A case of late-onset central hypoventilation syndrome with hypothalamic dysfunction: through a new phenotype

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Congenital central hypoventilation syndrome (CCHS) is a rare disorder with uncertain nosology that usually presents early in life. The syndrome is characterized by ventilatory response impairment to carbon dioxide and may result in respiratory failure at birth. Recent reports have identified a similar clinical presentation beyond infancy called late-onset central hypoventilation syndrome (LO-CHS) as a disease continuum of CCHS with similar and overlapping pathophysiology. However, some have proposed that the syndrome accompanied by hypothalamic dysfunction (HD) be classified as a distinct clinical entity, LO-CHS/HD.

To the best of our knowledge, the case reported herein is the oldest case of LO-CHS/HD in childhood, at 13 years old. He suffered from recurrent pulmonary edema, acute convulsive seizures, hypersomnia, hyperphagia, obesity, impaired glucose tolerance test, and hypercapnia, diagnosed as LO-CHS/HD, and was successfully treated with nasal bi-level positive airway pressure.

Key words: late-onset central hypoventilation syndrome, hypothalamic dysfunction, late childhood, bi-level positive airway pressure (BiPAP).

Central hypoventilation syndrome (CHS) is a rare disorder characterized by persistent central alveolar hypoventilation. It is termed congenital central hypoventilation syndrome (CCHS) due to the age onset with absent hypercapnic ventilatory response during infancy, and is worsened by sleep without any evidence of underlying pathology of pulmonary, cardiac or primary neuromuscular diseases.¹ Late-onset central hypoventilation syndrome (LO-CHS) is a disease continuum of CCHS presenting later in life with similar genetic mutations and overlapping pathophysiology, and is often associated with disorders of neural crest migration, such as Hirschsprung disease and neural crest tumors.² Recent reports suggested that a subset of patients presenting hypothalamic dysfunction (HD), including hyperphagia, hypersomnolence, thermal dysregulation, emotional lability, and endocrinopathies, with accompanying LO-CHS, represented a distinct clinical entity called LO-CHS/HD.³ Katz et al.⁴ suggested that essential features of LO-CHS/HD included the sudden onset of hyperphagia/obesity in previously well children, hypercapnic respiratory failure and HD without identifiable central nervous system lesions. Although there is a debate on consensus regarding description of these syndromes, distinction of LO-CHS/HD and CCHS has been emphasized.³⁵ This article aimed to describe a patient with LO-CHS/HD diagnosed at the age of 13 years who was successfully treated with nasal bi-level positive airway pressure (nBiPAP). We also discuss awareness of the existence of LO-CHS/HD with recurrent acute convulsive seizures accompanying pulmonary edema and our treatment experience in older ages of childhood.

Case Report

A 13-year-old boy was admitted to Bakırköy Research and Training Hospital suffering from recurrent pulmonary edema. He had no notable...
health problem, but in the previous three years had had three episodes of pneumonia and acute convulsive seizures complicated with hypercapnic respiratory failure. He was born at term, weighing 3000 g from non-consanguineous parents after an uncomplicated pregnancy and delivery. On his medical history, his parents had recognized stuttering and strabismus at two years of age. His school performance was poor and the parents complained of hypersomnia and rapid weight gain in the last four years. The patient had two subsequent hospital admissions for acute convulsive seizure accompanied by fever, hypoxia, generalized tonic-clonic seizure, and unconsciousness at 10 and 12 years of age. His discharge diagnoses were pneumonia after neurological and cardiac examinations with normal cranial computerized tomography (CT), electroencephalography (EEG) and echocardiography.

