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Case Report

## A Rare Cause of Hypothalamic Obesity, Rohhad Syndrome: 2 Cases Şiraz et al. Two Cases with Rohhad Syndrome

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### What is already known on this topic?

Rapid-onset obesity with hypoventilation, hypothalamic dysfunction and autonomic dysregulation (ROHHAD) syndrome is a rare disease. There are around 80 reported patients due to lack of recognition.

### What this study adds?

ROHHAD syndrome should be considered in differential diagnosis obese patients with hypothalamic dysfunction and autonomic alterations. We aimed to increase awareness in this regard by presenting two patients diagnosed at the same clinic.

### Abstract

Rapid-onset obesity with hypoventilation, hypothalamic dysfunction and autonomic dysregulation (ROHHAD) syndrome is a rare disease that is difficult to diagnosis and distinguish from genetic obesity syndromes. The underlying causes of the disease has not been fully explained. Hypothalamic dysfunction causes endocrine problems, respiratory dysfunction and autonomic alterations. There are around 80 reported patients due to lack of recognition.

We present two female patient suspected of ROHHAD due to weight gain since early childhood. The presented symptoms, respiratory and circulatory dysfunction, hypothalamic hypernatremia, hypothalamo-pituitary hormonal disorders such as santral hypothyroidism, hyperprolactinemia and santral early puberty are completely matched the criteria of ROHHAD syndrome.

ROHHAD syndrome should be considered in differential diagnosis since it is difficult to distinguish from causes of monogenic obesity.

Early identification of the disease reduces morbidity of the syndrome and patients require regular follow-up by a multidisciplinary approach.

**Keywords:** Rohhad Syndrome, hypothalamic dysfunction, endocrinological disorders

### Introduction

ROHHAD (Rapid-onset Obesity with Hypothalamic Dysfunction, Hypoventilation and Autonomic Dysregulation) syndrome is a rare cause of obesity, which is characterized by early and rapid onset of obesity, hypoventilation, hypothalamic dysfunction and autonomic derangements. So far, 80 patients with ROHHAD have been defined in the literature (1, 2, 3). Since the obesity and endocrine abnormalities comprise major component of syndrome, it should be kept in mind in differential diagnosis, particularly by pediatric endocrinologists.

The syndrome begins with uncontrollable eating impulse and rapid weight gain at early childhood (particularly 2-4 years of age). In this period, apnea episodes and cyanotic attacks are added due to respiratory distress caused by weight gain and hypothalamic dysfunction. In addition, hyponatremia and/or adipsic hypernatremia may also be seen due to involvement of thirst center. Abnormalities of hypothalamo-hypophyseal hormones may present with diabetes insipidus, hyperprolactinemia, growth hormone deficiency, central hypothyroidism, secondary adrenal insufficiency and early or delayed puberty (2, 4, 5).

There may be findings of autonomic dysfunction including thermal dysregulation (hypothermia/hyperthermia), cold and pallor hands and feet (Raynaud's phenomenon), excessive sweating, decreased pain sensitivity, impaired pupillary response to light, bradycardia, hypotension and gastrointestinal dysmotility (2, 6, 7).

Moreover, patients may present with psychiatric problems such as anxiety, aggressive behaviors and personality disorder (8). Majority of patients have an underlying neural crest tumor (5).

This rare syndrome can manifest with various clinical and endocrine findings. Here, we discussed 2 cases presented with distinct clinical symptoms for evaluation of obesity.

