Rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation in Saudi Arabia

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ABSTRACT

Rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is a rare disease, but could be fatal if not diagnosed early. It mimics many other diseases and it may take few years after the onset of rapid obesity to have the other clinical features. Therefore, any patient with rapid-onset obesity after the age of 2 years should have high index of suspicion and long term follow up. We report a case of ROHHAD in Saudi Arabia and we highlight the clinical features and the importance of early diagnosis and management.

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threshold seems to be altered. She does not complain or cry when she get needle phlebotomy. The father and mother are not related. The patient has 3 sisters and one brother and none has similar symptoms.

On physical examination, she looked well with no apparent respiratory distress despite bluish discoloration of lips and her SpO\textsubscript{2} of 75% on room air. She was obese with weight of 45 kilogram (kg), height of 126 centimeter (cm) and body mass index (BMI) of 28. Tanner stage was 3 with early puberty signs. Rest of physical exam was unremarkable with normal muscle power and neurological exam.

Her initial laboratory investigations showed normal complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and Chest x ray (CXR). However, she had a marked hypernatremia with serum sodium (Na) of 186 millimole/liter (mmol/l). In addition, arterial blood gas (ABG) was consistent with chronic hypoventilation as noted of elevated arterial partial pressure carbon dioxide (PCO\textsubscript{2}) of 50 millimeter mercury (mm hg), normal acidity (pH) of 7.36 and bicarbonate (HCO\textsubscript{3}) of 29 mmol/l. Renal and pelvic ultrasound, electrocardiogram, echocardiogram and contrasted brain magnetic resonance imaging (MRI) were normal. She had a very high prolactin level (197 nanogram per liter (ng/l), normal range 3.3-24) and normal thyroid and cortisol levels. Overnight polysomnogram was carried out later and showed severe hypoventilation with mean end tidal CO\textsubscript{2} (EtCO\textsubscript{2}) of 56 mmhg, maximum EtCO\textsubscript{2} of 68 mm hg and patient spent 100% of total sleep time with EtCO2 >50 mm hg (Figure 1).

Lowest oxygen (O2) saturation was 65% especially during Rapid eye movement sleep and patient had intermittent hypopneas. All these events of sleep disordered-breathing were corrected using bi-level positive airway pressure (BiPAP) in spontaneous/timed (S/T) mode with inspiratory positive airway pressure (IPAP) of 16 centimeter of water pressure (CWP), expiratory positive airway pressure (EPAP) of 6 CWP, back up respiratory rate of 15/minute and inspiratory time (I-time) of 1 second. This was delivered through small nasal mask with minimal leak and patient tolerated it well. She continued to tolerate being on BiPAP therapy during a year of follow up.

**Discussion.** Late onset-central hypoventilation syndrome (LO-CHS) has been described since 1965. Initially, it was thought that it is related to CCHS since patients share similar feature of absent ventilatory response to hypercapnia and leading to respiratory failure.\textsuperscript{1} It was not until 2000, when Katz et al\textsuperscript{2} reported a new case and reviewed previous 10 reported cases. It was proposed that this would be a new entity and not related to CCHS. They suggested that both diseases may have similar pathophysiology since both diseases associate with the development of neural crest tumor.\textsuperscript{4,5} However, LO-CHS clearly presents at a later

![Figure 1](image-url) - Severe hypoventilation with hypoxia noted on polysomnogram, REOGM2 - right electrooculogram, LEOMGM - left electrooculogram, CEMG - chin electromyogram, F3M2 - frontal electrode at mastoid, F4M1 - frontal electrode at mastoid, C3M2 - central electrode, C4M1 - central electrode, O1M2 - occipital electrode, O2M1 - occipital electrode, ECG - electrocardiogram, ETCO\textsubscript{2} - end tidal PCO\textsubscript{2}, Capno - capnogram, TFlow - thermal flow, Presflow - pressure flow, THO - chest, ABD - abdomen, SPO\textsubscript{2} - oxygen saturation, BODY - body position, S - supine, N - sleep stage

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age and is associated with hypothalamic dysfunction which is not seen in patient with CCHS. In 2007, Ize-Ludlow et al extensively reviewed 15 patients with diagnosis of LO-CHS and performed genetic testing on them. They found that these patients do not exhibit PHOX2B sequencing similar to patient with CCHS. Therefore, they suggested that LO-CHS is a different entity and suggested naming it ROHHAD.

