Congenital central hypoventilation syndrome: A rare disorder in a neonate

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Introduction

The first case of congenital central hypoventilation syndrome (CCHS) in an infant was reported in 1970 by Mellins and colleagues under the term Ondine's curse[1]. The name was derived from German folklore, where a human was cursed to forget performing all bodily functions, including breathing, causing him to die. Prevalence of CCHS is 1 in 200,000 live births[2]. We report a neonate presenting with CCHS.

Case report

A term, 2.9 kg female neonate was born to a 31-year-old mother via normal vaginal delivery at a local hospital. The obstetric history and antenatal period were uneventful except for gestational diabetes mellitus for which she was on diet control. No maternal risk factors for sepsis were identified. There was no significant family history or history of consanguinity. She has a healthy 6-year-old girl born via normal vaginal delivery. At birth, baby had cried well with Apgar scores of 9, 10 and 10 at one, five and 10 minutes. There was no birth trauma or hypoxic events other than 1 episode of peripheral cyanosis for which baby was admitted to the paediatric baby unit. After providing warmth to correct mild hypothermia, cyanosis improved. Approximately 6-8 hours after birth, baby developed frequent desaturation episodes without respiratory distress while on room air for which high-flow nasal prong oxygen was given. Septic screening was done and baby was started on empirical antibiotics and intravenous (IV) aminophylline. While on maximum settings of high-flow nasal prong oxygen, baby developed further desaturation episodes without features of respiratory distress. Blood gases revealed pCO_2 of 72 mmHg, pH of 7.24 and HCO_3 of 23 mmHg. Baby was intubated and given synchronised intermitted mandatory ventilation (SIMV). Post-intubation chest roentgenogram confirmed endotracheal tube (ET) position and showed cardiomegaly but excluded lung pathology. Electrocardiogram (ECG) was normal on day one of life and ultrasound scan (USS) of brain was normal apart from a periventricular flare. Partial septic screen was negative. On day 2 at the local hospital, baby had desaturated while being ventilated and was transferred to Teaching Hospital Anuradhapura (THA) Special Care Baby Unit for further management.

On admission to THA, baby had an ET tube and umbilical venous catheter (UVC) *in situ*. There was no respiratory distress and abdomen was soft. Baby was connected to SIMV on low settings. 2D echocardiography revealed a small patent foramen ovale and an atrial septal defect. Baby was extubated on day 3 to high-flow nasal prong oxygen but within several hours became apnoeic and desaturated without features of distress and was re-intubated. First line antibiotics were changed to IV amikacin and IV colistin. On day 4, two blood cultures, ET secretion culture and UVC tip culture, were found to be negative. Baby was clinically well except for moderate jaundice. Serum bilirubin was estimated and she was started on double phototherapy. Repeat serum bilirubin on day 6 was above the exchange range and triple phototherapy was started. There were no features of kernicterus and no ABO/Rh incompatibility, both mother and baby being O positive with negative direct antiglobulin test. Blood picture showed no evidence of haemolysis and reticulocyte count was 2%. Subsequent bilirubin levels decreased and baby was taken off phototherapy by day 8. On days 4 and 5, there were 2 failed self-extubation attempts needing re-intubation and ventilation on low settings due to frequent desaturation episodes, apnoea and hypercapnia and hypoxaemia in blood gas. However, there was no respiratory distress. Baby was given 3 doses of dexamethasone and extubated on day 7. Post-extubation blood gas had significant respiratory acidosis/ hypercapnia with apnoeic episodes. Attempt to manage the baby on high-flow nasal prongs with supportive care failed leading to re-intubation. On days 7 to 8, baby developed right-sided focal convulsions and IV midazolam infusion was started. Later, IV midazolam was weaned off with commencement of IV levetiracetam. Repeat USS of brain revealed a grade 1 germinal matrix haemorrhage but no cerebral oedema or parenchymal changes.

