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Rapid-Onset Obesity, Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysfunction (ROHHAD)

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Abbreviations
ROHHAD: Rapid-Onset Obesity, Hypothalamic Dysfunction, Hypoventilation and Autonomic Dysfunction

Introduction

Rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysfunction (ROHHAD) is a rare syndrome that was initially described more than 50 years ago. However, the term ROHHAD and its criteria for diagnosis were not distinguished as a separate entity except in 2007 [1,2]. To date, literature from Saudi Arabia shows two reported cases. Moreover, fewer than 100 cases were described in the literature worldwide [3-5]. Despite that there is no diagnostic test that can detect ROHHAD; Keeping it in mind while excluding other etiologies is important; since the prognosis of ROHHAD mainly depends on how early the case is diagnosed and managed in the aims to decrease severe complications and mortality. Symptoms of the disease, particularly rapid weight gain, can present as early as one year and a half of age, followed by gradually developing symptoms of hypothalamic dysfunction, autonomic dysregulation, and hypoventilation, leading the parents to seek medical attention.

Currently, management of ROHHAD syndrome is largely symptomatic, focusing mainly on improving the quality of life and preventing potentially fatal sequelae in patients with this disease. As for medical management, clinical trials are still ongoing [3,6].

In this paper, we report a case of a 3-year-old girl who initially presented with rapid-onset obesity followed by multiple features of ROHHAD symptoms over time. In this paper, we aim to raise awareness of the presence of such cases in our community and to increase knowledge about the management of such cases.

The Case

A 3-year-old and 2-month-old Saudi girl, not known to have any medical illness, was referred from a regional hospital because of a significant increase in weight over the past 8 months. She was in her usual state of health until 8 months back when the mother noticed that our patient's appetite started to increase and that she started to gain weight. The mother tried to restrict the patient's caloric intake over the past 2 months, yet the patient's weight was not going down and stayed stable at 33 kgs. The mother also noticed an increase in the patient's water consumption, and increased urination frequency. In the past 4 months, the patient was waking up from sleep due to difficulty of breathing. Other symptoms included a sudden onset of squint (right eye) for the last 2 months, increased sweating, increased tolerance to pain that was specifically noticed after self-inflicted injury while playing with sharp objects. The mother also noticed a change in the patients' personality in the form of increased irritability, and increased fear of pools and stairs. The family sought medical advice in a regional hospital. Investigation of cortisol level and thyroid function test was found to be normal. The patient had no previous medical history and was not on any medications when she was presented to us. Her developmental milestones were appropriate for her age. She had her vaccination schedule completed up to 2 years of age. She is a product of full-term caesarean section delivery due to fetal distress and her birth weight was 3 kgs. There were no post-natal or antenatal complications. Her parents are first degree cousins. There is no history of any similar conditions nor history of obesity in the family. Both parents have a bachelor's degree and are working as teachers. They appear to have good socio-economic status. On examination the patient looked noticeably obese, she was active, not in distress, and no dysmorphic features were seen. There was no lymphadenopathy, and the patient seemed well-hydrated. On admission, her vital signs were as follows: temperature (Oral?) 37°C, blood pressure 108/54 mmHg, peripheral pulse 125/min, respiratory rate 36/min, and O2 sat: 94% on room air. She weighed 30.5 kg, which is 8 SD above the mean, and her height was 104 cm, which is in the 97th percentile. Her BMI was 28, which is 8 SD above the mean. Head and neck examinations were normal except for exotropia of the right eye. Chest exam revealed good bilateral air-entry and no added sounds. On cardiovascular exam she had normal heart sounds, and no murmur was heard. She seemed well-perfused with a capillary refill time of less than 2 seconds; however, the patient was tachycardic. On abdominal exam, the abdomen looked obese but otherwise soft, and lax, and there was no organomegaly. A neurological exam yielded normal cranial

