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CLINICAL BRIEF

Congenital Central Hypoventilation Syndrome with *PHOX2B* Gene Mutation: Are We Missing the Diagnosis?

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Abstract Congenital Central Hypoventilation Syndrome is a rare disorder of autonomic and central nervous system dysfunction with impaired control of breathing. The authors report a 37- d-old girl infant with recurrent apnea requiring repeated mechanical ventilation with no evidence of neuromuscular, cardiac or lung disease. A mutation analysis of *PHOX2B* gene revealed 25 polyalanine repeat expansion mutation on chromosome 4p12. This article aims at raising awareness among pediatricians about molecular basis and availability of confirmatory genetic testing for diagnosis and to help with prognosis in this disorder.

Keywords Congenital central hypoventilation syndrome (CCHS) · *PHOX2B* gene · Polyalanine repeat expansion mutation (PARM) · Apnea

Introduction

Congenital central hypoventilation syndrome (CCHS), also called Ondine's curse, is a disorder characterized by inadequate respiratory response to hypercapnia and hypoxemia especially during sleep and/or awake state [1]. An association with Hirshsprung disease and neural crest tumors (ganglioneuroma, neuroblastoma, ganglioneuroblastoma) has been described in 20% and 6% of cases, respectively [1].

In 2003, the paired-like homeobox gene 2B (*PHOX2B*) on chromosome 4p12 was identified as the disease-defining gene for CCHS [2]. *PHOX2B* was first recognized in mice to encode a highly conserved transcription factor involved in autonomic medullary reflexes [3]. There are 3 case reports of CCHS in infancy from India but none were proved by genetic testing [4–6]. Here, the authors report an infant with CCHS in whom the diagnosis was confirmed by genetic testing of *PHOX2B* gene and discuss the role of mutation analysis in disease prognosis.

Case Report

A 37 d-old girl was referred from a private hospital to the authors' emergency room for pneumonia. She was born at 34 wk gestation with an appropriate weight of 1.9 kg to a primigravida female with no parental consanguinity. She required bag and mask ventilation at birth due to poor respiratory efforts, was mechanically ventilated for 24 h and discharged on day 4. The investigations at that time including sepsis screen, serum electrolytes, calcium, cranial ultrasound and CXR were normal. She was readmitted to a private hospital on day 8 of life for progressive lethargy and decreased feeding where she was ventilated for apnea and managed as a case of septicemia. After 3 wk, she was extubated and referred to the authors' hospital. On examination, the pulse rate was 122/min, respiratory rate 30/min with no distress and saturation 93% on oxygen. The chest examination showed few crepitations bilaterally with normal cardiovascular and neurological examination. Investigations showed a positive sepsis screen and right lower lobe consolidation on CXR. The serum electrolytes were within

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normal limits but arterial blood gas revealed respiratory acidosis. She was re-intubated and shifted to the ICU for ventilation where she received antibiotics. The blood culture grew *Pseudomonas aeruginosa*. Gradually she was weaned off the ventilator and extubated on day 53. Within 24 h of extubation, she developed poor respiratory efforts requiring re-intubation. Investigations for cardiac and lung disease including ECG, echocardiography and CECT chest were normal. The gastroesophageal reflux scan and MRI brain (for structural brainstem lesion) were within normal limits. Two more attempts at extubation failed. On T-piece, her respiratory rate varied between 16 and 22/min. There was gradual worsening of respiratory acidosis over 3 d but no increase in respiratory drive despite significant hypercapnea. A diagnosis of CCHS was considered likely and mutation analysis of the *PHOX2B* gene was sent for confirmation. The polyalanine repeat coding sequence in exon 3 of *PHOX2B* was amplified and analysed as described previously [2] at Rush Children's Hospital, Chicago.

The infant was heterozygous for polyalanine repeat expansion mutation with 25 polyalanine repeats. The parents were counseled on the nature of disease and probable need for prolonged ventilation. The child was successfully weaned off ventilator support by 3 mo of age and discharged with a plan for polysomnography. She is thriving and doing well at 7 mo of age with no requirement for ventilation.

Discussion

CCHS was suspected in the present case due to (1) the episodes of hypercapnia and hypoxia with no increase in respiratory drive and (2) lack of neuromuscular, cardiac, lung or brainstem lesion. The diagnosis was confirmed by a demonstration of a polyalanine expansion mutation in *PHOX2B*.

PHOX2B has two polyalanine repeat regions in exon 3, the second of which is responsible for CCHS. This polyalanine repeat comprises any one of four codons (GCA, GCT, GCC or GCG) each encoding the amino acid alanine. Normal individuals have 20 alanines (20/20 genotype) in the polyalanine repeat stretch in the *PHOX2B* gene product. *PHOX2B* gene codes for a transcriptional factor responsible for regulating expression of genes involved with development of the autonomic nervous system. Studies have shown that polyalanine repeat expansion mutations (PARM) are associated with decreased transcription of these genes [2]. Over 92% of patients with CCHS have PARMs in the *PHOX2B* gene, ranging from 24 to 33 alanines (resulting in a 20/24 to 20/33 genotype). The length of the expansion determines the severity of disease including autonomic dysfunction and degree of ventilator dependence [7]. In the remaining 8%, non-polyalanine repeat mutations (NPARMs) consisting of deletions/insertions result in frameshift, missense, nonsense, and stop codon mutations of *PHOX2B* and are associated with more severe manifestations of CCHS [3].

Patients with 26 PARMS have hypoventilation during non-REM sleep which can be diagnosed by polysomnography and a variable need for ventilatory support during the awake state. Those with 27–33 PARMs and NPARMS typically require 24-h ventilatory support. Hirschsprung disease and neural crest tumors are associated with >26 and >29 PARMS, respectively. NPARMS virtually always result in Hirschsprung disease and neural crest tumors [7].

The 24 and 25 PARMs are the shortest disease-causing mutations, resulting in a milder disease course [8, 9]. Patients with 25-polyalanine repeats have severity ranging from totally asymptomatic to recurrent cyanosis and death in infancy in the absence of artificial ventilation support [9]. There may be a history of seizures unresponsive to medication and intellectual subnormality. Some patients may be diagnosed late as adults with sleep apnea, polycythemia, and chronic right heart failure [10]. Individuals with 25 PARM rarely require 24-h ventilatory support; the mild form of mutation explains the good prognosis in the present patient who has not required ventilator support after 3 mo of age.

Most PARMS arise de novo but around 10% are transmitted from an affected or unaffected parent, hence there is a role for genetic counseling. Affected parents transmit the mutation as an autosomal dominant trait. When PARMS >25 repeats are inherited from an unaffected parent, the parent is always mosaic for the mutation, indicating a somatic mutation in the parent. The 24 and 25 PARMS exhibit autosomal dominant inheritance with incomplete penetrance [8, 9] and hence non-mosaic parents carrying the mutation may be asymptomatic.

The diagnosis of milder forms of CCHS is frequently delayed or missed due to lack of knowledge of this entity. The American Thoracic Society has issued an updated statement on the diagnosis and management of CCHS and a high index of suspicion is recommended in cases of unexplained alveolar hypoventilation, delayed recovery from sedation, anesthesia or respiratory infection, unexplained seizures or neurocognitive delay [11]. The purpose of this report is to create awareness among pediatricians about CCHS and to illustrate the availability of confirmatory genetic testing with *PHOX2B* mutation analysis to help with diagnosis, prognosis and genetic counseling.

Conflict of Interest None.

Role of Funding Source None.

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