At 13 years of age, he was admitted to our emergency service with a diagnosis of respiratory failure and convulsive seizure. He had a two-day history of cough, fever and tachypneic respiratory pattern. His physical examination revealed an unconscious male with cyanosis and generalized tonic-clonic seizures. He was dyspneic, tachypneic and tachycardic (heart rate 140 beats/min). On auscultation of the lung, there were decreased breath sounds and diffuse rales. His abdomen was soft with palpable liver tip on the right. The patient was noted to have hypoxemia and acidosis. Arterial blood gas on room air demonstrated pH: 7.24, PaO₂: 31.8 mmHg, PaCO₂: 76 mmHg, and HCO₃: 31.4 mmol/L. Laboratory studies revealed normal laboratory values for electrolytes, hemotocrit, amino/organic acids, lactate, and ammonia. Seizures resolved spontaneously with only oxygen supplementation following a post-ictal period of 30 minutes. Pulmonary edema was recognized on chest X-ray and CT. Cardiac evaluation with echocardiography excluded cardiac anomalies. Neurological counseling was normal with the EEG of normal tracing. Further workup revealed normal spinal and brain magnetic resonance imaging. His body mass was 26 kg/m². Both his genital stage and pubic hair stage were Tanner I, and history of learning disability, hyperphagia and rapid weight gain directed us to endocrinological and genetic consultation. Oral glucose tolerance test (OGTT) showed impairment (glucose: 133.8 mg/dl, insulin: 118 mU/ml in 2nd hour), but we obtained normal levels of thyroid hormones, cortisol, prolactin, and luteinized and follicle stimulating hormone. Abdominal ultrasonography evaluation excluded the presence of abdominal lesions. Genetic screening for Prader-Willi syndrome verified normal genetic structure. Pulmonary function testing and pulmonary perfusion scintigraphy were normal.

Although overnight capnometry was not performed, detection of daytime hypercapnia in arterial blood gas without signs of respiratory efforts after pulmonary status had been stable and recognition of recurrent pulmonary edema in the medical history raised the suspicion of central hypoventilation. Overnight polysomnography revealed that an oxygen saturation of 77% on room air during wakefulness decreased 50% without snore or any remarkable respiratory effort at sleep onset. Additionally, we observed bradycardia which was synchronized with oxygen desaturations (Fig. 1). Central hypoventilation was confirmed by polysomnographic recordings. Treatment with medroxyprogesterone acetate at 10 mg/day was initiated. We observed medication efficacy on hypercapnia only in the daytime but not during sleep and the patient achieved resolution of the hypersomnia. Since increase in continuous positive airway pressure (nCPAP) from 4 cm H₂O to 10 cm H₂O did not improve the abnormal respiratory pattern and the patient could not tolerate it, we switched to nBiPAP.

![Fig. 1. Overnight polysomnography report of the case.](image-url)
His nBiPAP settings at an inspiratory positive airway pressure of 7 cm H$_2$O and expiratory positive airway pressure of 4 cm H$_2$O were noted to be effective. LO-CHS/HD was diagnosed and he was discharged to remain on nBiPAP at home. He is now 14 years old and treatment and follow-up have been successful.

Discussion

Idiopathic central hypoventilation can be associated with variable clinical outcomes depending on age onset, associated disorders such as Hirschsprung disease and tumors of neural crest origin and HDs. HD is proposed to be a distinct entity among the clinical and genetic heterogeneous group of patients with late-onset central hypoventilation, referred to as LO-CHS/HD$^3,4$. We determined the presence of central hypoventilation with variable increases in carbon dioxide saturation (60-80 mmHg) and bradi-tachyarrhythmias with different levels of oxygen saturation (30-77 mmHg) as described in LO-CHS$^6$. The present study describes a patient with HD form of LO-CHS characterized by hyperphagia, rapid-onset obesity and hypersomnolence.

The most characteristic manifestations of LO-CHS/HD present in the first 10 years of life$^5$. Typically, rapid-onset obesity, which began in early life due to sudden onset of HD, is the initial feature in these patients with normal growth, development and cognitive function until 1.5-4 years of age$^4$. Alveolar hypoventilation is generally noted later in the course of the disease, with a mean of 1.5-3 years$^3,5$. Our experience with the present case is consistent with a previous case report in which a previously well child aged 9 years demonstrated similar signs and symptoms with alveolar hypoventilation confirmed by polysomnography. Although there is a wide variation in the reported age at onset of alveolar hypoventilation and accompanying disorders, most emphasize younger ages of childhood, especially before 10 years. Alveolar hypoventilation was revealed at the age of 10 years but was diagnosed three years later in our patient. In particular, LO-CHS/HD is an uncommon but important group of respiratory control disorders in infants and children, and awareness of the existence of LO-CHS/HD in older ages of childhood has led to the recognition of such patients, which can help to protect them from life-threatening problems.

