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Dr. Santhosh George
Specialist Pediatrician and Neonatologist, Aster Hospital Mankhool, Dubai, UAE

Dr. Anjana Kannoth
Specialist Paediatrician, Aster Hospital Mankhool, Dubai, UAE

Dr. Nisha Ravindran
Specialist Paediatrician, Aster Hospital Mankhool, Dubai, UAE

Dr. Abdul Mohid Syed
Specialist Paediatrician, Aster Hospital Mankhool, Dubai, UAE

Corresponding Author:
Dr. Santhosh George
Specialist Pediatrician and Neonatologist, Aster Hospital Mankhool, Dubai, UAE

A rare case of congenital central hypoventilation syndrome in a premature neonate with multiple coexisting morbidities: A comprehensive clinical analysis

Dr. Santhosh George, Dr. Anjana Kannoth, Dr. Nisha Ravindran and Dr. Abdul Mohid Syed

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Abstract
We present a complex case of a premature neonate born at 27 weeks and 6 days gestation, exhibiting a spectrum of medical issues. Despite exhaustive medical interventions and a prolonged hospital course, the neonate experienced a sudden cardiac arrest on day 237. Whole exome sequencing revealed a PHOX2B gene mutation, confirming congenital central hypoventilation syndrome (CCHS). This case report delves into the intricate diagnostic challenges, therapeutic interventions, and the interplay of coexisting morbidities that shaped the clinical trajectory of this neonate.

Keywords: Premature neonate, congenital central hypoventilation syndrome, whole exome sequencing, respiratory failure, multiple morbidities, tracheostomy, ventilator-associated pneumonia

Introduction
Premature neonates often present with a plethora of complications, and this case highlights the unique challenges faced in managing a premature neonate with congenital central hypoventilation syndrome (CCHS). The presence of extreme prematurity, respiratory distress syndrome, intraventricular hemorrhages, seizures, sepsis, and other comorbidities added layers of complexity to the clinical course. Congenital central hypoventilation syndrome (CCHS) is a rare genetic condition that impacts respiratory regulation and autonomic nervous system (ANS) function due to mutations in the PHOX2B gene. Mellins *et al*. [1] documented the initial instance of congenital central hypoventilation syndrome (CCHS) in a newborn with alveolar hypoventilation stemming from central nervous system causes, marked by severe and persistent respiratory acidosis that improved with assisted ventilation (AV) following the exclusion of primary cardiac, pulmonary, neuromuscular, and chest wall conditions. Although assisted ventilation with a negative pressure ventilator was provided, the infant developed pulmonary hypertension and passed away at 14 months old due to complications from congestive heart failure [1]. Individuals with Congenital Central Hypoventilation Syndrome typically exhibit symptoms such as respiratory failure, apnea, cyanosis, hypoxemia, and hypoventilation, which are more pronounced during sleep than when awake, usually appearing in the newborn period [2]. The discovery of the PHOX2B gene as the cause of CCHS has enabled quicker diagnosis confirmation, implementation of appropriate treatment, and assessment for related disorders [3, 4].

Case Presentation
The neonate, born extreme premature at 27 weeks and 6 days of gestation, with a very low birth weight of 1.007 kg, displayed labored breathing immediately post-birth. Prematurity posed a significant challenge, as it is a major cause of apnea in newborns which improves as the baby matures. However, the neonate could not be extubated from ventilator due to persistent hypoapnoea and poor respiratory efforts. Despite multiple attempts to wean from ventilator support, the baby remained ventilator-dependent for 237 days due to apnoea and profound hypercapnoea during each weaning attempt. Diagnostic investigations included imaging studies, upper airway assessments, and genetic testing. Whole exome sequencing revealed a PHOX2B gene mutation, confirming a rare genetic condition CCHS.

Clinical Course

The neonate's hospitalization was marked by a series of convoluted medical interventions aimed at addressing a multitude of complex morbidities. Following delivery in the Emergency Room, the neonate required immediate intubation and surfactant administration due to labored breathing and respiratory distress syndrome (RDS). Early attempts to wean from mechanical ventilation were impeded by the neonate's inability to trigger spontaneous breaths, leading to repeated reintubations. Despite employing various noninvasive respiratory support modalities, including continuous positive airway pressure (CPAP), nasal intermittent positive pressure ventilation (nasal IPPV), and nasal high-frequency oscillatory ventilation (nasal HFOV), success was elusive.

Efforts to optimize ventilation through conventional and high-frequency ventilation modes were challenging, resulting in recurrent ventilator-associated pneumonia episodes and necessitating multiple courses of antibiotics. Dexamethasone was administered for mild bronchopulmonary dysplasia changes, while respiratory stimulants such as caffeine citrate, acetazolamide, and progesterone failed to elicit the desired response. The decision to undergo tracheostomy on 11/04/2023 was made due to the prolonged and uncertain dependency on mechanical ventilation.

