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CASE SERIES

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Three generations of a family diagnosed with congenital central hypoventilation syndrome: A case series

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Abstract

Congenital central hypoventilation syndrome (CCHS) is an autosomal dominant disorder characterized by alveolar hypoventilation and autonomic dysregulation secondary to mutations of the *PHOX2B* genes. We present five cases from three generations within the same family with varying degrees of phenotypic expression of the *PHOX2B* gene mutation. The cases were diagnosed following identification of CCHS in index case at birth. This case series underscores the importance of screening first-degree relatives of individuals with confirmed CCHS and alerts the clinicians to maintain a high degree of suspicion in asymptomatic family members given the high degree of phenotypic variability of CCHS.

KEYWORDS

BPAP, CCHS, infants, PHOX2b, tracheostomy

INTRODUCTION

Congenital central hypoventilation syndrome (CCHS) is a rare disorder of the respiratory and autonomic nervous systems associated with a mutation in the paired-like homeobox 2B (*PHOX2B*) gene.[1] The disorder results in ventilatory impairment characterized by alveolar hypoventilation which worsens in sleep and occurs in individuals with otherwise normal pulmonary mechanics. Presentation is typically in the neonatal period with apnoea, hypoxaemia and hypercarbia in the absence of respiratory distress.[2] Hypoventilation is more pronounced during non-rapid eye movement sleep.[3] Although most patients present in infancy, milder late-onset presentation in toddlers, children and adults has been infrequently described.[4]

Diagnosis is based on the identification of a pathologic variant in the *PHOX2B* gene in the absence of primary pulmonary, cardiac or neuromuscular disease or a causative brainstem lesion.[5] Almost 90% of cases are secondary to polyalanine repeat mutations in the *PHOX2B* gene. Initially thought to be due to de novo mutations, an autosomal dominant mode of inheritance has been documented.[6] Reports of CCHS in identical twins, female siblings and male–female half siblings, as well as parent–child transmission, have been described.[6,7]

We describe a series of five cases from three generations within the same family with varying degrees of phenotypic expression of the *PHOX2B* gene mutation. These cases not only highlight the challenges of managing this rare disease, but also underscore the importance of genetic counselling and screening among first-degree relatives and extended family members.

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Methods

The identification of CCHS in the index case after birth prompted evaluation of other family members (Figure 1). Genetic testing and counselling were performed for all family members. All members with a confirmed diagnosis of CCHS underwent a complete assessment including polysomnography, neurologic and ophthalmologic examination and cardiac assessment using electrocardiography and echocardiography. The two children in the family were managed at the same institution by the authors. The three adults diagnosed following the index case were managed by their respective physicians.

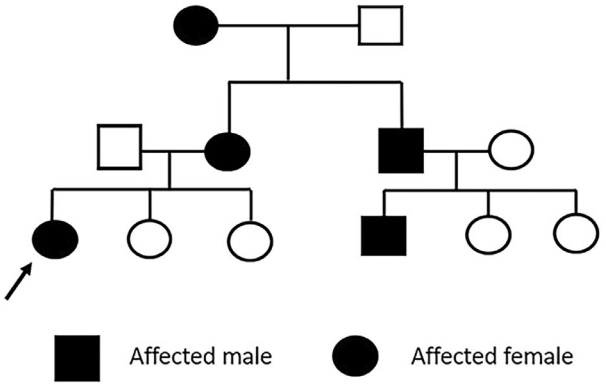

FIGURE 1 Family pedigree of members affected with congenital central hypoventilation syndrome

Index case

The index case is a 2-year-old infant who was born at term with a weight of 4590 g. Hypoxia, respiratory distress and hypotonia were noted soon after delivery. Her initial capillary blood gas revealed respiratory acidosis with pH 7.18 and pCO_2 90 mmHg. She was placed on nasal mask bi-level positive airway pressure (BPAP) due to hypercarbia and hypoxaemia. Investigations including creatine kinase, urine metabolic screen, echocardiography, ophthalmology review, thyroid function testing, amplitude integrated encephalography, brain magnetic resonance imaging, comparative genomic hybridization array and spinal muscular atrophy gene testing were all normal. Nasoendoscopy showed only mild laryngomalacia. In view of unexplained hypercarbia, *PHOX2B* gene testing was requested. Pending this result, polysomnography was requested to better characterize her gas exchange. DNA testing revealed a 25-repeat polyalanine expansion mutation of the *PHOX2B* gene confirming the diagnosis of CCHS. In discussion with her family, it was decided to ventilate this child non-invasively and not perform a tracheostomy. At our centre, non-invasive ventilation as an option to tracheostomy is offered to carefully selected patients. Ventilation was managed non-invasively using BPAP only during sleep. The average volume-assured pressure support (AVAPS) feature was used for ventilation resulting in more consistent gas exchange.[8]

The child continues to develop normally and is followed up regularly at our Non-invasive Ventilation Clinic. Titration studies are performed on a regular basis to ensure ideal pressure support settings. She has developed midface hypoplasia, an anticipated consequence of long-term non-invasive ventilation, and is under regular review by the orthodontic team.

