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CASE REPORT

Rapid-onset obesity, hypoventilation, hypothalamic dysfunction, autonomic dysregulation syndrome

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ABSTRACT

Rapid-onset obesity with hypoventilation, hypothalamic dysfunction and autonomic dysregulation syndrome is a rare disorder that presents with rapidly evolving obesity with several endocrine disorders during early childhood. We present here a documented case of a 6-year-old Syrian girl with the characteristic symptoms of rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation, associated with an abdominal mass (mature ganglioneuroma).

Key words: Ganglioneuroma, hypoventilation, obesity, rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation syndrome

INTRODUCTION

Rapid-onset obesity with hypoventilation, hypothalamic dysfunction and autonomic dysregulation (ROHHAD) is a rare clinical constellation of symptoms that attracted medical attention in the year 2000 by Katz *et al.* who described a case of late-onset central hypoventilation syndrome (LO-CHS) and hypothalamic dysfunction (HD). The case was treated by nasal intermittent positive pressure ventilation with a comprehensive review of previously published 10 similar cases of (LO-CHS/HD).[1] The name "ROHHAD" was first suggested by Ize-Ludlow *et al.*[2]

The presenting complaint of ROHHAD syndrome is rapid-onset obesity, associated with abnormalities in the hypothalamus functions-represented by one or more of the following symptoms: Hyperphagia, hyperprolactinemia, blunted response in growth hormone (GH) levels to provoking tests, disturbed antidiuretic hormone (ADH) secretion.

These findings when associated with hypoventilation (central and/or obstructive), in addition to some signs that could be attributed to autonomic nervous system dysregulation-represented by thermal regulation instability, pupillary reaction disorders, nonparalytic strabismus, gastrointestinal motility disorders. Then ROHHAD syndrome is considered.

In many of the reported cases, a concomitant ganglioneuroma or ganglioneuroblastoma was present. Moreover, in those cases, the term ROHHAD and neural crest tumor syndrome (ROHHAD-NET) was suggested.[3]

Our case is a ROHHAD syndrome with a resected abdominal ganglioneuroma, as described in the next section.

CASE REPORT

A 6-year-old girl was admitted to the Children Hospital at Damascus University, with the diagnosis of abdominal mass, discovered incidentally by ultrasonography during the workup of rapid onset obesity.

During the last year, her parents noticed increased appetite resulting in noticeable weight gain. This was associated in the last 2 months with nighttime urinary incontinence, premature thelarche, snoring and witnessed episodes of obstructive sleep apnea (OSA).

The perinatal history was unremarkable with a birth weight of 3.2 kg and a length of 50 cm. The past medical history

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was negative, with no history of genetic, neurological or endocrinological diseases in the family.

On physical examination we recorded obesity (weight: 38 kg [>3 standard deviation (SD)], height: 119 cm [77.6% between 1 and 2 SD]). Weight/height percentile is 99.8%. body mass index = 26.8 (percentile 99.7% >95%) [Figures 1 and 2], round face, (with no other signs of Cushingoid habitus), and no skeletal malformations. Premature thelarche represented by breast budding Tanner phase 2–3.

Neurological examination was normal, apart from a noticeable alternate strabismus in both eyes for the last few months with a normal ophthalmological exam.

Radiologically

abdominal computed tomography scan demonstrates a mass lesion measuring 3.5 cm × 8 cm attaching the ventral surface of the lumbar and sacral vertebrae, with incongruous contrast enhancement, pushing the right iliac artery and vein to the right side [Figures 3 and 4].

Left hand and wrist radiograph showed a bone age of 8 years (according to Gerulic and Pyle) compatible with 0.73 of predicted adult height (mid parental target height = 162.5 cm). (advanced bone age > 2 SD). Brain magnetic resonance imaging was normal.

Laboratory tests [Table 1] were not significant apart from the negative GH provocative test (using oral clonidine). Bilateral bone marrow study was negative. Neuro-specific enolase, urine vanillylmandelic acid levels were within normal limits.

The surgical consult recommended a surgical biopsy by laparoscopy. However, due to an uncontrolled bleeding complication, an emergent complete surgical excision of the tumor was performed. The tumor was attached intimately to the right iliac great vessels and to the right ureter. During the postsurgical period, the girl developed tachypnea with cyanosis, which was not explained by a clear pathophysiology. She was managed by hydration, analgesia, broad-spectrum intravenous antibiotics and supplemental oxygen.