The neonate's clinical course was further complicated by late-onset sepsis, urinary tract infections (UTIs), and additional ventilator-associated pneumonia (VAP) episodes, all requiring antibiotic treatments. Gastrointestinal issues, including abdominal distension and bilious aspirate, were managed with bowel rest and gradual reinitiation of feeds, ultimately achieving full oral gastric tube (OGT) feeds. Neurological complications, such as refractory seizures requiring multiple anticonvulsants, were associated with cerebral infarcts and intraventricular hemorrhages, evident on neuroimaging studies which was thought to be the cause of persistent apnoea initially. Throughout the hospital stay, the neonate's condition remained clinically active, with normal tone and movements, indicating resilience despite the challenging medical course. This comprehensive medical course underscores the complicated and multifaceted nature of managing a premature neonate with congenital central hypoventilation syndrome, emphasizing the necessity for a holistic and multidisciplinary approach to address the diverse array of coexisting morbidities. Despite reaching 37 weeks postmenstrual age, the neonate failed to trigger spontaneous breaths, and upper airway assessments were unremarkable, ruling out mechanical causes for hypoventilation. The decision for tracheostomy was prompted by uncertainty surrounding weaning from ventilator support. The neonate underwent multiple courses of antibiotics for sepsis, with negative cultures on most occasions. Intraventricular hemorrhages, refractory neonatal seizures, and coexisting morbidities such as retinopathy of prematurity (ROP) further added to the complexity of the case.

Table 1: Diagnostic results concerning phenotype

Gene (Phenotype Number/ OMIM number)	Disease and Inheritance	Chromosome and Position	Variant details
PHOX2B (OMIM number: 209880)	Central hypoventilation syndrome, congenital, 1, with or without Hirschsprung disease (AD - Autosomal Dominant)	g.41746028 417 46029 ins CGCG GCCGCCGCCG CIGCTGC	Exon: Exon 3
			Nucleotide change: c.729_ 749dup
			Amino Acid Change: (p.A1a254 Ala260dup)
			Transcript Id: NM 003924.4

Discussion

Idiopathic congenital central hypoventilation syndrome (CCHS), commonly referred to as 'Ondine's curse', is a rare condition marked by irregular breathing control without neuromuscular, lung, heart issues, or a detectable brainstem lesion. Individuals affected usually exhibit cyanosis and elevated carbon dioxide levels during sleep within the first hours of life. Patients breathe properly while awake, but experience hypoventilation characterized by normal respiratory rates and shallow breathing during sleep. More severely affected patients exhibit hypoventilation both while awake and asleep. An impairment in the autonomic regulation of breathing leads to insufficient or minimal breathing and alertness reactions to high levels of carbon dioxide and low levels of oxygen. The PHOX2B gene encodes a protein crucial for prenatal development as shown in Table 1. The PHOX2B protein aids in the development of nerve cells (neurons) and controls the maturation process that allows neurons to perform certain activities (differentiation). Protein is active in the neural crest during neuron development, which is a collection of cells in the early embryo responsible for generating various tissues and organs. Neural crest cells migrate to create components of the autonomic nervous system, regulating bodily activities like respiration, blood pressure, heart rate, and digestion. Neural crest cells also contribute to the development of various tissues in the facial and cranial regions, as well as other types of tissues and cells. The protein derived from the PHOX2B gene features two regions with repetitive sequences of the amino acid alanine. Polyalanine tracts are stretches of alanines also known as poly (A) tracts. Congenital central hypoventilation syndrome poses challenges in both diagnosis and management. The simultaneous presence of multiple comorbidities, including intraventricular hemorrhages, seizures, and sepsis, complicated the clinical picture. The lack of response to standard treatments for respiratory stimulation and the need for a tracheostomy underscored the severity of the condition. Furthermore, the clinical characteristics of CCHS may change as time progresses. Thus, a coordinated and complete multidisciplinary approach to care is crucial to achieve the best outcomes at every stage of life. Coordinating care amongst different specialties can be complex and difficult for patients and their families [5].

Conclusion

This case emphasizes the intricate nature of managing a premature neonate with congenital central hypoventilation syndrome and highlights the importance of considering rare genetic disorders in cases of refractory apnea. A

multidisciplinary approach is crucial for comprehensive care, given the interplay of multiple morbidities. Further research is needed to explore the relationship between CCHS and other neonatal complications, providing valuable insights into optimal management strategies.

Conflicts of Interest

The authors assert that they do not have any conflicts of interest.

Authors' Contributions

All authors participated in the case report design, examined the initial draft critically, endorsed the final version, and agreed to take responsibility for the work. All authors have complete access to the manuscript and all the study data.

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