Case Report with Review of Literature

Rapid-Onset Obesity with Hypoventilation, Hypothalamic Dysfunction, and Autonomic Dysregulation Neuroendocrine Tumor Syndrome: A Rare Cause of Hypothalamic Obesity – A Case Report with Review of Literature

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Abstract

Background: Rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation (ROHHAD) syndrome is a rare cause of obesity, characterized by early and rapid onset of obesity, hypoventilation, hypothalamic dysfunction, and autonomic dysfunction. When there is an associated neuroendocrine tumor, (NET) it becomes ROHHAD NET. Hypothalamic dysfunction causes endocrine problems, respiratory dysfunction, and autonomic alterations. It is difficult to distinguish this clinically from other obesity syndromes of genetic origin unless an individualized strategic approach is used. **Clinical Description:** We present a case of a 5-year-old developmentally normal girl with excessive weight gain starting in early childhood and the development of a squint. The clinical phenotype of central hypoventilation and autonomic dysfunction, central hypothyroidism, and central precocious puberty satisfied the criteria for ROHHAD syndrome. **Management:** A right-sided paraspinal supradiaphragmatic mass was identified that was excised and diagnosed as neuroblastoma on histopathology. Since there was no evidence of metastases, chemotherapy was not indicated. Alpha and beta-blockers were started for autonomic dysfunction and high catecholamine levels. Lack of improvement in behavioral manifestations prompted a trial of immunosuppressive therapy, but yielded no results. She ultimately succumbed to a probable cardiorespiratory arrest during sleep. **Conclusions:** ROHHAD syndrome should be considered a differential diagnosis in rapid-onset monogenic obesity and should be managed with a multidisciplinary approach. Prognosis is guarded due to sudden life-threatening events secondary to autonomic dysfunction.

Keywords: Autonomic dysregulation, neuroblastoma, precocious puberty, rapid-onset obesity, self-mutilation

Rapid-onset (RO) obesity with hypoventilation (H), hypothalamic (H) dysfunction, and autonomic dysregulation (AD) or ROHHAD syndrome is characterized by impulsive and uncontrollable eating leading to rapid weight gain that starts in early childhood, around 2–4 years of age. The underlying pathophysiology is an abnormal hypothalamo-hypophyseal axis that may result in diabetes insipidus, hyperprolactinemia, growth hormone (GH) deficiency, central hypothyroidism, and/or secondary adrenal insufficiency. The diagnostic criteria include all of the following: (1) rapid-onset obesity and alveolar hypoventilation during sleep that starts after the age of 1.5 years; (2) evidence of hypothalamic dysfunction, as defined by at least one of the following findings: rapid-onset obesity, hyperprolactinemia, central hypothyroidism, disordered water balance, failed GH stimulation test, cortocotropin deficiency, or altered onset of puberty (delayed or precocious); and (3) absence of a congenital central hypoventilation syndrome (CCHS)-related paired-like homeobox 2B mutation, to differentiate ROHHAD syndrome from CCHS at the genetic level. The clinical manifestations include early or delayed puberty,[1-3] features of autonomic dysfunction (such as bradycardia, hypotension, thermal dysregulation, excessive sweating, Raynaud's phenomenon, decreased sensitivity to pain, impaired pupillary responses, and gastrointestinal dysmotility), psychiatric manifestations (i.e., anxiety, aggressive behavior, and personality disorders), and underlying neural crest tumors in around 40% of patients,

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in which case it is referred to as ROHHAD neuroendocrine tumor (NET) syndrome.[1,3-5] To date, 80 patients with ROHHAD have been reported globally.

We report a child who underwent a detailed evaluation for obesity and was ultimately diagnosed with ROHHAD NET syndrome. The details of the earlier cases that have been reported from India are compiled in Table 1.[3,6-8] Since early diagnosis improves the clinical management and prognosis in ROHHAD syndrome, and there is a strong association with neural crest tumors,[1] this condition should be considered a differential in any child with rapid- and early-onset obesity and screened accordingly, as we did in this case.

