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CASE REPORTS

Adult With *PHOX2B* Mutation and Late-Onset Congenital Central Hypoventilation Syndrome

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PHOX2B 20/27 polyalanine repeat mutation (PARM) in patients with congenital central hypoventilation syndrome (CCHS) is generally associated with full-time ventilator dependence, Hirschsprung disease, and increased risk for cardiac asystole. We follow a 14-year-old boy with CCHS *PHOX2B* 20/27 PARM who is full-time ventilator dependent via tracheostomy and has Hirschsprung disease. His mother, age 52 years, has a history of prolonged recovery from anesthesia and an elevated serum bicarbonate level of 45 mEq/L discovered on routine blood chemistry. *PHOX2B* gene mutation analysis was performed and showed an identical 20/27 PARM, diagnostic of CCHS. Late-onset CCHS has been reported in those with 20/24, 20/25 *PHOX2B* PARM, and in nonpolyalanine repeat mutations. This is the first report of a patient with *PHOX2B* 20/27 PARM with a mild phenotype diagnosed during adulthood. This unusual presentation supports the screening for *PHOX2B* mutations in parents of children with CCHS.

Keywords: CCHS, congenital central hypoventilation syndrome, *PHOX2B*

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INTRODUCTION

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder of the autonomic nervous system due to a mutation in the paired-like homeobox 2B (*PHOX2B*) gene.[1] Most patients with CCHS present in the neonatal period with apnea or hypercapnia requiring assisted ventilation. CCHS has been diagnosed beyond the newborn period and as late as during adulthood where the presentation is respiratory compromise following general anesthesia or respiratory infections.[1] In these reported cases, patients have 20/24, 20/25 polyalanine repeat mutations (PARM), and nonpolyalanine repeat mutations (NPARM) of the *PHOX2B* gene.[1,2] A few asymptomatic adults with 20/27 PARM *PHOX2B* mutation with mosaicism have also been reported in the literature.[3,4] Most *PHOX2B* mutations occur de novo but can be inherited in an autosomal dominant pattern, although with variable penetrance. The current recommendation is to screen parents of children with CCHS for *PHOX2B* gene mutations. The reported cases were identified by screening the parents of patients with CCHS.

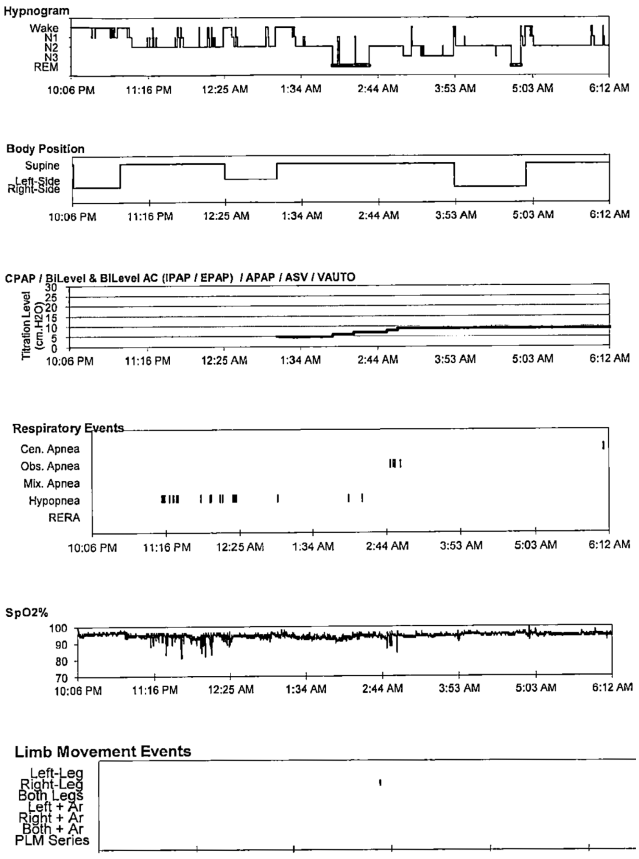
We report a 52-year-old woman with 20/27 PARM *PHOX2B* mutation expected to have a more severe phenotype.