#### **Case 1**

A 7 years 4 months old girl presented with excessive weight gain. In history, it was found out that she was born at term with birth weight of 2900 g. Parents reported that she began to gain weight rapidly upon 1.5 years of age. There was no consanguinity between parents and she had 2 healthy siblings (one at 11 years of age and other 9 months of age). In physical examination, body weight was 61 kg ( $\pm 3.9$  SD) and height was 130 cm ( $\pm 1.8$  SD) with a body mass index (BMI) of 36 kg/m<sup>2</sup> ( $\pm 3.3$  SD). She had plethoric facial appearance, axillary acanthosis nigricans, pallor/blue fingers and toes, and bilateral stage 2 thelarche. The patient was admitted to hospital for further evaluation. During follow-up, it was observed that she had episodes of excessive sweating and body temperature as low as 35.4 °C. Blood pressure was found to be 95/60 mmHg (95 percentile: 120/80 mm/Hg). In laboratory evaluation, following results were obtained: Na, 156 mmol/L (135-145 mmol/L); AST, 87 U/L (8-45 U/L); ALT, 57 U/L (7-55 U/L); urine density, 1024; Remaining biochemical parameters and complete blood count were found to be normal. The patient had no polydipsia; thus, hypernatremia was considered as adipic and oral fluid replacement was given, which corrected hypernatremia (Na: 141 mmol/L). Impaired glucose tolerance (141 mg/dL on hour 2) was detected in oral glucose tolerance test performed due to morbid obesity and acanthosis nigricans; thus, metformin was prescribed to patient. The patient underwent abdominal sonography due to elevated transaminase levels, which revealed grade 3 hepatic steatosis. Pituitary evaluation revealed following results: free T4, 0.7 ng/ml (0.98-1.6 ng/ml); thyroid stimulation hormone (TSH), 4.8  $\mu$ IU/ml (0.5-4.3  $\mu$ IU/ml); adrenocorticotrophic hormone (ACTH), 24 pg/ml (10-60 pg/ml); cortisol, 1.5  $\mu$ g/ml (3-21  $\mu$ g/ml); LH, 1.3 mIU/ml (Prepubertal Normal: <0.3 mIU/ml); Estradiol, 12.9 pg/ml (Prepubertal Normal: <12 pg/ml); prolactin (PRL), 33 ng/ml (4.7-23.3 ng/ml). The insulin like growth factor-1 (IGF-1: <25 ng/mL) and insulin like growth factor binding protein 3 (IGFBP3: 1870 ng/mL) were low and bone age was compatible with 10 years of age. Peak cortisol response to low dose ACTH stimulation test was found to be low (9.9  $\mu$ g/mL). Hydrocortisone, LT4 and leuprolide acetate was initiated with diagnoses of secondary adrenal insufficiency, central hypothyroidism and central precocious puberty. No further evaluation or treatment was considered for growth hormone (GH) deficiency due to normal height and predisposition to neural crest tumor in the patient although IGF-1 and IGFBP3 values were found to be low. Brain and pituitary magnetic resonance (MR) imaging studies were found to be normal and IQ score was 65. The fadedness at fingers was considered as Raynaud's phenomenon (Figure 1). Alterations in body temperature and Raynaud's phenomenon were attributed to autonomic dysfunction. Pulmonary hypertension was detected on echocardiography; thus, nifedipine was prescribed. Imaging studies due to possibility neural crest tumor was found to be normal.

#### **Case 2**

A 5 years old girl with suspected epileptic seizures was referred for evaluation of obesity. The patient also had sleep apnea and aggressive behaviors. In history, it was found out that she was born at term with a birth weight of 2800 g and she had uncontrollable eating behaviors upon 2 years of age with rapid weight gain. There was no consanguinity between parents and she had 2 healthy siblings. In physical examination, body weight was 11 kg ( $\pm 3.7$  SD) and height was 101 cm ( $\pm 1.7$  SD) with a BMI of 30.4 kg/m<sup>2</sup> ( $\pm 5.7$  SD) (Figure 2). The patient had central cyanosis and blood pressure was 90/60 mm/hg (95 percentile: 115/75 mm/Hg). Axillary body temperature measurements varied from 35.6 to 39.5°C.

In laboratory evaluation, following results were obtained: Na, 164 mmol/L (135-145 mmol/L); urine density, 1018; Remaining biochemical parameters, liver enzymes and lipid profile were found to be normal. The patient was considered as adipic hypernatremia; thus, oral fluid replacement was given, which normalized Na value (Na: 140 mmol/L). Pituitary evaluation revealed following results: fT4, 0.8 ng/ml (0.98-1.6 ng/ml); TSH, 1.8  $\mu$ IU/ml (0.5-4.3  $\mu$ IU/ml); PRL 56 ng/ml (4.7-23.3 ng/ml). Remaining pituitary hormones were found to be normal. Treatment was given for central hypothyroidism and mild hyperprolactinemia was persisted but no treatment was needed. Brain and pituitary MR imaging studies were found to be normal. 15q11-q13 (SNRPN gene) deletion was found to be negative in genetic tests for Prader Willi Syndrome. In addition, the gene sequence did not identify any PHOX2B variation for congenital hypoventilation syndrome. IQ was compatible to 3 years of age. Imaging studies for neural crest tumor was found to be normal. Sleep apnea was persisted and central cyanosis progressed. The patient was admitted to intensive care unit due to development of carbon dioxide retention (PH: 7.27, PCO<sub>2</sub>: 55 mm/Hg) and mechanical ventilation was initiated. Since the patient needed continuous ventilator support, she was discharged with home ventilator after tracheostomy.

Clinical and laboratory characteristics of patients are summarized in Table 1.

#### **Discussion**

ROHHAD syndrome characterized by high morbidity and hypothalamic dysfunction is a rare cause of obesity, in which etiology is unknown (7). It is thought that the syndrome is associated to underlying genetic, autoimmune

and paraneoplastic factors and studies aiming such factors are ongoing (4). However, no genetic defect was detected in these studies (9).

The Smiths-Magenis syndrome (SMS) presented with hyperphagia at late childhood and adolescent as well as dysmorphic facial appearance is caused by point mutation in RAI1 which is a transcription factor involved in craniofacial and neural development (10). In 2015, a novel mutation was detected in RAI1 gene in a boy aged 11 years who presented with clinical findings of ROHHAD syndrome; the patient was considered as overlap syndrome with SMS (11).