The diagnosis of ROHHAD should be considered if rapid-onset obesity develops after the age of 2 years. Careful questioning regarding hypothalamic dysfunction should be carried out to see if the patient may exhibit findings suggestive of hypothyroidism, adrenal insufficiency, delayed or precocious puberty, disordered water balance, polyuria, hyper or hyponatremia, and/or hyperprolactinemia. Usually the patient will progress gradually and the symptoms of autonomic dysfunction will start to be apparent, which include altered sweating, gastrointestinal dysmotility, ophthalmic manifestation, thermal dysregulation and altered perception of pain. However, it may take few years after the onset of rapid weight gain, to start having other symptoms of hypothalamic dysfunction, autonomic dysregulation or hypoventilation. This makes it difficult to reach the diagnosis and long term follow up with high index of suspicion is needed.

In conclusion, once the diagnosis is suspected, then comprehensive respiratory assessment during wakefulness and sleep is needed with possible need for BiPAP titration to eliminate hypoventilation. However, when the diagnosis is confirmed, it is important to follow up the patient with repeated polysomnogram every 3-6 months to ensure optimal oxygenation and ventilation. These patients also need regular screening for neural crest tumors every 1-2 years by doing chest and abdominal imaging. They also require a multidisciplinary team approach to include general pediatrician, pulmonologist, endocrinologist, and other pediatric subspecialties if needed, such as cardiology and oncology.

The clinical picture and progression of the presented case resemble what have been reported in the literature. It is important to raise the awareness of this disease in order to prevent misdiagnosing or delay the right diagnosis, which may have a catastrophic event that may lead to brain damage or even death.

References

1. Fishman LS, Samson JH, Sperling DR. Primary Alveolar Hypoventilation Syndrome (Ondine’s Curse). Am J Dis Child 1965; 110: 155-161.
2. Katz ES, McGrath S, Marcus CL. Late-onset central hypoventilation with hypothalamic dysfunction: a distinct clinical syndrome. Pediatric pulmonology 2000; 29: 62-68.
3. Ize-Ludlow D, Gray JA, Sperling MA, Berry-Kravis EM, Milunsky JM, Farooqi IS, et al. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation presenting in childhood. Pediatrics 2007; 120: e179-188.
4. Swaminathan S, Gilsanz V, Atkinson J, Keens TG. Congenital central hypoventilation syndrome associated with multiple ganglioneuromas. Chest 1989; 96: 423-424.
5. Del Carmen Sanchez M, Lopez-Herce J, Carrillo A, Moral R, Arias B, Rodriguez A, et al, Late onset central hypoventilation syndrome. Pediatr Pulmonol 1996; 21: 189-191.
6. Ouvrier R, Nunn K, Sprague T, McLean C, Arbuckle S, Hopkins I, et al. Idiopathic hypothalamic dysfunction: a paraneoplastic syndrome? Lancet 1995; 346: 1298.
7. Gallego J, Dauger S. PHOX2B mutations and ventilatory control. Respir Physiol Neurobiol 2008; 164: 49-54.
8. Amiel J, Laudier B, Artic-Bitach T, Trang H, de Pontual L, 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: 459-461.
9. Rand CM, Parwari PP, Rodikova EA, Zhou L, Berry-Kravis EM, Wilson RJ, et al. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation: analysis of hypothalamic and autonomic candidate genes. Pediatr Res 2011; 70: 375-378.