Clinical Description

A 5-year-old girl presented with sudden onset of a nontraumatic left lateral squint for 1.5 months. There was an associated history of excessive weight gain (11 kg) over 6 months secondary to the development of a voracious appetite [Figure 1]. It was accompanied with recurrent episodes of temporal headaches and abnormal behavior, mood swings, self-mutilation (biting at fingertips, lips, and tongue), aggression, social withdrawal, altered sleep pattern (frequent nighttime awakening and increased daytime drowsiness), and insensitivity to pain. We calculated that her diet (that comprised frequent meals and large amounts of junk food) was equivalent to the consumption of around 1820 calories per day, against an expected daily allowance of 1350 calories/day. The rapid and excessive weight gain had resulted in difficulty in moving around and restricted physical activities; she was mostly confined to bed.

The history was not contributory. The child had not been started on any drug for these symptoms, allopathic or alternative. She was the firstborn to healthy nonconsanguineous parents with no significant family history of similar presentations, obesity, or psychiatric illness in any family member. The antenatal, natal (her birth weight was 2.9 kg), and perinatal periods had been uneventful. Acquisition of developmental milestones was described as normal by the parents, and her immunization was age-appropriate.

Evaluation of her vital parameters revealed tachycardia (heart rate 162 beats/min), hypertension (blood pressure 138/78 mmHg and >99th centile for height and age), a temperature of 98.2°F, and respiratory rate of 22 breaths/min, despite the presence of mild hypercarbia (pCO_2 55 mmHg on arterial blood gas analysis). Her body weight was 61 kg (+3.9 standard deviation [SD]), height 130 cm (+1.8 SD), and body mass index 36 kg/m^2 (+3.3 SD). Salient findings on general physical examination were a plethoric facial appearance, generalized obesity, axillary acanthosis nigricans, and mutilated fingers of her right hand [Figure 2]. There was no overt facial dysmorphism or presence of major/minor external congenital anomalies. The spine and paravertebral

Table 1: Clinical comparison of Indian patients with rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation syndrome

Author	Manifestations	Investigation	Management	Outcome
Sanklecha *et al*., 2016	7-year-old girl, unsteady gait, nystagmus, aggressive behavior, followed by developing hyperplasia and persistent hypoventilating episodes with CO_2 retention; polyuria with dyselectrolytemia suggesting diabetes insipidus	CT scan: Paravertebral mass which when biopsies confirmed ganglioneuroblastoma, MRI brain: Bilateral hypoxia changes due to persistent hypoventilation; Alternating hyponatremia and hypernatremia; raised prolactin; negative PHOX2B mutation	Chemotherapy for ganglioneuroblastoma and surgical removal; quetiapine given for psychiatric issues; initial mechanical ventilation followed by nasal home BIPAP for hypoventilation; cyclophosphamide given	Sudden demise following blocked tube during hospitalization
Jeyasutha Chokkian 2021	3-year-old (gender not mentioned) increasing body weight, breathing difficulty during sleep, hypoventilation, strabismus, and imbalanced coordination	MRI: Multiple hyperintense foci on T2 Chest X-ray: Ill-defined mass in the presacral region Polysomnography: Inadequate respiratory efforts with oxygen saturation at 80% Serum thyroxin low, TSH normal	BIPAP support and chest physiotherapy	Not specified
Tiwari *et al*., 2022	4-year-old girl, hyperphagia, weight gain, and inappropriate laughter	Weight for age +2.2 SD, bone age, thyroid, cortisol normal; MRI brain: Diffuse cerebellar atrophy with mild atrophy of midbrain and normal hypothalamus, suggestive of cerebellitis; MRI spine: Left paravertebral solid lesion 2.3 cm × 2.5 cm × 3.8 cm from T2 to T5 with extradural spinal canal extension without cord compression	Thoracoscopic excision of tumor which on biopsy revealed ganglion cells but no neuroblastoma component	At 1-year follow-up, the child was doing well with no features of hypoventilation
Karnik *et al*., 2022	3-year-old female, severe weight gain of 29 kg in 1 year, hyperphagia, constipation, tachycardia, temperature dysregulation, hyperglycemia, snoring, and nighttime awakenings	Polysomnography showed severe obstructive sleep apnea with AHI of 12.8, echocardiography – mild pulmonary hypertension, PHOX2B gene negative, ACTH levels normal; CT abdomen – well-defined tumor in the sacral region of 5 cm × 3.5 cm × 5 cm	Not commented on except on anesthetic implications	Was discharged home on nighttime BIPAP

CT: Computed tomography, MRI: Magnetic resonance imaging, PHOX2B: Paired-like homeobox 2B, BIPAP: Bilevel positive airway pressure, TSH: Thyroid-stimulating hormone, SD: Standard deviation, AHI: Apnea hypopnea index, ACTH: Adrenocorticotropic hormone