Chest X-ray showed a slightly increased cardiac index. Echocardiography showed just a slight tricuspid regurgitation. Laboratory investigations are shown in Table 2. The patient improved within the next 3 days. The pathology result was compatible with mature ganglioneuroma [Figures 5 and 6]. Abdominal

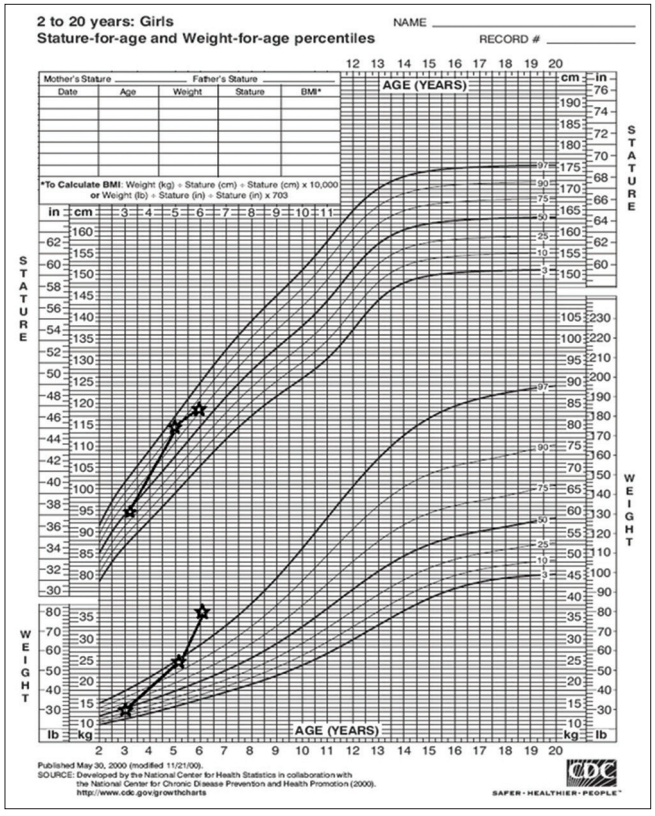

Figure 1: A growth chart showing the weight and stature for age. According to CDC growth charts

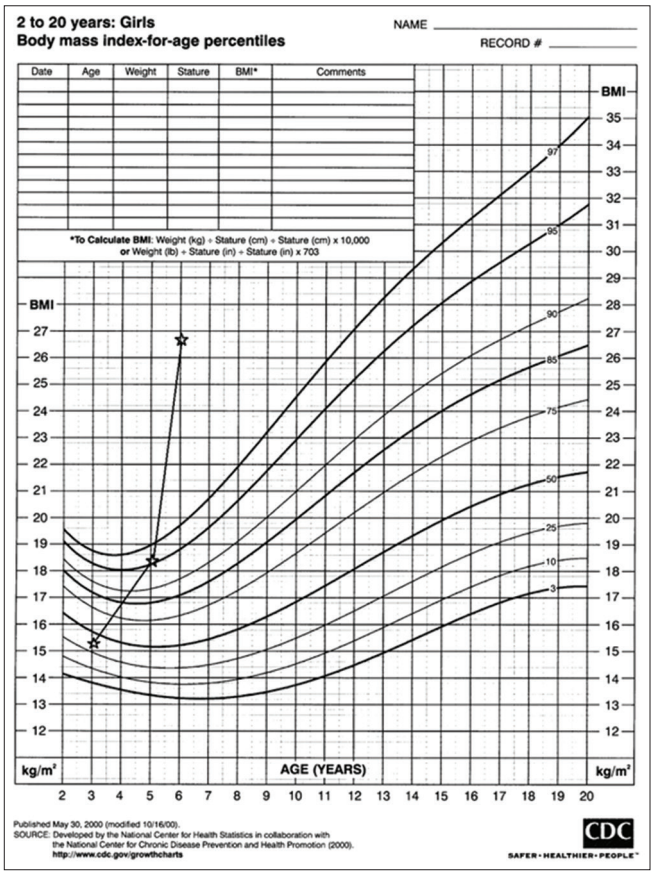

Figure 2: A chart showing the body mass index for age. According to CDC growth charts

