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

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ABSTRACT

تتمثل صفات متلازمة (روهاد) بالسمنة سريعة الظهور وخلل بغدة المهاد ونقص التهوئة وإعتلال بالأعصاب اللاإرادية وهي مرض نادر من الممكن أن يكون مميتاً إذا لم يتم تشخيص الحالة مبكراً. لكون أعراض المتلازمة تحاكي العديد من أعراض أمراض أخرى فربما يستغرق التشخيص بعضاً من الوقت وخاصة أن الأعراض المصاحبة تأخذ وقتاً هي الأخرى بعد ظهور السمنة السريعة. لذلك يجب الاشتباه مبكراً والمتابعة لأي طفل يعاني من السمنة سريعة الظهور بعد العام الثاني من أجل هذا نقدم تقريراً عن حالة لمتلازمة روهاد في المملكة العربية السعودية ونسلط الضوء على المظاهر السريرية وأهمية التشخيص والعلاج المبكر.

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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Late onset-central hypoventilation syndrome (LO-CHS) has been recognized since the mid-1960.[1] It was noticed that it has some features that resemble congenital central hypoventilation syndrome (CCHS).[2] However, it was not until 2007 when a new name to LO-CHS was proposed as Rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysfunction (ROHHAD).[3] These patients present with hypoventilation and rapid onset obesity which is usually presents after the age of 2 years and associated with different features of hypothalamic dysfunctions and autonomic dysregulations. The aim of reporting this case is to raise the awareness of this disease and its manifestations. The disease could be missed easily with other pathologies, which may lead to wrong management.

Case Report. A 7.5 year old female presented with a progressive fatigue, bluish discoloration of the skin and fever for few days. There were no symptoms of cough, chest pain, headache or upper respiratory tract infection. Patient's past history was significant to recurrent episodes of shortness of breath, interrupted breathing, fever, and bluish skin discoloration, which seems to have approximately 2 months prior to this hospitalization. The patient's mother reports a rapid weight gain, which started around the age of 5 years. Breasts enlargement at the age of 4 years and acne development was also noticed 2 months prior to this hospitalization. In addition, there has been a history of slow mental function and weak memory with very poor school performance. This has been accompanied with history of worsening fatigue, sleepiness, cold intolerance, and excessive sweating. Also, her pain

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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_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_2) of 50 millimeter mercury (mm hg), normal acidity (pH) of 7.36 and bicarbonate (HCO_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_2 ($EtCO_2$) of 56 mmhg, maximum $EtCO_2$ 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.[1] It was not until 2000, when Katz et al[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.[4-6] However, LO-CHS clearly presents at a later

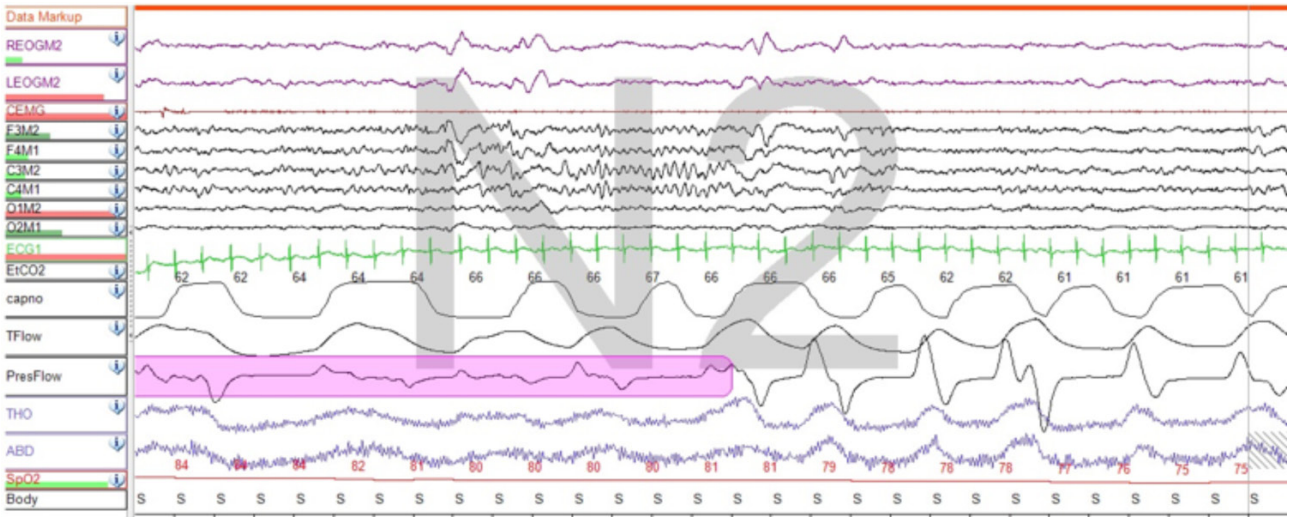

Figure 1 - Severe hypoventilation with hypoxia noted on polysomnogram, REOGM2 - right electrooculogram, LEOMGM - left electooculogram, CEMG - chin electomyogram, F3M2 - frontal electrode at mastoid, F4M1 - frontal electrode at mastoid, C3M2 - central electrode, C4M1 - central electrode, O1M2 - occipital electrode, O2M1 - occipital electrode, ECG - electocardiogram, $ETCO_2$ - end tidal PCO_2, Capno - capnogram, TFlow - thermal flow, Presflow - pressure flow, THO - chest, ABD - abdomen, SPO_2 - oxygen saturation, BODY - body position, S - supine, N - sleep stage

age and is associated with hypothalamic dysfunction which is not seen in patient with CCHS.[2] In 2007, Ize-Ludlow et al[3] 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.[7,8] 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.[3] However, it may take few years after the onset of rapid weight gain, to start having other symptoms of hypothalamic dysfunction, autonomic dysregulation or/and hypoventilation. This makes it difficult to reach the diagnosis and long term follow up with high index of suspicion is needed.[9]

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.[3] 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.

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