CLINICAL CASE REPORTS

Early-onset Congenital Central Hypoventilation Syndrome – a case report of atypical presentation

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ABSTRACT

Introduction: Congenital Central Hypoventilation Syndrome (CCHS) is a rare genetic disorder characterised by central hypoventilation, mainly during sleep, and abnormal ventilatory responses to hypercapnia and hypoxia. It typically presents soon after birth with severe hypercapnic respiratory failure requiring ventilatory support, but may also manifest later following a respiratory event or anaesthesia.

Case Report: A 22-day-old female neonate was evaluated after a choking episode, with multiple episodes of desaturation during sleep and no other clinical signs. Diagnosis of CCHS was confirmed by identification of a missense variant c.305G>T (p. Arg102Leu) in the PHOX2B gene.

Discussion: Identification of an NPARM variant complicates genotype-phenotype correlation. Nonetheless, NPARM variants in exon 2 have been linked to milder and later-onset clinical forms, as observed here. This case highlights the possibility of subclinical CCHS manifestations in the neonatal period, presenting as unexplained desaturation episodes, which may delay diagnosis.

Keywords: atypical manifestation; Congenital Central Hypoventilation Syndrome; PHOX2B gene; NPARM

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INTRODUCTION

Congenital Central Hypoventilation Syndrome (CCHS) is a rare and likely underdiagnosed genetic disease, with an estimated incidence of 1 in 150,000–200,000 live births.[1] It is an autosomal dominant inherited disorder associated with pathogenic variants in the PHOX2B gene, and it is characterised by dysfunction of the autonomic nervous system.[1,2] Most pathogenic variants occur *de novo*, with approximately 90% involving a polyalanine repeat expansion variants (PARM) in exon 3 (with an additional 4 to 13 alanine residues).[2,3] The remaining 10% comprise frameshift, missense, or nonsense variants, referred to as non-polyalanine repeat variants (NPARM),with frameshift variants in exons 2 and 3 being the most common.[2,3] There is growing evidence of a clear, albeit not absolute, correlation between the severity of clinical features and PHOX2B variants.[2,3] In general, findings suggest that longer PARMs and NPARMs variants result in a more severe clinical phenotype.[2,3]

The majority of individuals present during the newborn period with signs of alveolar hypoventilation, most apparent during sleep, and usually without a ventilatory response to hypercapnia and hypoxia.[2] CCHS should be considered in a newborn with severe hypercapnic respiratory failure requiring ventilatory support, who is unable to tolerate reductions in ventilator rate settings and/or experiences unexpected failed extubations.[2] Due to an abnormal response to hypoxia and hypercapnia, these patients do not show signs of respiratory distress such as nasal flaring, tachypnoea, or intercostal retractions.[2] When diagnosed within the first month of life, it is classified as early-onset CCHS.[1] However, CCHS can also manifest in childhood or even in adulthood– late-onset CCHS – with symptoms triggered by respiratory infection, anaesthesia or medications such as opioids, benzodiazepines or antiepileptics.[1] CCHS may be associated with Hirschsprung's Disease (HD), neural crest tumours and other manifestations of autonomic nervous system dysregulation, such as cardiac sinus pauses, pupil abnormalities, altered oesophageal and gastrointestinal motility, decreased pain perception and altered diaphoresis.[1,2]

CASE REPORT

A 22-day-old female neonate was brought to the emergency department due to a choking episode after feeding, without loss of consciousness. On admission, peripheral oxygen saturation (SpO_2) ranged between 89 and 95% on room air, with no signs of respiratory distress and normal cardiopulmonary auscultation. The parents did not report any abnormal respiratory patterns during sleep or wakefulness. The pregnancy had been monitored and was uneventful, with normal maternal serologies and prenatal ultrasounds. She was born at 39 weeks, with an Apgar score of 9/9/10, and required no resuscitation. Neonatal screenings were unremarkable. She was exclusively breastfed, with normal growth and infrequent episodes of regurgitation.