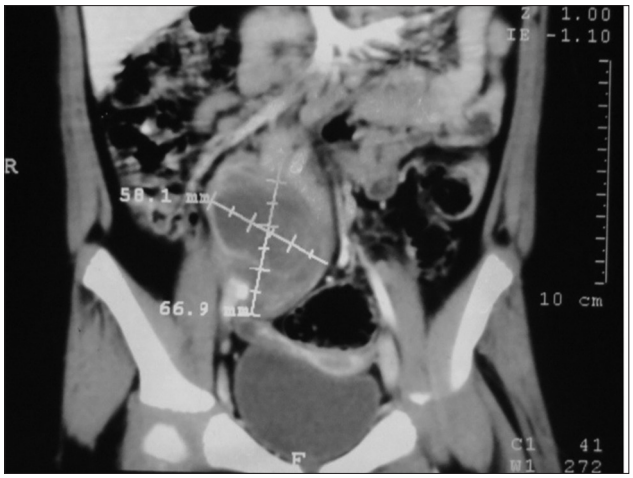

Figure 3: Abdominal computed tomography scan with contrast. Coronal section showing the mass

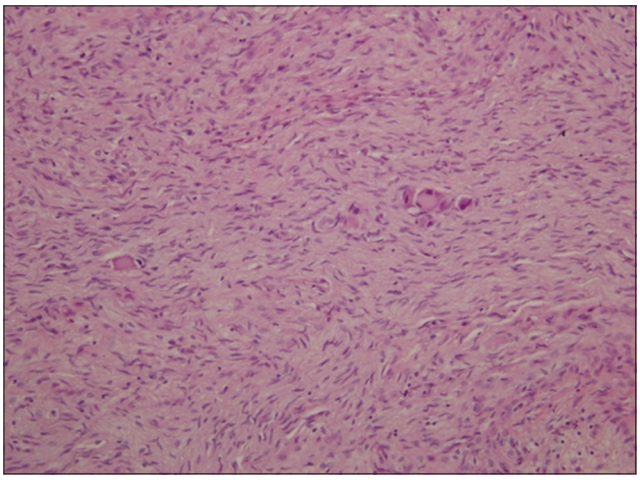

Figure 5: Schwannian stroma-rich neoplasm. H and E (×10)

ultrasonography revealed a right sided hydroureteronephrosis, treated by nephrostomy (a second look operation revealed an iatrogenic ureteral injury).

Later, elevated liver function tests were noted, but the subsequent tests were positive for hepatitis C type 1A infection. She had received the peg-interferone/ribavirin regimen with 67,392 copies/ml, and after 6 months of treatment 62,795 copies/ml, therefore the gastroenterologist decided to stop the treatment.

The ROHHAD syndrome diagnosis was built on the following points: The history of rapid weight gain, with hyperphagia concomitant with the discovery of an abdominal ganglioneuroma, the new onset bilateral nonparalytic alternate strabismus, the blunted GH provocative response and the respiratory problems (OSA episodes).

Following the diagnosis, the patient had worsening respiratory symptoms requiring the use of home BiPAP

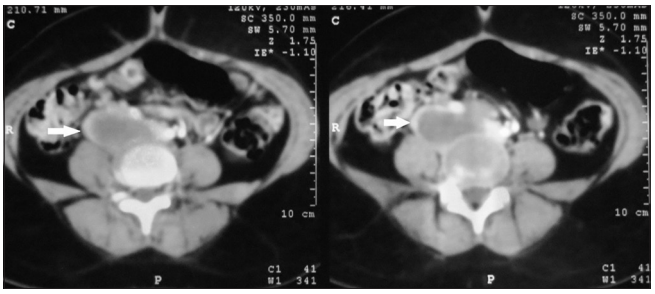

Figure 4: Abdominal computed tomography scan with contrast. Cross-section showing a 4 cm × 5 cm mass (white arrow) on the right side of the 5th lumbar vertebra, medial to the Psoas muscle

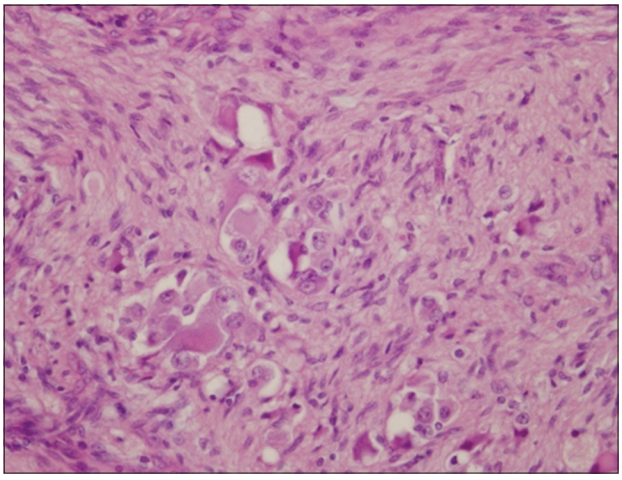

Figure 6: The neoplasm is composed of exclusively Schwannian cells with accompanying individually distributed small groups of mature ganglionic cells. No aggregates of neuroblasts were noted (×40)

machine. Moreover, later the patient had right nephrectomy due to worsening renal function not responding to nephrostomy tube placement.

