

Late-Onset Central Hypoventilation Presenting as Extubation Failure

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Congenital central hypoventilation syndrome typically presents in the newborn period, primarily manifesting as sleep-associated respiratory insufficiency, characterized by markedly impaired ventilatory responses to hypercarbia and hypoxemia during sleep and resulting in severe hypoventilation that may be life threatening [1]. Several reports described patients who were diagnosed with central hypoventilation later in life, during childhood or adulthood [2]. Most individuals with the CCHS phenotype carry a mutation in the *PHOX2B* gene leading to an expansion of the 20 copy alanine stretch [3], the number of which correlates with the severity of the CCHS phenotype. We present the case of a previously asymptomatic healthy girl who presented with extubation failure after being ventilated for severe pneumonia.

PATIENT DESCRIPTION

A generally healthy 12 year old girl presented with respiratory disturbance during sleep. The first of two girls, she was born of unrelated healthy parents

CCHS = congenital central hypoventilation syndrome

of Arab origin, with no family history of disease, allergy, asthma or other chronic illness. The patient showed normal growth and psychomotor and behavioral development. Her medical history was unremarkable until the age of 12 years when she contracted severe pneumonia leading to respiratory failure, requiring mechanical ventilation for 4 days due to hypoxia and hypercarbia. Repeated attempts to wean her failed due to hypoxia and elevated arterial partial pressure of CO₂ levels while she was asleep. Extubation was possible with continuous non-invasive ventilation, which was subsequently needed during sleep only. She was discharged home, ventilated by non-invasive mechanical ventilation bi-level positive airway pressure during sleep, with no ventilation required during the day. Since then, she sleeps well without snoring or night sweats. She did suffer from severe headaches during the day if she refrained from using the BiPAP during sleep, but feels well, with no shortness of breath, and continues to be an athlete and good student.

At presentation to our center her pulse oximeter oxygen saturation on room air was 97%, her heart rate and blood pressure were normal; her nutritional status was normal and her body mass index was 23 kg/m². She had no digital clubbing and the rest of her physical examination was unremarkable.

An overnight polysomnography showed normal SpO₂ and normal end-

BiPAP = bi-level positive airway pressure
SpO₂ = pulse oximeter oxygen saturation

tidal CO₂ when awake; however, while asleep several events of hypoxemia occurred with SpO₂ on room air decreasing to 78%, end-tidal CO₂ rose to 57 mmHg, with a venous bicarbonate level of 27 mmol/L. The hypoxia events occurred clearly in the absence of any observable obstruction. Additional blood tests, e.g., complete blood count, biochemistry (electrolytes, liver, renal, thyroid function tests), immunoglobulins, and metabolic workup (lactate, ammonia, pyruvate and carnitine) were all within normal limits. The neurologic follow-up (magnetic resonance imaging of the brain and the spinal cord, electroencephalography), electrocardiography and echocardiography were all normal. Myasthenia gravis, Guillian-Barré syndrome and axonal diseases were ruled out. Respiratory tests (chest and sinus X-ray, chest computed tomography scan and lung function tests), and additional imaging tests (abdominal ultrasound and fluoroscopy), as well as ophthalmologic examination were normal.

The patient was subsequently titrated for the non-invasive positive pressure ventilation by nasal mask. Optimal pressures were set for inspiratory positive airway pressure 12 cm/H₂O and expiratory positive airway pressure 6 cm/H₂O with a back-up respiration leading to normalization of end-tidal CO₂ and oxyhemoglobin saturation. She was diagnosed with late-onset central hypoventilation. By direct sequencing of the *PHOX2B* gene, an in-frame duplication of 15 bp on one allele was identified, expanding the normal 20 alanine stretch by 5 additional

alanines within the PHOX2B protein [4], which confirmed the diagnosis of LO-CHS. The mutation was not detected in her mother or sister; her father was not available for analysis.