Hospitalisation was decided for monitoring, during which several desaturation episodes during sleep were observed, with a minimum SpO_2 of 65%, without respiratory distress or bradycardia/tachycardia. Most episodes resolved spontaneously, though some required supplemental oxygen via face mask. Venous blood gas analysis revealed CO_2 retention and secondary bicarbonate retention (pH 7.36, pCO_2 54.0 mmHg; HCO_3^- 30.5 mmol/L). Laboratory workup, urine dipstick test, chest radiography, and respiratory virus screen were all negative. Transthoracic echocardiogram showed a structurally normal heart, cranial ultrasound was normal, and electroencephalogram (EEG) revealed no unequivocal interictal epileptic activity. She was transferred to the Paediatric Pulmonology Unit on the 29thday of life for further investigation. Given the suspicion of CCHS and the unavailability of urgent polysomnography (PSG), an EEG with additional thoracic and abdominal respiratory bands and cardiorespiratory monitoring was performed. During sleep, multiple desaturations (down to 60%) without respiratory effort were evident and no heart rate (HR) or respiratory rate (RR) response was found. Central hypoventilation was assumed, and non-invasive positive pressure ventilation (NPPV) during sleep, with BiPAP S/T, was initiated. Cerebral MRI showed no abnormalities. Genetic testing could confirmed the diagnosis of CCHS, revealing a missense variant c.305G>T (p.Arg102Leu) in heterozygosity in the PHOX2B gene. Further investigations included 24-hour Holter monitoring, abdominal ultrasound, and ophthalmologic assessments, all of which were normal.

During hospitalisation, nocturnal NIV parameters were adjusted, resulting in the resolution of nocturnal desaturations and improvement in blood gas values. No respiratory compromise was observed while awake. She maintained exclusive breastfeeding, without any episodes of choking or gastro-oesophageal reflux and a normal intestinal transit. Growth was within the 15th–50th percentiles for weight, height and head circumference (WHO growth charts), and neurodevelopment was normal. Parental training on ventilation and resuscitation was provided. She was discharged after 34 days and referred for follow-up in pulmonology, cardiology, ophthalmology, and neurodevelopmental outpatient clinics. The venous blood gas analysis three months after starting NPPV showed improvement, with pH 7,41, pCO_2 46 mmHg and HCO_3^- 26.2 mmol/L.

Both parents underwent molecular genetic testing, which identified the same variant in the father. He had already undergone polysomnography, which demonstrated obstructive sleep apnoea with rare central apnoeas (1 event per hour).

DISCUSSION

CCHS is a rare genetic disease, with the majority of the individuals presenting during the newborn period with alveolar hypoventilation leading to severe respiratory failure requiring ventilatory support.[1] This is the classical phenotype associated with early-onset CCHS.[1] In late-onset CCHS, manifestations are atypical, and the diagnosis is established after the first month of life.[1] In our case, manifestations occurred in the neonatal period but were subclinical, with sleep-related desaturations accidentally found, and no reports of abnormal respiratory patterns. The case was classified as an early-onset CCHS, as it was diagnosed within the first month of life.

Before the discovery of the PHOX2B gene, polysomnography was essential for diagnosis, showing central hypoventilation, particularly in NREM sleep, without an appropriate cardiorespiratory response.[1] Nowadays, genetic testing is most frequently used, particularly in classical cases.[1] PSG is still useful when clinical manifestations are atypical, but it is an expensive and frequently unavailable test.[1] EEG complemented with plethysmography and cardiorespiratory monitoring can help characterise respiratory patterns during sleep.[6] In this case, multiple desaturations without respiratory effort, along with an absent cardiorespiratory response to hypoxia during sleep, suggested central hypoventilation related to CCHS.

