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BEYOND RECURRENT PNEUMONIA: A PHOX2B-CONFIRMED CASE OF CONGENITAL CENTRAL HYPOVENTILATION SYNDROME PRESENTING WITH PERSISTENT HYPERCAPNIC RESPIRATORY FAILURE IN INFANCY

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ABSTRACT **Background:** Congenital Central Hypoventilation Syndrome (CCHS) is a rare disorder of autonomic respiratory control, most commonly caused by pathogenic variants in the PHOX2B gene. It classically presents in the neonatal period with hypoventilation, apnea and cyanosis, but delayed recognition may occur when the presentation is masked by recurrent respiratory infections.**Case Presentation:** We report a 1-year-old female child born to non-consanguineous parents who presented with cough, fever, progressive respiratory distress, poor feeding and lethargy. She had recurrent lower respiratory tract infections since infancy, congenital left eyelid ptosis, gross motor delay, hypotonia and neuroregression following acute illness. On admission, oxygen saturation was 75% on room air. Arterial blood gas analysis revealed pH 7.28, pCO2 65 mmHg and HCO3- 28 mEq/L, consistent with type II respiratory failure. Chest radiograph showed persistent right upper lobe collapse with hyperinflated lung fields. Echocardiography, MRI brain and metabolic workup were non-contributory. Persistent hypercapnia disproportionate to pulmonary findings raised suspicion of central hypoventilation. Genetic testing confirmed a heterozygous pathogenic duplication in exon 3 of PHOX2B, c.691_698dup; p.Gly234AlafsTer78. Parental testing showed absence of the variant in both asymptomatic parents, supporting a de novo mutation. The child was stabilized with ventilatory support and continued on non-invasive BiPAP.**conclusion:** CCHS should be suspected in infants with recurrent respiratory failure and persistent hypercapnia unexplained by pulmonary, cardiac, neuromuscular or metabolic disease. Early PHOX2B testing enables definitive diagnosis, timely ventilatory support and genetic counselling.

KEYWORDS : Congenital Central Hypoventilation Syndrome, PHOX2B, type II respiratory failure, hypercapnia, infant, BiPAP.

INTRODUCTION

Congenital Central Hypoventilation Syndrome (CCHS) is a rare, lifelong disorder of automatic respiratory control characterized by inadequate ventilatory response to hypercapnia and hypoxemia, most prominently during sleep. It was historically described as Ondine's curse and is now recognized as a disorder of autonomic nervous system dysregulation rather than an isolated respiratory disease. The disease-defining gene is PHOX2B, which has a central role in autonomic nervous system development. Current guidelines emphasize that demonstration of a pathogenic PHOX2B variant is required for definitive diagnosis.[1-4]

Most affected children present in the neonatal period with apnea, cyanosis and ventilatory failure. However, the clinical spectrum has widened, and later presentations during infancy, childhood and adulthood are increasingly recognized. Such cases may be misdiagnosed as recurrent pneumonia, chronic lung disease, neuromuscular weakness or metabolic illness. Recognition becomes especially difficult when respiratory infection coexists with unexplained carbon dioxide retention. We report a genetically confirmed case of CCHS in a 1-year-old child presenting with recurrent respiratory illness and persistent hypercapnic respiratory failure, highlighting the importance of early suspicion in infants with disproportionate hypoventilation.[5]

CASE PRESENTATION

A 1-year-old female child, born to non-consanguineous parents, was admitted with cough and cold for 15 days, fever for 10 days, increasing difficulty in breathing for 5 days, and decreased feeding with lethargy for 3 days. She had recurrent lower respiratory tract infections since infancy, often requiring hospital admission and oxygen therapy. There was no history of seizures, recurrent vomiting or documented cyanotic spells. Birth history was unremarkable; she was born at term by normal vaginal delivery, cried immediately after birth and had a birth weight of 3 kg. Family history was notable for early neonatal death in a sibling due to unexplained respiratory failure.

Developmental history revealed delayed gross motor milestones. The child could sit with support at 10 months and was not yet walking. Congenital left eyelid ptosis had been present since birth. Neurological concerns documented during evaluation included motor delay, hypotonia, hyporeflexia, delayed pupillary response and neuroregression following acute illness.

On examination, the child was pale, lethargic, tachypneic and in respiratory distress. Oxygen saturation was 75% on room air. Respiratory examination revealed reduced air entry over the right upper zone with bilateral fine crepitations. Cardiovascular and abdominal examinations were normal. Neurologically, she was drowsy but arousable and had mild hypotonia.

