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Case Report

Late onset congenital central hypoventilation syndrome in a child with Down syndrome

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ABSTRACT

Congenital central hypoventilation syndrome (CCHS), also known as Ondine syndrome, is a rare genetic disorder characterized by alveolar hypoventilation and dysregulation of the autonomic nervous system. Late onset congenital central hypoventilation syndrome (LOCCHS) has been infrequently reported, particularly in patients with Down syndrome. This case report presents an 8-year-old girl with Down syndrome who developed late onset CCHS. Clinical assessments, laboratory tests, and imaging studies were performed to evaluate her condition. The patient exhibited severe respiratory acidosis and hypoxemia, necessitating intubation and mechanical ventilation. Despite multiple extubation attempts, the patient demonstrated no spontaneous breathing. The diagnosis of LOCCHS was considered after excluding other conditions. Unfortunately, the child expired within 24 hours following extubation. LOCCHS should be contemplated in children with unexplained hypoventilation who are challenging to extubate, particularly in the absence of underlying neurological, pulmonary, or cardiac diseases.

Keywords: LOCCHS, Down syndrome, Mechanical ventilation, India

INTRODUCTION

Congenital central hypoventilation syndrome (CCHS), commonly associated with genetic mutations affecting the respiratory control systems, has an estimated prevalence of 1 in 200,000 live births.[1] We report an interesting, rare case of late onset congenital central hypoventilation syndrome (LOCCHS) in an 8-year-old girl with Down syndrome who required continuous ventilatory support without evidence of primary lung or cardiac disease.

CASE REPORT

An 8-year girl presented with history of fall from few stairs followed by lethargy and rapid breathing. On examination she had a heart rate of 110/min, respiratory rate (RR) 28/min, central cyanosis and central breathing pattern, blood pressure (BP) 100/70mm of Hg, temperature 98.8 F with SpO2 78% at room air. She had clinical features suggestive of down syndrome, later confirmed on karyotyping. No evidence of any musculoskeletal trauma was there. Central nervous system (CNS) examination showed normal cranial nerves, motor (except mild hypotonia) and sensory functions. Chest and cardiovascular system examination was unremarkable. There was no adeno tonsillar hypertrophy.

Arterial blood gas (ABG) showed hypoxemia with severe respiratory acidosis (narcosis with pH 6.91 and pCO_2 128 kpa). Chest radiograph and computed tomography (CT) imaging of brain and chest were normal (Figure 1). Patient was intubated and put on ventilation.

After intubation, we noticed pinpoint miotic pupils (due to narcosis) with sluggish light reflex. Respiratory acidosis subsided and pupils returned to normal size after 8 hours. After stabilization of patient, we tried to wean her off ventilator, but there were hardly any breathing efforts

though patient remained conscious and responsive on ventilatory support. Multiple attempts of extubation failed over 7 days.

Negative pyridostigmine test ruled out Myasthenia gravis. Bed side cardiography was also normal. Diagnosis of late onset congenital central hypoventilation syndrome (LO CCHS) was considered excluding other causes and parents were counselled for need of long-term home ventilatory support with tracheostomy. However, the parents being poor, refused any further treatment and took the child against advice. Sleep study and mutation analysis could not be done to confirm CCHS. Unfortunately, the child expired within 24 hours of extubation.

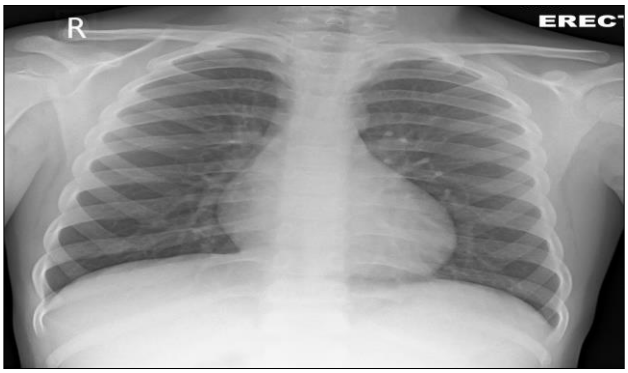

Figure 1: Normal chest X-ray.

