (PaO_2) < 60 mmHg; arterial partial pressure of carbon dioxide ($PaCO_2$) > 50 mmHg]. She was intubated with synchronized intermittent mandatory ventilation (SIMV) with good saturation and normal CO_2. However, failure of extubation occurred because of CO_2 retention. She was then transferred to our children's hospital in Beijing.

On admission, she was well and alert on SIMV. A physical examination revealed a body temperature of 37 °C, weight of 2.9 kg (below third percentile for age), and no facial abnormalities. No lymphadenopathy was present in the neck, and the trachea was positioned at the midline. Crackles were heard in both lungs. The heart beat had a regular rate and rhythm without a murmur. The abdomen was soft and tender without distention. Neither skin rash nor nail bed cyanosis was seen. Her muscle tone was low and no neonatal reflex was obtained. When transferred to continuous positive airway pressure on room air, the arterial blood gas analysis showed metabolic acidosis (pH, 6.92; $PaCO_2$, 118 mmHg; PaO_2, 86 mmHg; bicarbonate, 24.3 mmol/L; base excess, −8.4 mmol/L). Continuous positive airway pressure was therefore converted back to SIMV with normal blood gas.

Infiltrates were present on both sides of the chest radiograph. The patient's electrolyte levels, liver function, and thyroid function were normal. An echocardiogram revealed mild pulmonary hypertension and an enlarged right heart. Brain magnetic resonance imaging findings were normal. A urinalysis and blood screening for inherited metabolic disorders showed no abnormalities. The surgeon excluded Hirschsprung disease based on a medical history and abdominal radiographs, and the neurologist excluded neuromuscular diseases.

The patient's history of shallow breathing and cyanosis during sleep and the requirement for ventilatory support during sleep shortly after birth were clinical clues to the diagnosis of CCHS. Furthermore, polysomnography (PSG) revealed O_2 desaturation while asleep as well as a climbing partial pressure of CO_2 (PCO_2), which was monitored by transcutaneous CO_2 equipment. The examination revealed no evidence of central apnea or periodic breathing. The patient was able to breathe normally and had normal O_2 saturation and PCO_2 when awake.

A genetic test using polymerase chain reaction followed by direct sequencing of exon 3 of the PHOX2B gene revealed 18 inserts of alleles at c.758–759 in the DNA and 6 alanine repeats at 252 in the protein sequence. CCHS was finally diagnosed.

Although the American Thoracic Society recommends positive-pressure ventilation via tracheostomy for treatment of patients with CCHS in their first several years of life, the family of our patient declined invasive ventilation despite being told the risks of mask ventilation. The patient's parents were concerned about the lack of home health care services for patients with tracheostomy from public hospitals as well as the patient's quality of life. Several studies have shown that noninvasive ventilation can be used in infants and young children with CCHS,[3,4] and noninvasive ventilation simplifies the complexity of the homecare program compared with ventilation via tracheostomy. The patient underwent BPAP titration via a ResMed infant nasal mask (ResMed, San Diego, CA, USA). The BPAPS/T mode was used with an inspiratory positive airway pressure of 15 cmH_2O, expiratory positive airway pressure of 4 cmH_2O, and backup respiratory rate of 30 breaths/min. The patient tolerated the ventilator very well, and her saturation and CO_2 returned to normal. She was discharged home at the age of 2.5 months, and her parents were trained in ventilation care and muscle rehabilitation training, such as touch and massage.

The patient did well with BPAP during both nighttime sleeping and daytime napping for 7 years, during which time she was followed up every 6 months. At each follow-up, she underwent PSG and adjustment of the BPAP pressure and respiratory rate. Every 1 to 2 years, she also visited the department of neurology for neurocognitive evaluations, all of which showed normal results. Her

echocardiogram showed no abnormalities at her most recent follow-up (24 April 2019) as of this writing. During the follow-up period, the patient was hospitalized once for pneumonia, for which she was treated with an antibiotic and respiratory support by her own ventilator. At the time of this writing, she was developing normally and was a happy child in grade 1 in primary school. Holter monitoring and screening for neural crest tumors will be performed for this child in her next visit.

