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Late Onset Central Hypoventilation Syndrome due to a Heterozygous Polyalanine Repeat Expansion Mutation in the PHOX2B Gene

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Abstract

This report describes a 6 year old girl with late onset central hypoventilation syndrome due to a heterozygous polyalanine repeat expansion mutation in the PHOX2B gene. This report aims to increase the awareness of this condition among physicians to allow earlier clinical and genetic diagnosis and management of cases of unexplained hypoventilation.

Keywords: Late onset central hypoventilation syndrome; Alveolar hypoventilation; Autonomic nervous system; Hirschsprung disease; Polyalanine repeat; PHOX2B; Heterozygous.

Introduction

Congenital central hypoventilation syndrome (CCHS), known as the literary misnomer "Ondine's curse" (Mendelian Inheritance in Man number: 209880), is a rare disorder of respiratory control with related autonomic nervous system deregulation/ dysfunction.[1,2] It is characterized by alveolar hypoventilation and decreased sensitivity to hypercarbia and hypoxemia, particularly during sleep in the absence of neuromuscular or lung disease, or an identifiable brain stem lesion. The symptoms of autonomic nervous system deregulation or dysfunction are frequently seen in CCHS. Associations of Hirschsprung disease and tumors of neural crest origin, namely; neuroblastoma, ganglioneuroblastoma, and ganglioneuroma have been reported in some CCHS cases.[2]

Mutations in paired-like homebox (*PHOX*) *2B* gene, which encodes a highly conserved transcription factor known to play a key role in the development of autonomic nervous system reflex circuits in mice, were identified in patients with CCHS.[3] The great majority (>90%) of patients with CCHS are heterozygous for a polyalanine repeat expansion mutation involving the second polyalanine repeat sequence in exon 3 of *PHOX2B*.[3-5] Expansions range from 15- 39 nucleotide insertions, resulting in the expansion of the normal 20-repeat polyalanine tract to 25-33 repeats.[4,5] Most expansion mutations occur *de novo* in CCHS probands. However, these mutations can be inherited as an autosomal dominant trait as they were identified in a small number of families segregating the condition.[5] Polyalanine repeat expansion size has been associated with severity of a number of symptoms of autonomic nervous system dysfunction and ventilatory dependence.[5,6]

Individuals with the shortest of the *PHOX2B* polyalanine expansion mutations known to cause CCHS may survive into older childhood or even adulthood without manifesting the early respiratory failure classically associated with the CCHS phenotype.[7] Moreover, somatic mosaicism has been observed among the family members of probands with CCHS,[8] thus explaining variable expression and incomplete penetrance of *PHOX2B* mutations.[5,9,10]

Case Report

A 6-year old girl was referred to the Pediatric Intensive Care Unit, Royal Hospital, Oman, from another tertiary hospital where she underwent dental extraction under appropriate weight determined dose general anesthesia (fentanyl, midazolam hydrochloride and rocuronium bromide). Post surgery, she had 3 failed attempts of extubation due to shallow breathing and apnea.

The patient was born at term after an uneventful pregnancy. She had no neonatal problems. Her gross and fine motor developments were normal, there was no concern about her breathing and was never noticed to have breathing problems during sleep. She never complained of visual changes or headache. On detailed past history, there was no history suggestive of episodes of cyanosis, fainting, loss of consciousness, nausea, gastroesophageal reflux, constipation, altered perception to pain, altered sweating, or urinary incontinence. Her parents and seven siblings are apparently healthy. There was no family history of breathing difficulty or constipation.

She was alert and comfortable on low ventilatory settings of mechanical ventilation via endotracheal intubation. Her weight and height were both below the third centile for her age and sex. Her head circumference was within normal centiles for her age and sex. She was hemodynamically stable and had no dysmorphic features or external neurocutaneous lesions. She had normal abdominal and respiratory examination and normal heart sounds with no murmur. She was examined by the neurologist when she was fully awake and off ventilation. She had normal examination of pupils and cranial nerves. There was no facial weakness. Her tongue was midline with no fasciculation and had normal bulk and

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movements. On motor examination, she had normal strength, tone and bulk of muscles and there was no grip myotonia or fatigability. There were no cerebellar signs and deep tendon reflexes were all present.