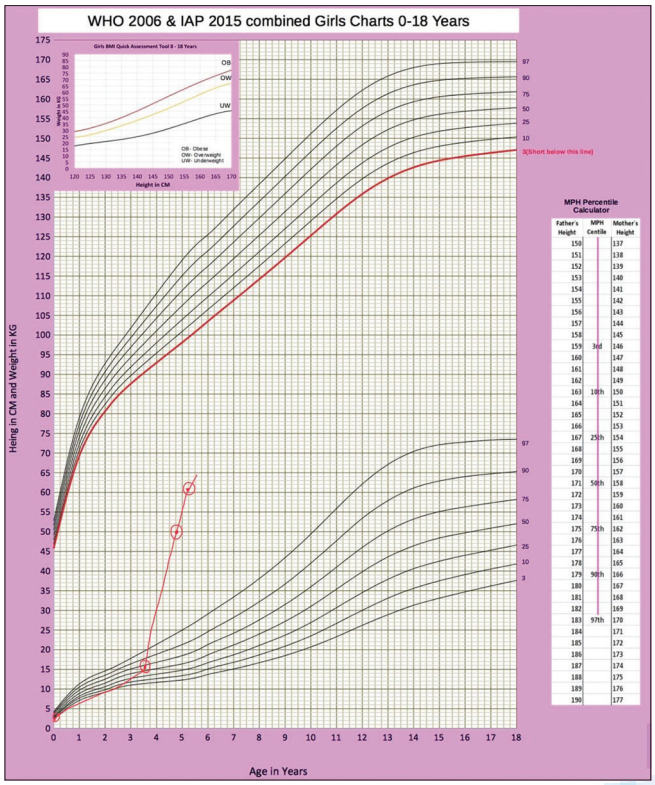

Figure 1: IAP growth chart depicting rapid gain in weight for age. IAP: Indian Academy of Pediatrics

areas were normal. The sexual maturity rating corresponded to stage 3 with bilateral thelarche and pubarche indicative of precocious puberty.

Significant findings on examination of the central nervous system were agitation, ability to follow instructions initially that later changed to progressive drowsiness and nonresponsiveness, and altered pain perception (on sensory examination). There were no clinical manifestations of increased intracranial tension, and the fundus examination did not show any sign of papilledema. Examination of the cardiovascular system did not reveal any abnormality. The remaining systemic examination was within normal limits. Psychometric assessment of the emotional and behavioral status by the Weiss Functional Impairment Rating Scale was suggestive of moderate functional impairment.

Based on the clinical phenotype of ROHHAD, we kept ROHHAD syndrome (rapid-onset obesity impairment and early puberty) and Prader–Willi Syndrome (rapid-onset obesity with delayed cognitive impairment, although there is no hypothalamic dysregulation) as the top two differential diagnoses. Less likely, differentials that were also considered included CCHS (since the hypoventilation and hormonal dysregulation are of neonatal onset) and Lesch–Nyhan syndrome (although in addition to self-mutilation, there should have been clinical features such as developmental delay/intellectual disability, microcephaly, and spasticity). Investigations to explore the extent of hypothalamic

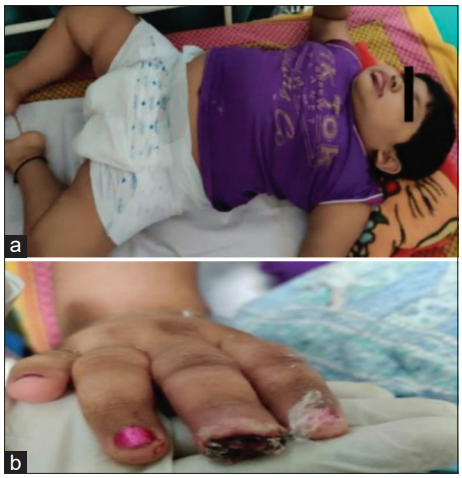

Figure 2: Physical appearance of the child, 1 month after the onset of disease (a, top). And the destruction of the right middle finger due to self-mutilation (b, bottom)

dysfunction and screening for neural crest tumors were planned.