Since patients with ROHHAD syndrome resemble congenital hypoventilation syndrome, PAIRE-like home BOX 2B-PHOX2B, a genetic factor responsible from hypothalamic embryogenesis, was studied but results were negative (9). Congenital hypoventilation syndrome manifests with autonomic dysfunction, respiratory problems and gastrointestinal motility disorders at neonatal period in most instances. In our cases, onset of obesity was after 18 months of age and autonomic dysfunction was developed later on course of disease.

Prader-Willi syndrome is also included in differential diagnosis due to early onset of obesity. However, there may be mental retardation, small hands and feet, ocular findings and hypogonadism (2, 10, 12). It wasn't considered in differential diagnosis in first case due to presence of precocious puberty while genetic study was performed in second case, which was negative.

Leptin deficiency or resistance can be distinguished from ROHHAD syndrome by earlier onset of weight gain and associated immune deficiency although it also causes hyperphagia, obesity and deficiency in pituitary hormones. MRC4 receptor resistance-POMC deficiency is also a rare cause of monogenic obesity but obesity begins within first year of life in these patients and no autonomic dysfunction is described. In addition, there is reddish hair and extremely light skin color in POMC deficiency (13, 14).

Cushing syndrome should be kept in mind in the differential diagnosis of patients with ROHHAD syndrome. No hypercortisolism was detected in our patients and even secondary adrenal insufficiency was present in first case. Autonomic dysfunction is one of the common findings in patients with ROHHAD syndrome.

Tachycardia/bradycardia, cardiac arrest, constipation, hypothermia/hyperthermia, sleep apnea and narcolepsy can be seen. Dysfunction of hypocretin-1, involved in Ach release in autonomic nervous system, has been implied in autonomic dysfunction (7). There were hypothermia, excessive sweating and Raynaud's phenomenon in first case while there were hypothermia-hyperthermia episodes and sleep apnea in second case. Respiratory problems and obstructive sleep apnea can be observed in other monogenic obesity cases but no thermal dysfunction, excessive sweating and circulatory problems such as Raynaud's phenomenon is seen. In addition, adipsic hypernatremia is also lacking in other monogenic obesity cases.

Presence of lymphocyte infiltration in postmortem hypothalamic examinations suggested autoimmunity in ROHHAD syndrome and partial response was achieved to intravenous immunoglobulin (IVIG) and immunosuppressive therapies (5, 12). In addition, detection of oligoclonal band in cerebrospinal fluid (CSF) analysis supports intrathecal immunoglobulin synthesis (12).

Ganglioneuroma and neuroblastoma were detected in some cases with ROHHAD syndrome, suggesting paraneoplastic involvement of hypothalamus. Thus, there is a group of patients comprising 40% of all patients, which is termed as ROHHAD-neuroendocrine tumors (ROHHADNET) in recent years (15). We screened both cases for presence of such tumors but no mass lesion was detected.

ROHHAD syndrome is a rare cause of hypothalamic obesity, which is accompanied by autonomic dysfunction and pituitary hormone abnormalities. It is a multi-systemic disease with unclear etiology, requiring multidisciplinary palliative approach. It is thought that the diagnosis is missed in these cases which die due to respiratory or cardiac problems or underlying neoplasm. ROHHAD syndrome should be kept in mind in differential diagnosis since it is difficult to distinguish from causes of monogenic obesity.

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**Table 1:** Clinical and laboratory features of cases

	<b>Case 1</b>	<b>Case 2</b>
<b>Age at presentation (year)</b>	7 4/12	5 years
<b>Age at onset of hyperphagia (year)</b>	1.5	2
<b>Birth weight (g)</b>	2900	2800
<b>Weight (kg)-SD</b>	61 (3.9)	31 (3.7)
<b>Height (cm)-SD</b>	130 (1.8)	101 (-1.7)
<b>BMI (kg/m<sup>2</sup>)-SD</b>	36 (3.3)	30.4 (5.7)
<b>Endocrine pathology</b>	Central hypothyroidism Secondary adrenal insufficiency Central precocious puberty Hyperprolactinemia	Central hypothyroidism Hyperprolactinemia Adipsic hypernatremia

	GH deficiency Adipsic hypernatremia	
<b>Autonomic dysfunction</b>	Hypothermia Sweating Raynaud's phenomenon	Hypothermia/hyperthermia Sleep apnea
<b>Mental state</b>	IQ 65	Compatible to 3 years of age
<b>Respiration</b>	-	Sleep apnea Carbon dioxide retention Ventilator support
<b>Cardiac</b>	Pulmonary hypertension	-
<b>Neural crest tumor</b>	-	-
<b>Genetic</b>	-	15q11-q13 (SNRPN gene) (-) PHOX2B no variation

Uncorrected proof