Investigations sent on day 8 revealed a white blood count (WBC) of 30.1 $x10^3/\mu L$, absolute neutrophil count of 19.9 $x10^3/\mu L$, platelet count of 195 $x10^3/\mu L$ and C-reactive protein (CRP) of 52 mg/dL. Blood culture was positive for coliform and micrococcus. IV meropenem was commenced at this stage. IV amikacin and IV colistin were continued for 10 and 14 days respectively. IV glycopyronium was started due to thick secretions. Clotting profile suggested a mild coagulopathy which was corrected with fresh frozen plasma and platelet transfusions. However, by day 11, CRP was less than 5mg/dL, WBC was 17 $x10^3/\mu L$, absolute neutrophilic count was 11.4 $x10^3/\mu L$ and platelet count was 280 $x10^3/\mu L$. Repeat blood culture revealed no growth. As

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baby was clinically stable, on day 11, she was extubated successfully to high-flow nasal prong oxygen and from day 15 to 18, baby was on nasal prong oxygen. There were minimal apnoeic episodes during sleep while on nasal prong oxygen which were corrected with tactile stimulation. However, these episodes were not present when the baby was awake. Daily blood gases showed mild hypercapnia.

On day 18, CRP was significantly high (202 mg/dL) with leucocytosis and severe thrombocytopenia. She was managed as for late-onset sepsis, with IV meropenem for 21 days and IV vancomycin for 7 days. Lumbar puncture was planned upon improvement of thrombocytopenia. On the same day, blood gases showed significant hypercapnia with respiratory acidosis and baby started to have frequent apnoeic episodes during sleep but not when awake. Therefore, she was changed from nasal prong oxygen to non-invasive positive pressure ventilation (NIPPV). By day 20, apnoeic episodes during sleep became more apparent with hypercapnia. Thus, NIPPV with a continuous positive airway pressure (CPAP) mask was started. Although blood pressure was maintained throughout, there were occasional sinus bradycardic episodes suggestive of autonomic dysfunction. ECG monitoring did not identify any significant pathology. Multiple failed extubation attempts followed by frequent apnoeic episodes without respiratory distress especially occurring during sleep with hypoxaemia and hypercapnia, correctable respiratory acidosis following intubation and ventilation on minimal settings without needing supplemental oxygen led the authors to consider CCHS.

On day 21, fibre optic laryngoscopy excluded upper airway pathologies. A paediatric pulmonologist excluded lung pathologies. Upper gastrointestinal endoscopy was normal. Repeat USS of brain was normal. Magnetic resonance imaging (MRI) of brain showed appropriate myelination for age and normal brainstem, but there was diffuse white matter oedema, suggestive of diffuse white matter ischaemia. Over the next two weeks, baby developed frequent apnoeic episodes limited to sleep with respiratory acidosis. She needed constant tactile stimulation during sleep and had varying degrees of hypercapnia. Several attempts to wean off NIPPV with CPAP mask failed. Further investigations of liver and renal functions, lipid profile, creatine phosphokinase, lactate dehydrogenase, serum cortisol levels, acyl carnitine profile, amino acid profile, serum lactate levels, serum and urine organic acids, serum and urine ammonia, serum uric acids, and urine ketone bodies were within normal ranges, thus, excluding inborn errors of metabolism as well. Electromyography and nerve conduction studies were also normal. USS of diaphragm showed diaphragmatic movements which became sluggish at regular intervals. Investigations to exclude primary neurologic, neuromuscular, pulmonary, and cardiac disorders were normal and the diagnosis of CCHS was made by exclusion. Genetic diagnosis could not be established due to limited financial resources.

Currently, the baby is 3 months and 25 days old and was transferred to the paediatric ICU. The baby is awaiting tracheostomy which was delayed due to a lower respiratory tract infection. Other than difficulty in weaning off from NIPPV, the baby's weight is in the -3 SD but gradually increasing along the centile. Furthermore, a nutrition referral was done to optimise the nutritional status. The development assessment revealed a global development age of approximately 1-2 months and she was started on early stimulation to improve the development.