Initial investigations showed hemoglobin 8.1 g/dL and total leukocyte count 11,800/mm3 with neutrophilic predominance. Liver and renal function tests were normal. Arterial blood gas analysis showed pH 7.28, pCO2 65 mmHg and HCO3- 28 mEq/L, consistent with type II respiratory failure. Chest radiograph showed persistent right upper lobe collapse with hyperinflated lung fields. Echocardiography revealed a structurally normal heart, trivial tricuspid regurgitation and no pulmonary arterial hypertension. MRI brain was normal. Metabolic evaluation, including mitochondrial and amino acid profile, was normal. Electromyography showed motor axonal polyneuropathy; however, this did not adequately explain the persistent central hypoventilation and disproportionate hypercapnia. Polysomnography was not performed.

The child was initially managed for bronchopneumonia with oxygen therapy, nebulization, intravenous antibiotics and supportive care. In view of persistent hypercapnia despite appropriate treatment, recurrent respiratory failure, difficulty maintaining adequate ventilation, normal cardiac and brain imaging, and associated autonomic-neurodevelopmental features, CCHS was suspected. Genetic analysis identified a heterozygous 8-base-pair duplication in exon 3 of PHOX2B: chr4:g.41746064_41746071dup; c.691_698dup; p.Gly234AlafsTer78. This confirmed PHOX2B-related CCHS. Parental testing showed the same variant was absent in both asymptomatic parents, supporting a de novo pathogenic variant in the child.[6]

The child required pediatric intensive care with assisted ventilation and was stabilized on mechanical ventilatory support. After clinical improvement and stabilization of oxygenation, she was transitioned to home-based non-invasive BiPAP support. Parents were counselled regarding the lifelong nature of the condition, need for ventilatory assistance, warning signs of hypoventilation, infection precautions and need for multidisciplinary follow-up. Hirschsprung disease was clinically absent, and neural crest tumor screening was not performed. At current follow-up, the child is clinically stable.

DISCUSSION

This case illustrates a diagnostically challenging presentation of CCHS beyond the immediate neonatal period. The child presented with clinical features suggestive of respiratory infection, but the degree and persistence of hypercapnia were disproportionate to the radiological findings. While pneumonia can worsen ventilation in infants, persistent type II respiratory failure after appropriate treatment should prompt evaluation for central hypoventilation, particularly when cardiac, structural brain and metabolic causes are excluded.

CCHS results from impaired automatic control of ventilation. Affected individuals have reduced or absent ventilatory response to hypercapnia and hypoxemia and may not mount expected respiratory distress despite significant gas-exchange abnormalities. The absence of primary cardiac disease, normal MRI brain, normal metabolic workup and persistent carbon dioxide retention were therefore important diagnostic clues in this child.[4,7]

The associated neurological and autonomic features further strengthened the suspicion. Congenital ptosis, delayed pupillary response, hypotonia, hyporeflexia, developmental delay and neuroregression after illness suggested a broader autonomic-neurodevelopmental disorder rather than isolated recurrent pneumonia. CCHS is now recognized as a multisystem disorder of autonomic dysregulation, with possible gastrointestinal, ocular, cardiovascular, neurodevelopmental and tumor associations.[7,8]

The diagnosis was confirmed by identification of a pathogenic PHOX2B exon 3 duplication, c.691_698dup; p.Gly234AlafsTer78. Most CCHS cases are caused by polyalanine repeat expansion mutations, while a smaller but clinically important group have non-polyalanine repeat mutations, including missense, nonsense and frameshift variants. Non-polyalanine repeat mutations are often associated with more complex phenotypes and higher risk of associated autonomic manifestations. The absence of clinically evident Hirschsprung disease in this child emphasizes the variable expressivity of PHOX2B-related disease. The absence of the variant in both parents supports a de novo origin, although genetic counselling remains essential because parental germline mosaicism cannot be completely excluded.[2,3]

Long-term management of CCHS is supportive and preventive. The cornerstone is adequate assisted ventilation, delivered through tracheostomy ventilation, non-invasive ventilation or diaphragm pacing in selected cases. Contemporary reviews emphasize individualized ventilatory planning and multidisciplinary follow-up involving pulmonology, sleep medicine, neurology, cardiology, gastroenterology, genetics, developmental pediatrics and critical care. Recommended follow-up includes assessment of ventilation during sleep and wakefulness, cardiac rhythm surveillance, echocardiography, evaluation for autonomic dysfunction, neurodevelopmental monitoring and screening for associated conditions when clinically indicated.[4,5]

This case reinforces a practical clinical message: recurrent respiratory infections should not distract clinicians from recognizing persistent hypercapnia. In an infant with repeated respiratory admissions, developmental delay, ocular/autonomic signs and unexplained type II respiratory failure, early PHOX2B testing can shorten diagnostic delay and allow timely initiation of life-sustaining ventilatory support.

