Congenital central hypoventilation syndrome with PHOX2B mutation in Saudi Arabia: a- single center experience

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Introduction:

CCHS is a rare condition in which there is no respiratory response to hypoxia or hypercarbia during sleep in the absence of any lung or neuromuscular diseases or identifiable brainstem lesions. CCHS typically presents in the newborn period. Three cases with varying clinical presentations at the Pediatric ICU (PICU) at Prince Sultan Military Medical City (PSMMC) in Riyadh between 2008 and 2013 are reported. All cases involved sleep study findings that are typical of CCHS, and the diagnosis was confirmed by molecular genetic analysis.

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Case 1:

A 24-month-old boy who had required hospitalization since birth was referred in 2008 to a pediatric pulmonologist for failure to wean from the ventilator. He was born at PSMMC following a full term uneventful pregnancy with normal SVD and a BW of 3.6 kg. He remained hospitalized because of recurrent apnea requiring mechanical ventilation (MV), which was converted to nighttime only ventilation at 18 months of age. His physical examination (PE) while awake, CXR, ECG, echocardiogram, EEG, brain MRI, and metabolic screening produced normal results. An upper GI study revealed high-grade reflux, which was treated with anti-reflux medication. An overnight polysomnogram (PSG) showed baseline saturation on the SIMV ventilator of 100%, with an end tidal CO_2 of 25 mm Hg. When off the ventilator, the patient developed central apnea with shallow breathing and was unresponsive to hypoxia. His O_2 saturation was approximately 70% with hypercarbia up to 50 mm Hg in the NREM stage. A genetic study was positive for a heterozygous polyalanine repeat expansion mutation (PARM) up to 28 repeats in PHOX2B gene, which is consistent with CCHS. Non-polyalanine repeat mutations (NPARMs) were non-detectable. A tracheostomy tube was inserted, and MV was provided during sleep.The patient was discharged home at 26 months of age when his parents were confident that they could provide care for him; regular 2-month clinic follow-ups and annual screening for associated conditions were planned. He is currently doing well at age 7 under this management, without further complications.

Case 2:

An 18-month-old boy with recurrent attacks of apnea since 30 minutes of age was referred by the PSMMC NICU to pediatric pulmonology for consultation in April 2011. He was born FT at 39 weeks, with a history of maternal polyhydramnios. His BW was 3 kg, with a normal Apgar score. At 30 minutes of age, he had cyanosis and desaturated on room air to 68%. On PE, the baby was well appearing with no dysmorphic features, good breath and heart sounds, and good muscle tone. Initially, a trial of CPAP was administered, but he continued to have frequent episodes of apnea. The patient was intubated and repeatedly failed extubation because of recurrent apnea. In the PICU, his CXR, ECG, echocardiogram, septic screening, brain MRI, and metabolic screening were all normal. EEG showed frequent seizure activity. He was started on phenobarbital (3 mg/kg/day) with no improvement during 3 weeks of treatment, and a repeat EEG after he was off medication was normal. An overnight PSG revealed typical findings of CCHS similar to Case 1. Genetic analysis of PHOX2B revealed a homozygous 26 repeat polyalanine expansion. NPARMs were non-detectable. A tracheostomy tube was inserted, and nocturnal MV was initiated. Ventilatory support and parental ability to care for the child at home were assessed. He was discharged home at 20 months of age with regular clinic follow-up every 2 months, and annual screening for associated complications. Currently he is 4.5 years old and is doing well with no complications.

Case 3:

A female infant, delivered by Caesarian section preterm at 35 weeks following a gestation affected by polyhydramnios, had a BW of 2.5 kg and was referred at 23 days of age to PSMMC by a private hospital in 2013. Since birth, the patient had apneic attacks of 20 seconds duration, increasing with feeding and sleep and was on MV. She had no history of fever, decreased activity, abnormal movements, or cyanosis; however, there was a family history of stillbirth of unknown cause.

Examination was unremarkable. An upper GI study showed severe reflux, which was treated medically. All other investigations were normal, and overnight PSG revealed typical findings of CCHS, similar to the other cases. Genetic analysis revealed a heterozygous polyalanine expansion to 27 repeats in PHOX2B gene, with no other significant mutations. A tracheostomy tube was inserted, and 24-hour MV was started.

A detailed medical report about her condition and long-term management was provided to her parents, and she was transferred after 3 months to a medical care center closer to her home.

Discussion:

CCHS is a rare autosomal dominant genetic disorder affecting the autonomic nervous system that was first described in 1970 by Mellins.1 In 2003, the PHOX2B gene was found to be the disease-defining gene. There are a few reports of CCHS from the Middle East, including a single case report from Riyadh. That case, a 5-month-old boy who had been intubated since he was 5 minutes old, was referred to a sleep disorders center where the diagnosis was made 2. Our 3 cases from a single institution supplement the experience in SA and should help increase awareness of this serious disorder in those involved with the initial care of the newborn. CCHS is characterized by decreased sensitivity to hypoxia and hypercarbia during sleep, with diminished ventilatory and arousal responses, in addition to multiple nonspecific abnormal physiological, motor, and neuropsychological characteristics such as seizures. One of our cases exhibited seizure activity at the time of diagnosis, which resolved spontaneously. . In the review of 196 CCHS patients in 19 countries, 41.8% had a history of seizures. 3 Seizures were more common in children requiring 24-hour MV (70.0%) compared with those who were mechanically ventilated only during sleep (38.6%). Our single case discharged on 24-hour MV had no seizure history. Two of our cases had severe reflux, which is commonly associated with CCHS, although this is a nonspecific finding because approximately 50% of infants 0 to 3 months old have at least one episode of regurgitation per day (Nelson.1997). CCHS patients usually present at birth or in early infancy 4, but patients with milder forms are diagnosed later in childhood or even in adulthood (late-onset CCHS) during exposure to sedation, anesthesia, infection, or when evaluated for sleep apnea. As in our patients, 90% of CCHS cases are linked to de novo PARMs in PHOX2B gene. The normal allele contains 20 alanine molecules, and the repeat expansion mutation results in expansion to 24-33 repeats. Of these mutations, 20/25, 20/26, and 20/27 are the most common genotypes reported.4 figure-1.