Discussion

The typical presentation of CCHS is a full-term neonate, born without antenatal and intrapartum complications, presenting in the neonatal period with cyanosis or shallow/apnoeic breathing pattern during sleep as in the index case. This is suggestive of hypoventilation and hypoxaemia that can be confirmed with hypercapnia in blood gas measurements as observed from the carbon dioxide retention in blood gases of the index case. Similar to the reported child, the affected neonates do not exhibit any signs of distress or attempts to compensate for hypercapnia or hypoxaemia. As seen in the index case, most neonates will require frequent intubation and mechanical ventilation attempts due to frequent apnoeic episodes, severe hypercapnia and hypoxaemia. Since they do not have airway or lung pathologies, they require low ventilatory settings with minimal or no supplemental oxygen. When the neonate transitions from artificial ventilation to non-invasive ventilator support, blood gases show respiratory acidosis, often compensated by metabolic alkalosis as depicted in the reported child. The neonate in the index case also showed diminished ventilation during wakefulness, exacerbated during non-rapid eye movement sleep, and autonomic dysfunction mostly affecting the cardiovascular system which is another key feature of CCHS[2]. Patients with CCHS will exhibit abnormalities in cardiovascular physiology like lability of blood pressure, orthostatic hypotension and cardiac electrophysiological abnormalities like decreased heart rate variability, prolonged QTc interval and heart block[2].

Diagnosis of CCHS is considered in the index case upon evaluating the clinical presentation of ventilatory dysfunction in sleep without evidence of primary respiratory, cardiac and neurologic pathology, supported by hypercarbia, and hypoxaemia in blood gases. Thus, during clinical evaluation for CCHS, it is vital to monitor saturation by pulse oximetry to demonstrate hypoxaemia and blood gas measurements to identify severe respiratory acidosis with hypercapnia. Upper airway pathologies should be excluded by fibre optic laryngoscopy and primary pulmonary problems should be assessed by chest roentgenogram or computed tomography (CT) of chest as done in the index case. Polysomnography also has a role in detecting respiratory and gas exchange issues during sleep. Cardiac evaluation to exclude structural and functional abnormalities should include ECG, 2D echocardiography and Holter monitoring. In the index case echocardiography revealed only a small patent ductus arteriosus and small atrial septal defect which is unable to create the clinical picture explained above. USS of brain can identify brain abnormalities, but the gold standard is MRI to exclude brainstem malformation, which was normal in the index case favouring the diagnosis of CCHS. Patients with CCHS will only have nonspecific MRI features attributed to hypoxic or ischaemic events[6]. Nerve conduction studies and electromyography exclude neuromuscular diseases like spinal muscle atrophy and were performed in the index case to exclude other entities.

Fluoroscopy or USS of diaphragm excludes phrenic nerve injuries[7] and was also done in the index case.

Screening for inborn errors of metabolism (IEM) involves assessing serum glucose, electrolytes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). If neonates have hypoglycaemia, elevated ALT, AST and persistent acidosis despite ventilatory support, in-depth studies for IEM should be carried out. In CCHS neuromuscular evaluation and evaluation for IEM will be normal. Similarly, in the index case, preliminary investigations for IEM were negative. Furthermore, the detailed evaluation for IEM revealed normal findings.

Studies indicate that older children with CCHS may experience cognitive impairment and on average may score more than one standard deviation below the general population on the Wechsler intelligence scales[5].

Genetic defect causing CCHS is a paired-like homeobox gene PHOX2B, located at exon 3 on chromosome 4[3]. Over 90% of PHOX2B mutations are *de novo* mutations[2]. Normal PHOX2B has a 20-alanine coding repeat region. Approximately 90% of reported cases are due to heterozygous 5 to 13 amino acid expansion of the 20-polyalanine tract. Thus, genotypically, the disorder is categorized as polyalanine repeat mutation (PARM) and non-polyalanine repeat mutation (NPARM) of PHOX2B. Patients with NPARM typically have a severe ventilatory defect needing artificial ventilatory support during both wakefulness and sleep and a higher incidence of developing neural crest tumours and Hirschsprung disease[4].