REPORT OF CASE

The patient in the index case, now 14 years of age, was born at term by caesarean section. He had abdominal distension and hypoxemia at birth requiring intubation with mechanical ventilation. He failed extubation trials with resultant hypoxemia and hypercapnia requiring re-intubation with ventilatory support. A rectal biopsy confirmed the diagnosis of Hirschsprung disease, and a colectomy was performed. After extensive inpatient evaluation, the clinical diagnosis of CCHS was made. A gastrostomy tube was placed for swallowing dysfunction. Subsequently, tracheostomy was performed, and he was discharged home on full-time positive pressure ventilation (PPV) via tracheostomy. When the patient was 6 years old, *PHOX2B* gene mutation analysis became available and showed a 20/27 PARM that is diagnostic of CCHS. Strabismus developed during the patient's early childhood that required surgical correction. He continues to require full-time ventilatory support with PPV via tracheostomy. Periodic echocardiograms and Holter monitoring were normal. The patient attends regular school and does not have neurocognitive delays.

The patient's mother, age 52 years, was healthy until age 32 years. She was born at term by an uncomplicated normal vaginal delivery and had an uneventful neonatal course. She denied childhood seizures, constipation, or respiratory infections requiring oxygen or ventilatory support. She noted the ability to voluntarily hold her breath longer than others during her childhood. At 32 years of age, following surgery for a knee injury, she required inpatient hospitalization and oxygen therapy for 3 days. Attempts to wean from oxygen led to headache and desaturations on pulse oximetry. A similar pattern was noted in the following four surgeries requiring anesthesia. She had a routine blood chemistry performed by her physician that showed elevated serum bicarbonate of 45 mEq/L. She noticed desaturations during sleep using a pulse oximeter after her son received a diagnosis of CCHS. Her body mass index was 27 kg/m^2. Family history is significant for several first cousins in whom sleep apnea

Figure 1—Split-night sleep study shows OSA and episodic hypoxemia during the diagnostic portion and subsequent CPAP titration.



APAP = autotitrating positive airway pressure, ASV = adaptive servoventilation, CPAP = continuous positive airway pressure, EPAP = expiratory pressure, IPAP = inspiratory pressure, PLM = periodic limb movement, REM = rapid eye movement sleep, RERA = respiratory effort-related arousal.

was diagnosed and required continuous positive airway pressure therapy (CPAP).

PHOX2B gene sequence analysis was performed on the mother and was positive for 20/27 PARM, diagnostic of CCHS. Blood tests showed normal levels of hemoglobin of 14.2 g/dL and hematocrit 42.7%. Arterial blood gas showed pH 7.42, PCO_2 37 mmHg, PO_2 58 mmHg, and bicarbonate of 24 mmol/L while awake breathing room air. Pulmonary function test was normal. Echocardiogram showed normal right heart size and pulmonary artery pressure. Holter recording was normal. She reports an overnight polysomnography without capnography that showed obstructive sleep apnea (OSA) and sleep-related hypoxemia. A subsequent overnight polysomnography was performed as a split-night study, which consisted of a diagnostic portion and positive airway pressure titration (**Figure 1**). The diagnostic portion of the sleep study showed OSA with apnea-hypopnea index (AHI) of 14.4 events/h, baseline SpO_2 94% to 95%, minimum SpO_2 of 80%, and 2.5% sleep time with SpO_2 < 90%. During the remainder of the sleep study, CPAP was initiated and titrated to 9 cmH_2O without any residual OSA or hypoxemia. However, CO_2 monitoring was not performed during the sleep studies. Her first son, age 16 years, did not have any mutations in the *PHOX2B* gene.

Based on the mother's *PHOX2B* gene mutation, a repeat polysomnogram was recommended with end-tidal CO_2 monitoring and noninvasive PPV titration. Because her *PHOX2B* gene mutation is associated with life-threatening sinus pauses, annual Holter monitoring was recommended. Annual echocardiogram to assess for pulmonary hypertension was recommended as well. Because *PHOX2B* gene mutations are inherited in an autosomal dominant pattern, *PHOX2B* gene mutation testing was recommended for immediate family members and her siblings.

DISCUSSION

We present the case of a 52-year-old woman with 20/27 PARM *PHOX2B* mutation with a mild clinical phenotype, whereas the expected clinical phenotype with a similar genotype requires full-time ventilatory support, has Hirschsprung disease, and is at risk for sudden cardiac death from arrhythmias. This patient was evaluated and CCHS was subsequently diagnosed primarily by the presence of a family history of CCHS.