DISCUSSION

CCHS, also known as Ondine syndrome, is a rare genetic disorder characterized by the impairment of the automatic control of breathing during sleep, leading to hypoventilation and, in severe cases, respiratory failure. The hallmark features of CCHS are alveolar hypoventilation and autonomic nervous system dysregulation. The exact mechanism of CCHS is lack of adequate autonomic control of respiration with decreased sensitivity to hypercapnia and hypoxia in the absence of neuromuscular or lung disease or any identifiable brainstem lesion.[2] The pathophysiology of CCHS is primarily associated with mutations in the paired-like homeobox 2B (*PHOX2B*) gene mutation mainly resulting from polyalanine repeat expansion mutations.[3] This gene is involved in the development of neural structures related to respiratory control.[1] Patients with CCHS typically present in infancy, often following a pattern of hypoxemia and hypercapnia during sleep, while being neurologically intact during wakefulness.[3] While most of the cases of CCHS are diagnosed in early infancy, but late onset cases, can present at any age.[2,4] Review of literature reflects that CCHS can present differently in patients with Down syndrome, particularly concerning late-onset CCHS.[6,7] So far, only few cases of LOCCHS with Down syndrome and only one case of CCHS in Down syndrome with Hirschsprung disease have been reported.[5,9,11,12] To our knowledge, none has been reported from India.

The case of LOCCHS, as presented by Mahfouz et al introduces a unique dimension to our understanding of this condition.[2] This variant may emerge after external stressors such as general anesthesia or other medical interventions in patients who were previously asymptomatic. This finding highlights the potential for late key manifestations of a primary genetic condition that may not have been apparent during infancy or early childhood. The mechanisms underlying late-onset symptoms require further investigation, but they emphasize the importance of monitoring patients with a family history or underlying genetic predispositions for respiratory complications throughout their lives. Additionally, the association between CCHS and other congenital conditions, such as Down syndrome and Hirschsprung disease, emphasizes the multi-faceted nature of managing patients with CCHS.[5] LOCCHS is seen as a part of Haddad syndrome (a congenital disorder with CCHS in conjunction with Hirschsprung disease), and in patients of neuroblastoma. de Navas et al described a case of late-onset CCHS in a patient with Down syndrome, highlighting that symptoms can emerge well after the neonatal period and may be overlooked in standard assessments.[7] In a case reported by Peri et al, the intersection of Down syndrome and CCHS was further elucidated, emphasizing the necessity for increased clinical awareness and thorough screenings in patients with Down syndrome to ensure early diagnosis and intervention.[8] This viewpoint is reinforced by Tams et al, where a PHOX2B mutation was identified in a patient with late-onset CCHS with this genetic condition.[9,12]

In these patients, a multidisciplinary approach, including genetic counselling and specialized respiratory management, is essential to address the intricacies of their health needs. Sleep-disordered breathing is prevalent in individuals with Down syndrome, making them susceptible to exacerbations of hypoventilation, especially during sleep.[3,10]

This underscores the need for comprehensive assessments involving polysomnography in such populations to pre-emptively identify the risk for respiratory insufficiency.

Clinical management of CCHS involves vigilant monitoring during sleep, often through the use of home ventilatory support or continuous positive airway pressure (CPAP) therapy. The Positive pressure ventilation has been advocated via tracheostomy in the first 6 to 8 years of life followed by non-invasive ventilation in later life. Other treatment option includes diaphragmatic pacing which helps to generate breathing in active children. It keeps daytime ventilation free period.

The progression of treatment options and awareness of late-onset presentations can improve patient outcomes, as the risk of respiratory failure not only poses immediate threats but can also significantly impact quality of life.[4] Emerging guidelines suggest that families should be educated about the signs of respiratory distress and the importance of ongoing follow-up for timely interventions.

CONCLUSION

In conclusion, CCHS is a complex disorder that presents challenges both in early diagnosis and management, particularly in the context of other comorbid conditions. The recognition of late-onset CCHS reinforces the necessity for continuous clinical vigilance and adaptability in care strategies. Further research is warranted to elucidate the mechanisms behind late-onset presentations and to refine recommendations for monitoring and management across the lifespan. Late onset congenital central hypoventilation syndrome should be considered in children with Down syndrome presenting unexplained respiratory distress and failure to wean off mechanical ventilation, particularly in the absence of other respiratory, cardiac, or neurological disorders. Early identification and management are crucial to improving outcomes in this vulnerable population.

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