examination, normal tone power, and reflexes. The skin was intact, and no rashes were observed. There was also no joint swelling or tenderness. Her Complete blood count, urea/electrolytes, cortisol (AM: 528, PM: 411), ACTH (we need to know when), thyroid function test, liver function test, and lipid profile were all within the normal range. However, Prolactin was 2076 and the repeated result was 1490, which was high. Imaging included chest x-ray (normal), ultrasound of the abdomen (revealed mild hepatomegaly with fatty infiltration), MRI brain of the pituitary and hypothalamus (no definite focal lesion within the pituitary gland or the hypothalamic area, the overall volume of the pituitary appeared to be within normal limits. No definite abnormality was demonstrated intracranially), and CT abdomen and chest (showed a well-defined enhancing lesion seen at the right renal hilum, for which an excisional biopsy result was found to have benign mature adipose tissue and no evidence of malignancy. No other mass was identified in the chest or in the abdomen). Throughout her hospital stay, the patient had high systolic blood pressure (more than the 95th percentile for her age) with marked fluctuations in her blood pressure throughout the day and persistent tachycardia. An echocardiogram and 24-hour Holter monitor were requested. The echocardiogram showed a small PDA, mild Mitral regurgitation, mild ventricular dilatation, and right atrial dilatation. No ASD and no pulmonary hypertension were found. 24-hour Holter monitor showed only sinus tachycardia and no other arrhythmias. She was started on Atenolol for her high blood pressure and her subsequent blood pressure readings were within normal range for her age and height. We also noticed fewer fluctuations of her blood pressure readings. A sleep study revealed obstructive sleep apnea. She was put on CPAP during sleep. She had dietary adjustments in which her calories were restricted to 1500 kcal/day. The patient was also seen by behavioral and psychiatry teams and was diagnosed to have an anxiety disorder, obsessive traits, and a phobia of pools and stairs. She was advised to start psychotherapy and to consider Prozac as the next step in management if psychotherapy failed. The patient was discharged on Atenolol 7 mg once per day, and she was in good condition.

Discussion

Childhood obesity is becoming a worrisome concern with raising trends in its prevalence internationally (Lancet & JAMA) [7]. Medical literature has shown that obese children face many associated adverse health issues throughout their lifetime (Lancet). The cutoff point in defining childhood obesity is defined as BMI of ≥95th percentile [8].

Obesity in children is influenced by many environmental risk factors such as lifestyle, social status, and early life events (Int J Obes, Pediatrics) [9]. It can also be due to genetic, endocrine, hypothalamic, and metabolic causes.

ROHHAD syndrome is a rare cause of hypothalamic dysfunction-induced obesity. It is characterized by an initial presentation of rapid onset obesity in otherwise healthy children aging (1.5-9 years old) that is followed by hypothalamic dysfunction, autonomic dysregulation, and alveolar hypoventilation [6,10]. Weight gain usually starts at 3 years of age (around 9-15 Kg over a 3–12-month period) with mild hyperphagia and difficult weight loss even with a restricted diet [5,6]. Hypothalamic dysfunction and autonomic dysregulation typically occur around 6 months after the initial presentation of rapid-onset obesity. Hypoventilation usually occurs later in the course of the disease and may have life-threatening complications [3].

The syndrome is still not fully understood and has no clear etiology; therefore, the diagnosis of ROHHAD should be done by exclusion [6]. In our case, careful history and physical exam were taken. This helped us exclude possible environmental and lifestyle-influenced causes. Other distinct genetic etiologies and syndromic causes of obesity were also ruled out, such as Prader-Willi syndrome (PWS) which is the most common form of single gene defects causing obesity, since these syndromes usually present with characteristic features that were not present in our case. Iatrogenic causes were excluded as there was no history of medication usage such as glucocorticoids, antiepileptics, or psychoactive medications. Investigations done in our hospital revealed high prolactin level, which pointed more towards hypothalamic dysfunction and its related disorders.

We would like to emphasize on the importance of taking thorough history, physical examination, and proper investigations for cases that present with rapid onset obesity, keeping in mind the rarer but potentially life-threatening causes. Following the identification of ROHHAD, long term follow up is essential. This can be done by conducting a routine comprehensive respiratory assessment and periodic investigations to rule out the development of complications and associated manifestations such as neural crest tumors, the later which may occur in up to 40-50% of diagnosed ROHHAD cases [4,5]. Furthermore, long term multidisciplinary care is recommended. (Debra ABC).

We recommend further research to better understand this disease and its causes and use this knowledge to develop treatments that improve the quality of life of our patients affected by this disease [11-14].

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