Management and Outcome

Initial investigations revealed mild anemia (hemoglobin level of 10.9 g %), leukocytosis (11,700/mm^3) with neutrophilic preponderance (63%), and a normal platelet count of 3.47 L/mm^3. The serum C-reactive protein was significantly raised at 64 mg/L (normal <6 mg/L). She was initiated on a broad-spectrum antibiotic (meropenem) after sending cultures; although there was no clinical indicator for any particular focus of infection, the chest X-ray revealed a right perihilar homogeneous opacity. The serum levels of sodium and potassium were normal (137 mEq/L and 3.4 mEq/L, respectively), as was blood sugar (120 mg/dl); however, the lipid profile was deranged (cholesterol 180 mg/dl, LDL 142 mg/dl, and triglycerides 220 mg/dl). The hepatic and renal function tests were normal; Aspartate aminotransferase (AST) 37 U/L, ALT 45 U/l, albumin 4.0 g/dl, urea 29 mg/dl, and creatinine 0.5 mg/dl. The insulin-like growth factor-1 (IGF-1) was <25 ng/mL (<10th centile), and IGF binding protein 3 (IGFBP3) 1870 ng/mL (normal for age 1100–5200 ng/ml) suggested a normal GH activity. In view of tachycardia and hypertension, a cardiac evaluation was planned. Both the EEG and echocardiography were normal.

A detailed hormonal evaluation revealed central hypothyroidism with a thyroid-stimulating hormone level of 0.72 µIU/mI (normal: 0.5–4.3 µIU/mL) and FT4 level of 0.78 ng/dI (normal: 0.98–1.6 ng/mL), for which L-thyroxine was started at 4 mcg/kg/day. The adrenocorticotropic hormone was 24 pg/mL (normal: 10–60 pg/mL), and early morning (8 a.m.) cortisol level was 6 µg/mL (normal: 3–21 µg/mL). The luteinizing hormone was elevated (1.3 mIU/mL, prepubertal level <0.3 mIU/mL), as were estradiol at 12.9 pg/mL (prepubertal level <12 pg/mL) and prolactin of 33 ng/mL (normal: 4.7–23.3 ng/mL) indicative of precocious puberty.

This was supported by an advanced bone age of 8 years as per the Tanner–Whitehouse III staging. Leuprolide acetate (3.75 mg monthly) was initiated for central precocious puberty.

A contrast-enhanced magnetic resonance imaging (MRI) of the brain was performed to look for any hypothalamic or hypophyseal lesion that could attribute to hormonal dysregulation and squint. This revealed gliosis of the left oculomotor nerve nucleus at the level of the red nucleus. MRI of the abdomen, spine, and paravertebral regions performed to screen for a neural crest tumor detected a large, right-sided paravertebral supradiaphragmatic mass involving the T6 to T9 thoracic vertebral levels [Figure 3]. We planned a workup for suspected neuroblastoma. The 24-h urinary vanillylmandelic acid was 19.60 mg/24 h (normal: <13.6 mg/24 h), 24-h urinary normetanephrine was 765.75 µg/24 h (normal: <600 µg/24 h), and urinary normetanephrine creatinine ratio was 1546.97 µg/g (normal: 223–571 µg/g). A formal autonomic testing and sleep study could not be done.

Multidisciplinary consultations were taken in view of the final diagnosis of ROHHAD NET syndrome. Symptomatic medical management of the autonomic dysregulation and high catecholamine levels was started with prazosin (0.025–0.1 mg/kg) and propranolol (0.3 mg/kg), respectively. The surgical team decided to resect the mass through an open right-sided thoracotomy, in which a large (7 cm × 5 cm) intact mass was removed [Figure 3]. Histopathology examination was suggestive of a poorly differentiated, stroma-poor neuroblastoma, with an intermediate Mitosis-Karyorrhexis Index of 3%–4% (poor prognostic marker) with tumor cells expressing synaptophysin, a fairly sensitive marker for neuroendocrine tumors. A neuro-oncological opinion was taken, which advised a whole-body 18-fluorodeoxyglucose positron emission tomography-computed tomography scan. A normal report excluded metastasis and negated the requirement for additional chemotherapy. The hematological and biochemical tests remained within normal limits during the follow-up. However, when there was no improvement in the behavioral and autonomic manifestations even after 3 weeks postsurgery, an autoimmune paraneoplastic association was considered, and a trial of cyclophosphamide was planned (six cycles 2 weeks apart comprising 750 mg/m^2 per dose). The child was apparently doing well and was hemodynamically stable without any clinical or investigatory evidence of infection, but succumbed to what we presumed to be unexpected cardiorespiratory arrest during sleep after 5 days of completion of cyclophosphamide therapy. Since parental consent for autopsy was not given, the exact cause of death could not be ascertained. The genetic analysis had been considered earlier but was deferred due to financial constraints and the untimely death of the child.