CONCLUSION

CCHS is a rare but important cause of persistent hypercapnic respiratory failure in infancy. It should be suspected when carbon dioxide retention is disproportionate to pulmonary findings and persists despite appropriate treatment, especially in the presence of autonomic or neurodevelopmental clues. Genetic confirmation with PHOX2B testing is central to diagnosis. Early recognition allows timely ventilatory support, anticipatory monitoring, family counselling and improved long-term outcomes.

Table 1. Clinical And Investigative Profile Of The Child

Domain	Findings
Demography	1-year-old female child, born to non-consanguineous parents
Presenting complaints	Cough/cold, fever, respiratory distress, poor feeding, lethargy
Past history	Recurrent lower respiratory tract infections requiring hospitalization
Development	Gross motor delay; not walking at presentation
Autonomic/neurodevelopmental clues	Congenital left ptosis, hypotonia, hyporeflexia, delayed pupillary response, neuroregression after illness
Respiratory status	SpO2 75% on room air
ABG	pH 7.28, pCO2 65 mmHg, HCO3- 28 mEq/L
Chest radiograph	Persistent right upper lobe collapse with hyperinflated lung fields
Cardiac evaluation	Structurally normal heart, trivial TR, no PAH
CNS/metabolic workup	MRI brain normal; metabolic workup normal
Genetic finding	PHOX2B exon 3 heterozygous duplication: c.691_698dup; p.Gly234AlafsTer78
Parental testing	Variant absent in both parents; likely de novo
Management/outcome	Ventilatory stabilization; continued on home-based BiPAP; clinically stable

Table 2. Diagnostic Clues Favouring Cchs Over Primary Pneumonia Alone

Clinical issue	Expected in uncomplicated pneumonia	Finding in this child suggesting CCHS
Hypercapnia	Usually improves with clinical recovery	Persistent type II respiratory failure
Severity of gas-exchange abnormality	Usually proportional to lung findings	Hypercapnia disproportionate to radiology
Cardiac cause	May explain hypoxia or pulmonary hypertension	Echo normal; no PAH
Structural CNS cause	May explain central hypoventilation	MRI brain normal
Metabolic disorder	May cause episodic decompensation	Metabolic workup normal
Autonomic/neurodevelopmental clues	Usually absent	Ptosis, delayed pupillary response, hypotonia, developmental delay
Confirmation	Not applicable	Pathogenic PHOX2B variant detected

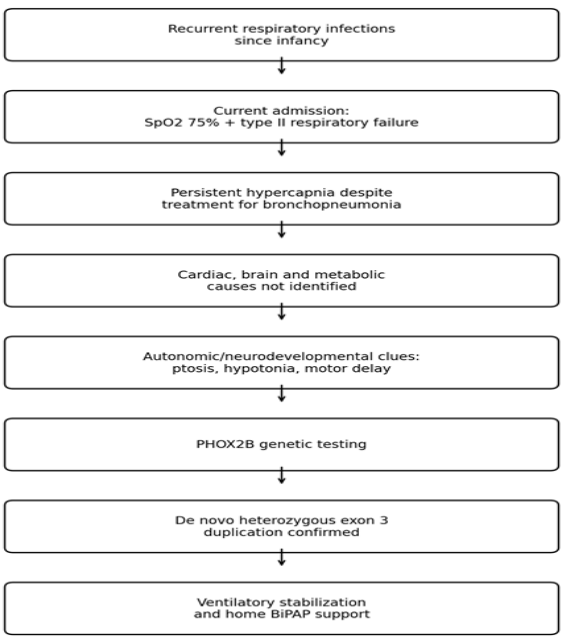

Figure 1. Diagnostic Timeline Of The Case

Authors' Contributions

Dr S and Dr BA conceptualized and conducted the study, collected data, and prepared the manuscript. Both authors contributed to data interpretation, manuscript revision, and approved the final version.

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Artificial intelligence tools were not used for data collection, data analysis, interpretation of results, or language editing of the manuscript.

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