Case 2

Soon after the diagnosis of the index case, her first cousin, aged 6 years, underwent adenotonsillectomy for obstructive hypoventilation following polysomnography performed at a different institute for investigation of snoring. This child had not yet been evaluated for the possibility of CCHS. A few hours after adenotonsillectomy, the child had a respiratory arrest, necessitating intubation and ventilation. Following recovery, *PHOX2B* genetic testing was performed which revealed one normal and one expanded polyalanine allele (genotype [20, 25]), confirming the diagnosis of CCHS. After discussion with the family, he was ventilated non-invasively using BPAP. High inspiratory pressures were needed to maintain adequate gas exchange. Adequate ventilation was achieved non-invasively using the AVAPS mode. Adherence to treatment remains excellent. He continues to develop normally and is regularly followed up at our clinic. Titration studies are performed on a regular basis to ensure ideal pressure support settings. She is regularly reviewed by an orthodontist to monitor for midface hypoplasia.

Family members

The diagnosis of the index case prompted screening of the remaining family members which consisted of the parents of the index case, the parents of the first cousin of the index case and the grandmother of the index case. All were asymptomatic at the time of evaluation. The uncle of the index case, however, had had a respiratory arrest following gall bladder surgery several years earlier. Following the diagnosis of the children, he was tested for a *PHOX2B* mutation which confirmed the diagnosis of late-onset CCHS. BPAP during sleep has been recommended and he is currently being followed up by an adult respiratory and sleep physician. The mother and grandmother of the index case also tested positive for a *PHOX2B* gene mutation. They remain asymptomatic. Both have been recommended BPAP for use during sleep.

The index case has had a sibling born since her diagnosis. The newborn sibling was monitored with transcutaneous CO_2 monitoring and oximetry in the immediate newborn period with no evidence of hypoventilation, hypoxaemia or autonomic dysfunction noted. Subsequent *PHOX2B* testing revealed no abnormality.

DISCUSSION

We report the unique occurrence of CCHS among five members of a single family in three generations with a varying degree of penetrance and expressivity resulting in diverse clinical manifestations ranging from newborn respiratory failure to asymptomatic adult presentation with hypoventilation in sleep. Had the index case been not identified, most members of the family would have remained undiagnosed.

Our study highlights the importance of genetic counselling and screening not only in immediate family members, but also in the extended family. Our report also raises awareness of this rare entity with varied clinical presentation

which should always be considered in cases presenting with hypoventilation and autonomic dysfunction where primary lung disease, ventilatory muscle weakness or obvious neurologic disorders have been excluded.

Providing positive pressure ventilation (PPV) in infants and children with CCHS poses many challenges. There are two approaches to PPV in infants: PPV via tracheostomy and non-invasive ventilation using a nasal mask. There is a geographic variation in the ventilatory management of CCHS. In North America, tracheostomy is the preferred route for ventilation in early childhood.[5] In Sweden, non-invasive ventilation is preferred.[9] At our centre, we approach the issue of ventilatory support on a case-by-case basis using non-invasive ventilation where possible. The challenges of using non-invasive BPAP in very young infants with CCHS include finding appropriate interfaces, ensuring proper parental education in the prompt institution of BPAP during daytime naps and overnight sleep and prevention of midface hypoplasia from mask use.

We have previously reported the use of the AVAPS mode in ventilating an infant with CCHS, thereby achieving more consistent ventilation.[8] Consistency is particularly important as patients with CCHS require lifelong assisted ventilation, at least during sleep, and weaning of ventilation is not advisable.

In conclusion, our study underscores the importance of rigorous genetic screening in at-risk family members of an individual with CCHS. Affected family members may not experience symptoms. Early diagnosis and adequate ventilatory management can prevent associated neurologic morbidity and improve long-term outcomes.

AUTHOR CONTRIBUTION

Vishal Saddi drafted the initial manuscript. Ganesh Thambipillay, Marina Pimenta, Bradley Martin, Gregory Blecher and Arthur Teng equally contributed to its development and approved the final version.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this case series and accompanying images.

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