CCHS is a lifelong condition with no specific cure or gene therapy. Treatment is entirely supportive. A multidisciplinary approach involves pulmonologist, neurologist, cardiologist, gastroenterologist, geneticist and ENT specialist. The index case was evaluated by the relevant specialist collectively before approaching the diagnosis of CCHS. Nutritionists, speech therapists, respiratory therapists, social workers and child behaviour specialists may have a role in long-term management and were involved in the management of the index case. Management of CCHS requires careful monitoring of oxygenation and ventilation during wakefulness and sleep. Home care for children with CCHS usually involves positive-pressure ventilation through a permanent tracheostomy. The severity of alveolar hypoventilation determines whether patients require ventilatory support only at night or around the clock. Periodic follow-ups should be arranged aiming to provide the best multidisciplinary care. CCHS has a significant impact on the family's emotional and social well-being[8].

Conclusion

CCHS is a rare genetic disorder characterized by abnormal control of ventilatory functions and abnormalities of autonomic function. It is important to investigate neonates presenting with unexplained apnoea needing assisted ventilation thoroughly to establish the diagnosis CCHS.

References

1. Emanuel H, Rennie K, Macdonald K, Yadav A, Mosquera RA. Screening children with a family history of central congenital hypoventilation syndrome. *Case Reports in Pediatrics* 2020; **2020**: 2713606. https://doi.org/10.1155/2020/2713606 PMid: 32274237 PMCid: PMC7136801
2. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, Keens TG, Loghmanee Da, Trang H, *et al.* An official ATS clinical policy statement: Congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. *American Journal of Respiratory and Critical Care Medicine* 2010; **181**(6): 626-44. https://doi.org/10.1164/rccm.200807-1069ST PMid: 20208042
3. Amiel J, Laudier B, Attié-Bitach T, Trang H, Pontual L de, Gener B, *et al*. Polyalanine expansion and frameshift mutations of the paired-like homeobox gene PHOX2B in congenital central hypoventilation syndrome. *Nature Genetics* 2003; **33**(4): 459-61. https://doi.org/10.1038/ng1130 PMid: 12640453
4. Weese-Mayer DE, Berry-Kravis EM, Zhou L, Maher BS, Silvestri JM, Curran ME, *et al.* Idiopathic congenital central hypoventilation syndrome: analysis of genes pertinent to early autonomic nervous system embryologic development and identification of mutations in PHOX2b. *American Journal of Medical Genetics A* 2003; **123A**(3): 267. https://doi.org/10.1002/ajmg.a.20527 PMid: 14608649
5. Zelko FA, Nelson MN, Leurgans SE, Berry-Kravis EM, Weese-Mayer DE. Congenital central hypoventilation syndrome: neurocognitive functioning in school-age children. *Pediatric Pulmonology* 2010; 45(1): 92-8. https://doi.org/10.1002/ppul.21170 PMid: 19960523
6. Weese-Mayer DE, Brouillette RT, Naidich TP, McLone DG, Hunt CE. Magnetic resonance imaging and computerized tomography in central hypoventilation. *American Review of Respiratory Diseases* 1988; **137**(2): 393-8 https://doi.org/10.1164/ajrccm/137.2.393 PMid: 3341630
7. Brouillette RT, Marzocchi M. Diaphragm pacing: clinical and experimental results. *Biology of the Neonate* 1994; **65**: 265. https://doi.org/10.1159/000244063 PMid: 8038293
8. Carnevale FA, Alexander E, Davis M, Rennick J, Troini R. Daily living with distress and enrichment: the moral experience of families with ventilator-assisted children at home. *Pediatrics* 2006; **117**(1): e48-60. https://doi.org/10.1542/peds.2005-0789 PMid: 16396848