CCHS is characterized by hypercapnia and/or hypoxemia, which is worse during sleep than during wakefulness. Patients with CCHS have absent or negligible ventilatory sensitivity to hypercapnia and hypoxemia, and do not exhibit signs of respiratory distress when challenged with hypercarbia or hypoxia.[5,6] This explains our patient's ability to hold her breath longer than others during early childhood. These subtle symptoms in childhood have been described in adults in whom CCHS was diagnosed.[1,3,7]

The diagnosis of CCHS must be confirmed with *PHOX2B* gene mutation. Different mutations in the *PHOX2B* gene lead to different levels of cellular dysfunction, influencing the phenotype of an individual patient with CCHS. In general, milder disease courses are expected with fewer PARM (20/25 or 20/26) and are not usually associated with neural crest tumors or Hirschsprung disease.[1] Patients with genotypes 20/27 to 20/33 usually require continuous ventilatory support and have clinical manifestations of autonomic dysfunction including Hirschsprung disease, strabismus, etc. as seen in our 14-year-old patient. Autosomal dominant inheritance with variable penetrance of the *PHOX2B* mutation could explain the mild phenotype seen in our patient's mother.[1] This phenotypic variability may be due to unknown modifier genes or environmental factors.[1,3] In this family, there is autosomal dominant inheritance, incomplete penetrance, and variability in phenotype.

Most patients with CCHS present during the newborn period. Some are asymptomatic until older childhood, adolescence, or adulthood when they present with unanticipated respiratory failure, seizures, pulmonary hypertension, or polycythemia following stressors such as viral illness, pneumonia, or exposure to anesthesia.[1,8] Thus, in these age groups, the diagnosis of CCHS should be considered in cases of unexplained alveolar hypoventilation, apnea, cyanosis, or seizures

after administration of anesthetics or central nervous system depressants, or with relatively mild respiratory infections.[1] Because of the rare incidence of this disease as well as presentation at a later age, this diagnosis can be missed by many clinicians who are unaware of CCHS.

Late-onset CCHS (beyond the newborn period) has been reported in patients with the milder 20/24, 20/25 PARM *PHOX2B* and in NPARMs.[1,2,7,8] Adults with 20/27 PARM *PHOX2B* mutation have been identified by testing parents of patients with CCHS. These adults had mosaicism of the 20/27 PARM *PHOX2B* mutation.[3,9,10] Our patient's mother was heterozygous for the 20/27 PARM *PHOX2B* mutation consistent with a diagnosis of CCHS. This case study is the first to demonstrate the 20/27 PARM *PHOX2B* mutation in an adult that is not attributed to somatic mosaicism.

PHOX2B mutations are inherited in an autosomal dominant pattern, but with incomplete penetrance. Thus, it is important to test both parents of an affected child for the *PHOX2B* mutation.[1] Early identification of parents with *PHOX2B* mutations can facilitate prompt evaluation and interventions to improve long-term outcomes, as well as genetic counseling for familial recurrence in parents planning to have offspring.

Our case study shows that relatively asymptomatic individuals with *PHOX2B* gene mutations can manifest later in life as suggested by the elevated serum bicarbonate seen in our patient's mother. Hence, periodic evaluation of cardiac and respiratory function in asymptomatic individuals with *PHOX2B* gene mutations are essential, and patients should be counseled on ventilatory disturbances that can be induced by anesthesia, alcohol, and respiratory infections.

Our study also highlights the importance of incorporating capnography in adult polysomnography protocols in individuals with *PHOX2B* mutations. Overnight polysomnography without monitoring for CO_2, as was performed in this case will not detect the alveolar hypoventilation that is present in individuals with CCHS.

Our case represents an atypical familial presentation of CCHS in an adult with 20/27 PARM *PHOX2B* mutation and emphasizes the importance of screening for *PHOX2B* gene mutations in relatively asymptomatic parents of children with CCHS.

ABBREVIATIONS

AHI, apnea-hypopnea index
CCHS, congenital central hypoventilation syndrome
CPAP, continuous positive airway pressure therapy
NPARM, nonpolyalanine repeat mutations
OSA, obstructive sleep apnea
PARM, polyalanine repeat mutations
PPV, positive pressure ventilation

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DISCLOSURE STATEMENT

Work for this study was performed at the Children's Hospital Los Angeles. All authors have reviewed and approved the manuscript. The authors report no conflicts of interest.