Patients with LO-CHS/HD were reported to have highly variable endocrine dysfunctions, especially hyperphagia, water imbalance problems, adrenal insufficiencies, and puberty disorders mostly advocated to HD$^4,5$. This patient had only hyperphagia and rapid-onset obesity, but we also demonstrated impaired glucose tolerance in the present study as a rare associated endocrine dysfunction of LO-CHS/HD.

Late-onset central hypoventilation syndrome with hypothalamic dysfunction (LO-CHS/HD) is a less well known but potentially related condition of autonomic dysregulation, developmental and behavioral disorders and neurologic findings$^3,5$. The most common autonomic dysregulation symptoms were ophthalmologic, such as papillary dysfunction and strabismus$^3,5$. Significant developmental problems were reported in children with LO-CHS, especially in memory functions, communication and daily living skills$^7$. These neurocognitive pathologies are also predominant in LO-CHS/HD and usually present at the onset of hypoventilation, but mental retardation seems to be especially notable in these cases$^3$. The etiology is difficult to assess, such as whether or not all the clinical symptoms experienced in our case can be attributed to hypoventilation and/or HD or only the course of the disease. Moreover, seizure activities were identified in some previous reports and should be considered in LO-CHS/HD$^8,9$. Ize-Ludlow et al.$^5$ reported that 33% of patients had generalized tonic-clonic seizures at the time of initial diagnosis or associated with subsequent episodes of hypoxemia. Our patient had acute convulsive seizures with severe respiratory deteriorations especially during respiratory tract infections at 10 and 12 years of age. The episodes were considered to be pneumonia/generalized tonic-clonic seizures, but were in retrospect proven to be lung congestion as a consequence of hypercapnia and hypoxemia. This confirms that hypoventilation may present with severe respiratory impairment during infectious events, and those patients should be considered at high risk for respiratory failure. Furthermore, clinicians should be aware of LO-
CHS/HD in the presence of convulsive seizures with hypercapnia during recurrent respiratory complications in older ages of childhood. Hypothalamic obesity with respiratory control abnormalities in the absence of a neuroanatomical lesion is also induced by Prader-Willi syndrome. Major clinical features of Prader-Willi syndrome include neonatal hypotonia with poor suck and poor weight gain in infancy, growth hormone insufficiency causing short stature, characteristic appearance, mental retardation, hypothalamic hypogonadism, childhood-onset obesity, and usually a demonstrable genetic disorder with the absence of expression of paternally inherited genes in the 15q11.2-q13 region\textsuperscript{10,11}. LO-CHS/HD is clearly distinguishable from Prader-Willi syndrome based on both clinic and genetic evaluation, as determined in our case\textsuperscript{3,4}.

Treatment modalities are still under discussion in alveolar hypoventilation syndromes. Respiratory stimulants such as theophylline, dexamphetamine and clomipramine are proposed to have limited value in current therapeutic procedures\textsuperscript{4,8,9,12,13}. Milerad et al.\textsuperscript{14} reported that medroxyprogesterone acetate was effective and even reduced assisted ventilation requirement in alveolar hypoventilation syndrome. We experienced the medication efficacy with medroxyprogesterone acetate only on hypercapnia in the daytime and found it unsuccessful in the disease management. Assisted ventilation methods such as positive pressure ventilation, negative pressure ventilation and diaphragmatic pacers seem to be the standard of practice in hypoventilation syndromes\textsuperscript{15}. Noninvasive positive pressure ventilation in infancy and older children often ameliorates respiratory events and has been used in both acute and chronic respiratory failure\textsuperscript{16}. Our patient suffering from chronic respiratory failure had hypercapnia during daytime and sleep. He was thus treated initially with nCPAP, but could not tolerate the high values. Nocturnal nBiPAP therapy was started and produced marked reduction in the respiratory disorders during sleep and daytime. Our LO-CHS/HD patient continues to use this form of ventilatory assistance without difficulties. We concluded that with proper noninvasive ventilation methods and adequate ventilatory support, these children can have good outcomes.

The conclusion from the current report is that there is a risk of fatal outcomes in children with LO-CHS/HD, but diagnosis may be underestimated due to the expression of this syndrome. We believe our case is worthy of particular attention because of the rarity of this condition in older ages of childhood and in view of our successful treatment experience of LO-CHS/HD in childhood.

REFERENCES