Results of a repeated polysomnography, 6 months post-diagnosis, again demonstrated central hypoventilation. Follow-up visits and adjustment of the BiPAP pressures are performed every 6 months.

COMMENT

CCHS commonly occurs during the neonatal period or early infancy and is characterized by an absence of adequate autonomic control of respiration with decreased sensitivity to hypercapnia and hypoxia, in the absence of neuromuscular or lung disease, or an identifiable brainstem lesion [1]. The core phenotype is associated with anomalies of the autonomous nervous system, including Hirschsprung disease and tumors of the sympathetic nervous system such as ganglioneuromas and neuroblastomas. O'Brien et al. [5] reported that children with CCHS show attenuated peripheral responses to sympathetic stimulation, thereby further confirming the presence of autonomic nervous system dysfunction as a consistent feature of this genetic condition. Since these patients have absent or negligible ventilatory sensitivity to hypercapnia and variable ventilatory sensitivity to hypoxemia during sleep [1], they are at risk of dying without ventilation during sleep. When awake, these patients lack a perception of dyspnea but maintain conscious control of breathing. During exercise, particularly during anaerobic exercise, these children may be at risk for hypercapnia and hypoxemia, although the degree of exercise and severity of CCHS likely impact on the individual response.

Polyalanine expansions in the PHOX2B protein were identified as the major mutations responsible for CCHS.

LO-CHS = late-onset congenital hypoventilation
CCHS = congenital central hypoventilation syndrome

PHOX2B, located on chromosome 4p12, encodes a protein that contains two polyalanine repeat sequences of 9 and 20 residues in length. Amiel and collaborators [3] demonstrated the presence of PHOX2B expression in early developmental human embryos in both central autonomic neuron circuits and in peripheral neural crest derivatives. Over 90% of confirmed PHOX2B expansion mutations occurred *de novo* in CCHS probands; up to 10% of unaffected parents are somatic mosaics for the expansion mutation seen in their child. The size of the PHOX2B polyalanine expansion mutation in children with CCHS varies from 5 to 13 nucleotide triplets. Patients carrying the shortest alanine expansions display a less severe phenotype. The wide range of presentations associated with the size of the expansion mutation, which extends from the newborn period to adulthood, raises the possibility that some individuals may remain undiagnosed throughout life. No information about the carrier rate of the gene in the unaffected population is yet available. However, it is possible that a spectrum of phenotypic presentations of the carrier state can occur depending on yet unknown modifying genes. In previous reports of LO-CHS, patients were diagnosed from infancy to adulthood and presented with cyanosis, cardiorespiratory arrest, pulmonary hypertension, chronic respiratory failure, nocturnal gasping, symptoms compatible with autonomic nervous system dysregulation (low body temperature, postural hypotension, pinpoint pupils minimally reactive to light, no shortness of breath despite markedly increased carbon dioxide levels), awakening with headaches, periods of disorientation for several years [2], or pulmonale.

This is the first report of LO-CHS in a previously asymptomatic healthy girl who presented with extubation failure after being ventilated for severe pneumonia. It is not clear why an environmental factor, i.e., pneumonia, triggered a genetic disease that was dormant for 12 years. It is conceivable that the patient suffered

from mild symptoms that were unrecognized, and the increased respiratory needs elicited the central hypoventilation. The differential diagnosis of extubation failure include upper and/or lower airway obstruction, excess of respiratory secretions, abnormal mental status, chest wall weakness or stiffness, decreased lung compliance, and – in the neonatal period – CCHS. In the current case, it is likely that while slightly sedated during the process of weaning from mechanical ventilation, the patient was unable to ventilate appropriately because of reduced sensitivity to hypercarbia. Extubation was feasible when she was on BiPAP, without sedation. She was able to ventilate while awake but required non-invasive ventilation during sleep. We suggest that LO-CHS be considered in patients with no previous illnesses and with no other cause for extubation failure. Confirmation by genetic testing for mutations in the PHOX2B gene is a simple diagnostic test that may have important implications on the patient's life.

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