DISCUSSION

CCHS is a lifelong disease that is classified as a respiratory disorder. It is also categorized as a rare neurologic disease characterized by the failure of automatic control of ventilation in the central nervous system.[5] Patients with CCHS typically have adequate ventilation while awake but alveolar hypoventilation during sleep, with a decreased tidal volume and respiratory rate.[1] Affected patients become hypoxemic and hypercarbia as a result of hypoventilation, but they typically lack responsiveness to these endogenous challenges in terms of ventilation and arousal during sleep. Patients with CCHS also lack perception of asphyxia during wakefulness with and without exertion.[5] Comprehensive assessment of respiratory physiology during wakefulness and sleep should be considered for children with a suspected diagnosis of CCHS. Such assessment results can reveal the degree of hypoventilation and the level of ventilatory support required. Shortly after birth, our patient exhibited shallow breathing and cyanosis during sleep and required ventilatory support during the night. PSG revealed desaturation and transcutaneous CO_2 monitoring revealed a climbing CO_2 level while asleep. The patient was able to breathe normally and had normal O_2 saturation and PCO_2 when awake. These findings were consistent with the clinical manifestations of CCHS.

The *PHOX2B* gene, located on chromosome 4q12, is responsible for CCHS.[6] Once the diagnosis of CCHS is suspected, blood should be sent to screen for mutations of the *PHOX2B* gene. If the screening test is negative and the patient's phenotype supports the diagnosis of CCHS or late-onset CCHS or the physician/family wants to completely rule out the diagnosis of CCHS, then the sequel *PHOX2B* sequencing test should be performed.[2] The intervention and treatment strategies for home care should be based on the etiology of hypoventilation; therefore, causes of hypoventilation other than CCHS should be ruled out.

The tests most commonly performed to rule out primary lung disease include chest radiographs and chest computed tomography. Comprehensive neurological assessment and potentially muscle biopsy can reveal ventilatory muscle weakness. Notably, abnormal ventilation control can occur in patients with cardiac disease, anatomic brain/brainstem lesions, and inborn errors of metabolism; therefore, these three conditions should be ruled out using echocardiography, magnetic resonance imaging and/or computed tomography of the brain and brainstem, and a metabolic screen, respectively. Our patient's genetic test revealed 18 inserts of alleles at c.758–759 in the DNA and 6 alanine repeats at 252 in the protein sequences, which were consistent with the genetic mutation that causes CCHS.

The American Thoracic Society recommends that children with CCHS should be treated by positive-pressure ventilation via tracheostomy in the first several years of life because only this treatment can ensure the necessary amount of oxygenation and ventilation needed for the development of neurocognitive function.[2] However, disadvantages of this treatment include risks of lower airway infection, dysphonia, tracheal dysplasia, and other conditions.[4] Several studies have shown that noninvasive ventilation techniques are possible from birth or young infancy.[3,4,7] The application of long-term noninvasive ventilation to appropriately selected patients at home can simplify the complexity of homecare programs, which is a major limitation of ventilation via tracheostomy, and can potentially reduce its cost. The present case report demonstrates that children as young as a few months of age can be successfully treated with BPAP at home. Initial evaluation and treatment by qualified professionals in experienced centers is highly advisable. Evidence has shown that facial growth can be affected by long-term use of tight-fitting masks, and this seems more likely to occur when BPAP is started before the age of 8 years because these children have a malleable mid-face that is prone to compression.[2] Our patient did not develop a facial abnormality. Use of a suitable mask and re-education of the muscles helps to avoid facial structure hypoplasia.

CCHS is a rare disease that manifests as sleep-related hypoventilation, and noninvasive ventilation can be used in young infants. Proper ventilation support can prevent hypoxia and CO_2 retention, greatly improve the growth and development of patients with CCHS, and make it possible for children with CCHS to have prolonged survival with good quality of life.

CONFLICT OF INTEREST

There are no conflicts of interest relevant to this article.

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