Basic investigations including serum electrolytes, urea, creatinine, glucose, hemoglobin, lactate and ammonia were all within normal ranges. Electrocardiogram and echocardiogram were reported normal but 24-hr Holter monitoring could not be performed. Magnetic resonance image of the brain revealed no structural abnormality.

Following each extubation tried, the patient developed drowsiness, tachycardia and profuse sweating. Serial arterial blood gases following extubations confirmed hypercarbia with PCO2 up to 133 mmHg and pH of 6.9. However, she showed dramatic improvement following re-intubation and mechanical ventilation, thus her arterial blood gas readings were corrected. She had no response to neostigmine, naloxone infusion and regular doses of caffeine. She underwent tracheostomy following several attempts of failed extubation. It took her about three weeks to adapt spontaneous breathing without mechanical support during daytime. Currently, she is dependent on mechanical ventilation only when she is asleep. Polysomnography and formal neurocognitive assessment could not be done because of the unavailability of these facilities in our hospital.

Deoxyribonucleic acid (DNA) was analysed for the length of the polyalanine tract in exon 3 of the PHOX2B gene in one of the accredited laboratories in the United Kingdom. She had a normal allele (20-residue polyalanine tract) and an expansion mutation. This expansion was confirmed and sized as approximately 5 alanines by bidirectional sequence analysis of the polyalanine tract. An expansion of this size is confirmatory for the diagnosis of late onset central hypoventilation syndrome. Further evaluation of other family members including genetic cascade screening was offered but the family decided to leave this issue at this stage.

Discussion

It is now clear that there is a range of presentations associated with expansion mutation in the PHOX2B gene, incomplete penetrance and variable expressivity due to somatic mosaicism, raising the possibility that some individuals may remain asymptomatic throughout life.[6-10] Antic et al. (2006) showed that many of the adults with central hypoventilation syndrome had laboratory evidence for the chronicity of their symptoms, including hypercarbia, polycythemia, and right heart changes before they were diagnosed.[7] Moreover, these cases presented with significant cognitive impairment, and the authors suggested the possibility that these adults suffered from neurocognitive sequelae of hypoxemia and hypercarbia. Our report along with previously published reports,[6,7,11-13] indicates that it is likely that there are children with yet undiagnosed central hypoventilation syndrome; thus highlighting the need for a high index of suspicion among health professionals and increased awareness of the importance of making such diagnosis, not only for further physiological compromise to be prevented, but also to avoid unnecessary work up in such scenarios.

Similar to the report by Mahmoud et al. (2007) of a child who had an unanticipated respiratory complications following an elective tonsillectomy and eventually required a tracheostomy and long-term ventilatory support.[14] Our case underwent elective surgery which could have been avoided if there was a family history and/or if the genetic test was available. This report supports what has been previously observed,[7,12] that later-onset cases with the 20/24 or 20/25 genotype have the mildest hypoventilation and are managed with nocturnal ventilatory support only.

With the growing number of reports of cases of central hypoventilation syndrome identified after the newborn period, with presentation from infancy into adulthood, an improved understanding of the molecular basis of the PHOX2B mutations and of the PHOX2B genotype/phenotype relationship may help to anticipate the clinical phenotype for each affected individual. Determining the genetic mutation in patients with this syndrome is important as researches confirmed that non-polyalanine repeat mutations produced more severe disruption of *PHOX2B* function and patients carrying these mutations should be evaluated for neural crest tumors.[15,16] Therefore, confirming the clinical diagnosis by molecular genetic analysis helps to avoid unnecessary surveillance in patients with polyalanine repeat expansion.

It is recommended that parents of any child with pathogenic expansion mutation have *PHOX2B* testing performed, both for counselling regarding recurrence risk in future children and because the carrier parent may have undiagnosed symptoms of hypoventilation requiring evaluation and intervention. Identification of mutation carriers in these families may allow for appropriate clinical monitoring and early implementation of treatment, if required.

Conclusion

Congenital central hypoventilation syndrome may present late with hypoventilation following general anesthesia and difficult recovery requiring invasive ventilatory support. Health professionals should be aware of this condition and it has to be one of the differential diagnoses in patients with failed or difficult extubation.

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