Cases with more than 26 poly alanine repeats are at risk of requiring 24-hour ventilatory support. Our Case 3, with 27 repeats, required 24-hour ventilation; however, Case 1 with 28 repeats was discharged home requiring mechanical ventilation only during sleep. Hirschsprung disease (HD) occurs in approximately 20% of CCHS patients; however, it occurs primarily in patients with NPARMs and has been reported with increasing frequency in PARM subjects who have increasing numbers of polyalanine repeats. None of our cases, with 26, 27, and 28 polyalanine repeats, showed signs and symptoms of HD. Neural crest tumors also occur frequently in patients with NPARMs; however, they have only been identified in PARM patients with 20/29 and 20/33genotypes.4 Figure 2.

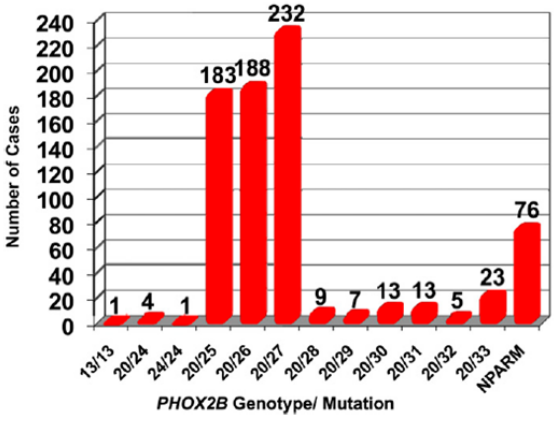

Figure 1. Number of *PHOX2B* polyalanine repeat mutations by genotype. The most common genotypes are 20/25, 20/26, and 20/27.

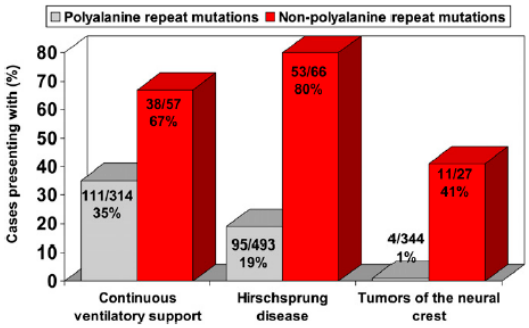

Figure 2. Rate of continuous ventilatory dependence, Hirschsprung disease, and tumors of the neural crest in congenital central hypoventilation syndrome (CCHS) cases with polyalanine repeat expansion mutations (PARMs) in *PHOX2B* compared with CCHS cases with non-polyalanine repeat expansion mutations (NPARMs) in *PHOX2B*. CCHS cases included in this figure were compiled from all known cases reported in the literature, including reports from groups in the United States, Italy, France, Japan, Germany, Taiwan, China, Australia, and The Netherlands. All PARM cases with tumors had large (29–33 repeat) expansion mutations.

As with our cases, children with suspected CCHS should be investigated to rule out primary lung, neuromuscular, and cardiac disease, or brain stem lesions that could have similar presentations. In addition, they should undergo a comprehensive respiratory physiology study during wakefulness as well as in REM and NREM sleep to determine the degree of hypoventilation and the level of ventilator support needed (in CCHS hypoventilation is typically worse in NREM sleep). The aim of CCHS management is to maintain adequate oxygenation and ventilation during wakefulness and sleep and to improve long-term outcomes by decreasing the risk of complications resulting from prolonged hypoxemia. Follow-up of CCHS patients should include regular assessment of development, annual ophthalmology examinations, cardiac evaluations, and screening for neural crest tumors and HD.4

Early diagnosis and immediate intervention are key to improving the survival and quality of life (QOL) of neonates with CCHS. Our cases exemplify the QOL and resource utilization burden that can result when CCHS is not suspected and diagnosed immediately in neonates who have characteristics of the condition. Our cases had been hospitalized since birth, with diagnosis at 24 months, 18 months, and <1 month. They were in hospital for a total of 26, 20, and 3 months, respectively, before they were discharged to home care. In a series of 196 CCHS patients in 19 countries, 44.9% were discharged by 6 months of age, and 26% were >12 months of age at the time of discharge.3

Conclusions:

These cases confirm that CCHS awareness is warranted in Saudi Arabia. We believe that there are many other undiagnosed cases that may have succumbed to the adverse possible outcomes when prompt and appropriate intervention were not provided; in addition, these cases may present a significant healthcare burden while they and their families suffer its effects on their QOL. Early, detailed differential diagnosis can contribute to developing an appropriate customized management plan that can significantly reduce resource utilization, help prevent serious complications, and improve the lives of these children and their families.

References:

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