Individuals with CCHS usually have *de novo* PARM variants in the PHOX2B gene.[1,2] A genotype-phenotype correlation is established, with disease severity associated with an increased number of alanine repeats.[2,3] NPARM variants, present in about 10% of cases, are associated with severe phenotypes requiring continuous ventilatory support and high risk of HD and neural crest tumours.[2,3] Recent studies have identified novel NPARM variants in patients with late-onset and milder presentations, suggesting that NPARM phenotypic expression varies widely depending on type and location of the pathogenic variant, making a consistent genotype-phenotype correlation impossible.[2,3] Zhou *et al.* demonstrated that exon 3 loss-of-function variants are associated with more severe clinical presentations than missense, in-frame or loss-of-function variants in exons 1 and 2.[4] They hypothesised that exon 3 variants may lead to mRNAs less prone to nonsense-mediated decay, allowing production of abnormal PHOX2B protein with dominant-negative effects.[4] Conversely, exon 1 and 2 variants may lead to mRNAs more likely to undergo degradation, resulting in haploinsufficiency as the main pathogenic mechanism, associated with milder, later-onset presentations.[4] In our case, the genetic test identified a missense variant in exon 2 c.305G>T (p.Arg102Leu). According to the Franklin Genoox clinical database, the variant is located in a conserved region of mammalian DNA and has an extremely low frequency in gnomAD population databases (ACMG classification PM2), leading to its classification as a variant of Uncertain Significance (VUS).[5] Computational prediction tools unanimously support a deleterious effect on the gene (ACMG classification PP3); the variant is a null variant in a gene where loss of function is a known mechanism of disease and the patient's phenotype is highly specific for this disease (ACMG classification PP4).[5] Together, these findings support consideration of a likely pathogenic classification. Nevertheless, although these findings are suggestive, they remain insufficient to support formal reclassification in pathogenic, and clinical management and genetic counseling should be conducted with caution. The milder manifestation in our patient was in correlation with the description in the literature of milder forms in CCHS cases with exon 2 pathogenic variants.

Patients with CCHS have a lifelong disorder, with artificial ventilatory support being the mainstay of care.[6,7] The choice of ventilatory support depends on age, disease onset, ventilatory dependence, medical team expertise, and patient/family preferences.[6,7] The decision must be individualised, weighing the risks and benefits of each modality.[6,7] For those under one year of age, optimal ventilation is usually provided via tracheostomy.[6,7] In this case, NPPV was chosen due to the milder presentation. As long-term use of NPPV can lead to mid-face hypoplasia, close monitoring for this complication will be important.[4]

A multidisciplinary approach is essential in CCHS follow-up to ensure early detection of comorbidities such as manifestations of the autonomic nervous system and neural crest tumours.[1] In our patient, cardiac, abdominal, and ophthalmology evaluations were conducted before discharge. Regular multidisciplinary evaluations will be needed during follow-up.[1]

Genetic counselling is essential for individuals diagnosed with CCHS.[1,6] Some NPARMs may be inherited from asymptomatic parents, indicating that pathogenic variants can follow an autosomal dominant pattern with incomplete penetrance or variable expressivity.[1,6] Parents who carry pathogenic variants may present with other autonomic nervous system dysregulation phenotypes, Hirschsprung's disease, or neural crest tumours, or may remain asymptomatic, only manifesting symptoms in situations such as respiratory infection, anaesthesia, or exposure to medications including opioids, benzodiazepines, or antiepileptics.[6] They also carry a risk of transmitting the disease to a subsequent child.[1,6] In our case, genetic counselling must be approached with caution, as a variant of Uncertain Significance (VUS) was identified in the patient. Nevertheless, the patient's phenotype is highly specific for this disease and may contribute to reclassifying the variant as likely pathogenic. This pathogenic variant was identified in the father, who currently shows no evidence of central apnoeas but remains under regular polysomnographic surveillance, as clinical manifestations may develop later in life due to the variable expressivity and incomplete penetrance of CCHS. Genetic counselling is important to discuss with the father the potential risk of transmission to a subsequent child and the limitations of current genotype–phenotype correlations.

CONCLUSION

This case highlights the possibility of CCHS presenting with subclinical manifestations in the first month of life, potentially hindering disease recognition and leading to delayed diagnosis. A novel NPARM variant in the PHOX2B gene, not previously documented in the literature, was identified. Genotype-phenotype correlation was difficult, but the location of the variant and the clinical presentation suggest a milder form of disease. Unexplained desaturation episodes in neonates should raise the hypothesis of CCHS, as atypical manifestations may be present at any age, and early recognition of the disease is crucial to the outcome.

AUTHORSHIP

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