DISCUSSION

Rapid-onset obesity with hypoventilation, hypothalamic dysfunction and autonomic dysregulation syndrome is a rare clinical entity. Diagnosis is based on clinical criteria that can be divided into three main groups:

Metabolic and endocrinological

The rapid gain of weight (obesity), which is noted to be acquired after the age of 2 years, and usually associated with hyperphagia. This complaint is present in 100% of cases (it was the first manifestation in 80% of cases).[2,4]

The other endocrinological manifestations include a spectrum of HD signs, which may present in a wide variability:

- Adrenocortical insufficiency (hypocortisolism), was present in approximately 26% of cases[2]
- Growth hormone abnormal response, that is, to have a

Table 1: General laboratory values

	Result	Unit
Calcium	9.8	mg/dl
Phosphorus	3.8	3.8 mg/dl
Alkaline Phosphatase	246	U/L
Triglycerides	103.2	mg/dl
Total Cholesterol	165.4	mg/dl
Oral Glucose test	Normal response	
Estradiol	17	pg/ml
FSH	3.4	mUI/m
LH	0.76	mUI/m
TSH	3.17	mUI/m
GH provocative response after 90 minutes	0.78	ng/ml
FT4	0.79	ng/dl
Serum Cortisol (morning)	11.6	ug/dl
ACTH (morning)	6	pg\ml
(post suppression)	0.09	
Free urine Cortisol	38 (normal: 36-137)	pg\ml
NSE	14.93 (normal: upto 18)	ug\L
a-FP	1.28	IU\ml

FSH= Follicle-stimulating hormone, LH= Luteinizing hormone, TSH= Thyroid-stimulating hormone, ACTH= Adrenocorticotropic hormone, NSE= Neuron-specific enolase

Table 2: Hormonic laboratory values

WBC	24100	Cell/mm^3
Neutrophils	80%	
Hemoglobin	10.9	g\dl
Sodium	156	mmol\l
Potassium	4.7	mmol\l
Glucose	77	mg\dl
Urea	56	mg\dl
Creatinine	0.74	mg\dl
Alanine transaminase	24	U\L
C-reactive protein	269	mg\dl

WBC= White blood count

maximal GH response of 10 ng/ml, which is generally considered as evidence for GH deficiency. This finding was present in about 58% of cases (30/51 patients)[4]

- Hypothyroidism, was present in (22/51 patients) 33%,[4] to (5/15 patients) 43%[2] of cases
- Hyperprolactinemia was present in 47% of cases (24/51 patients)[4]
- Puberty disorders (delayed or precocious), was present in (4/15 patients) 26%.[2] Precocious puberty was present in (5/51 patients) 9%,[4] while hypogonadism was present in (15/51 patients) 29%[4]
- Serum sodium (Na) disturbances: This problem is commonly noticed in the syndrome, and is attributed to variable inappropriate secretion and effects of ADH. Hypernatremia was present in 64% of cases (33/51 patients).[4] Hyponatremia was present in 27% of cases (14/51 patients) and syndrome of inappropriate ADH diagnosis was considered in one case.[4] On the other hand, diabetes insipidus (some cases were proven with water deprivation test) was present in only (9/51 patients) 17%,[4] (5/15 patients) 33%[2] of cases.

Central/obstructive hypoventilation

Obstructive sleep apnea and or episodes of respiratory arrest postminimal sedation.

Autonomic nervous system dysregulation

One or more of the followings:

- Thermal dysregulation: Was present in about 55% of cases (28/51 patients)[4]
- Excessive sweating: Was present in about 23% of cases (12/51 patients)[4]
- Ocular manifestations: Represented by strabismus which was present in about 35% of cases (18/51 patients),[4] and/or abnormal papillary reaction to light which was present in about 39% of cases (20/51 of patients),[4] and/or ptosis
- Cardiovascular manifestations: That may be attributed to autonomic dysregulation (arrhythmias, blood pressure dysregulation). On the other hand, in ROHHAD syndrome we commonly see variable degrees of cor-pulmonale secondary to the pulmonary involvement (central/obstructive hypoventilation)[4]
- Gastrointestinal dysmotility: Either chronic diarrhea or constipation. This was present in 66% of cases (10/15 patients).[2]

Other findings include:

- Neural crest tumor: ROHHAD syndrome could be associated with the development of neural crest tumors in 33% of its cases.[3,5] (So the term ROHHAD-NET "ROHHAD and neural crest tumor syndrome" was suggested). The associated tumors are usually either ganglioneuroma or ganglioneuroblastoma with thoracic or abdominal localization[2-5,4]
- Behavioral disorders: Even though well mentioned in the reviews of ROHHAD syndrome, they were mostly considered as secondary issues attributed to the whole clinical status. These were present in about 54% of cases (28/51 patients).[4] Many patients had a mood disorder (depressive), some exhibited some personality changes. While few patients exhibited psychosis.[2,4,6] Recently, we have thoughts of the interrelated importance of the behavioral and psychological manifestations with the main ROHHAD features, and the syndrome may come with these as a first complaint.[6]

Until date, nearly 80 patients with ROHHAD have been reported in the literature; however, the etiopathogenesis is still unclear and debated. Both genetic and paraneoplastic or immune-mediated causes have been supposed to be involved in this syndrome. Nonetheless, at this time, a diagnostic biomarker is not available, and diagnosis is based exclusively on clinical criteria.[2-5,4]

No clear correlation in the pathogenesis is established until now. Many theories could be suggested to explain this correlation:

Genetic theory

Supported by the similarities with congenital central hypoventilation syndrome (CCHS) also known as. Ondine's curse, which presents in the neonatal period. In CCHS, paired-like homeobox2B (PHOX2B) was identified as the disease-causing gene. However, various cases showed that PHOX2B mutation is not responsible for the ROHHAD manifestations,[2] even in a case report of a monozygotic twin involved.[7] For the other suggested variation of the HTR1A, OTP, and PACAP genes, studies have shown that they are not responsible for ROHHAD.[8]

Paraneoplastic/autoimmune theory

The correlation between ROHHAD syndrome and neoplasia is supported in the medical literature by noticing that nearly 33% of ROHHAD cases are ROHHAD-NET (i.e., associated with either ganglioneuroma or ganglioneuroblastoma).[5] This coincidence suggests that it could be a paraneoplastic phenomenon related to the neoplasia.

Here, we should mention that ROHHAD manifestations (respiratory support, obesity, endocrinological disorders,… etc.) did not resolve after tumor resection in the ROHHAD-NET syndrome cases.[3,4,9]

The persistence of these manifestations beyond the tumor resection supports the immune-mediated pathogenesis theory. In addition to a report describing two children with ROHHAD syndrome whose cerebrospinal fluid analysis revealed an intrathecal synthesis of oligoclonal bands.[10]

At autopsy performed in some of the cases, lymphocytic infiltration within the hypothalamus or brainstem has been demonstrated, and these findings suggested that an autoimmune-mediated process, similar to the opsoclonus myoclonus ataxia syndrome, might underlie ROHHAD syndrome.[11]

Paz-Priel et al. reported a 3-year-old patient with ROHHAD syndrome who had a favorable response to immunoablative treatment with high-dose cyclophosphamide 50 mg/kg/day on 4 consecutive days (after a short-lived relief wit rituximab "anti-CD20").[9] Moreover, in a Turkish case of ROHHAD-NET syndrome with ganglioneuroblastoma, an aggressive immunosuppression protocol was applied with a good relative improvement (using cyclophosphamide, intravenous immunoglobulin, dexamethazone, and then rituximab).[11] These data might pave the way to a therapeutic chance for ROHHAD syndrome by means of immunotherapy.

Neural crestopathy

This theory is supported by the united embryologic origin for the hypothalamus, the autonomic nervous system, and the neural crest tumors seen in more than third of ROHHAD cases. Moreover, by the common recent postulations of some diseases and syndromes associations attributed to the term neural crestopathy.

The management until now depends on supportive measures for the respiratory failure by using the noninvasive measures. Endocrinologically by replacing the deficient hormones (for hypothyroidism and hypocortisolism if present). Administration of a balanced diet to overcome the uncontrolled hyperphagia and the complicated severe obesity.

CONCLUSION

Rapid-onset obesity with hypoventilation, hypothalamic dysfunction and autonomic dysregulation syndrome is an emerging term, describing a vague rare medical illness. With the rapid weight gain beyond the period of late infancy as an early manifestation and the other autonomic, endocrinological and respiratory manifestations following.

Etiology is not clear and questions trying to solve the puzzle of this constellation are continuously asked. More immunological studies parallel to a more thorough genetic studies in order to elucidate this syndrome are required, which can focus on the neural crest cells differentiation and migration mechanisms, the targeted molecules and cells in the autoimmune process if proven.

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