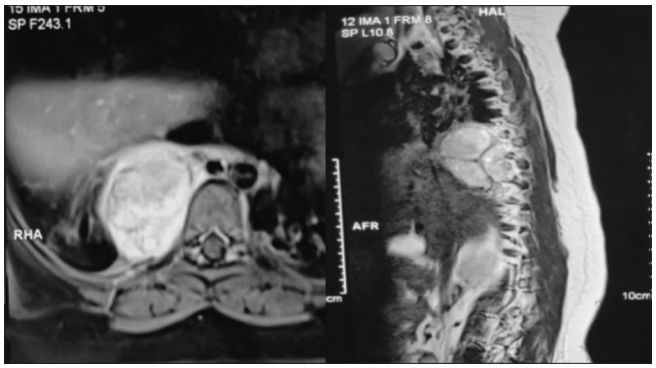

Figure 3: MRI of the spine showing the right-sided paraspinal supradiaphragmatic mass. MRI: Magnetic resonance imaging

Discussion with Review of Literature

The genetic syndromes that we considered in the differential diagnoses of this patient are characterized by rapid-onset obesity. Although the etiopathogenesis of ROHHAD syndrome is still unknown,[5] it has been suggested that it may be due to an interplay of hitherto unidentified genetic, autoimmune, and paraneoplastic factors, and there are many ongoing studies that are aimed at identifying these.[2] Smith–Magenis syndrome which presents with dysmorphism and hyperphagia in late childhood or adolescence is caused by a point mutation in RAI1, a transcription factor involved in craniofacial and neural development.[9] A novel mutation was detected in the RAI1 gene in a boy with ROHHAD syndrome that may suggest an overlap between both syndromes.[10]

Children with Prader–Willi syndrome have global developmental delay/intellectual disability, behavioral abnormalities, hypotonia, small hands and feet, ocular findings, and hypogonadism.[1,3] It was disregarded after initial consideration in our case due to the presence of precocious puberty and the absence of typical dysmorphism. Leptin deficiency or resistance also causes hyperphagia, obesity, and deficiency in pituitary hormones, but can be distinguished from ROHHAD syndrome by the even earlier onset of weight gain and immune deficiency. Proopiomelanocortin deficiency due to MRC4 receptor resistance is a rare cause of monogenic obesity characterized by reddish hair and extremely light skin color and the appearance of obesity in the 1st year of life.[11] There is no associated autonomic dysfunction. Cushing syndrome may also be kept as a differential diagnosis. However, in this case, secondary adrenal insufficiency was present, rather than the typical hypercortisolism.

The details of the earlier cases that have been reported from India are compiled in Table 1.[3,6-8] The cause of death in 16 cases of ROHHAD syndrome has been reported due to respiratory or cardiac problems or an underlying NET like ganglioneuromas or neuroblastomas.[3,12-15] It is thought that these tumors may lead to paraneoplastic involvement of the hypothalamus.[1] Autonomic dysfunction is also a common manifestation of ROHHAD syndrome that leads to life-threatening events such as arrhythmias, sudden cardiac arrest, sleep apnea, and/or narcolepsy. As there was no history

of respiratory symptoms or sleep disturbances, and metastasis had already been excluded in this case, we presumed a sudden cardiac event to be the most probable cause of death. Authors have attributed the dysfunction of hypocretin-1, which is involved in the release of acetylcholine in the autonomic nervous system.[5]

To summarize, ROHHAD syndrome is a rare cause of hypothalamic obesity accompanied by pituitary hormone abnormalities and autonomic dysfunction that should be kept in mind in the differential diagnosis of monogenic early-onset obesity, if clinical indicators are present. Since there is multisystemic involvement, management requires a multidisciplinary approach.

Lessons learned

- There are many genetic syndromes characterized by early-onset obesity and hyperphagia that can be ruled in or out using a strategic clinical approach
- All patients with ROHHAD syndrome should be screened for neuroendocrine tumors by imaging and biomarkers
- Management of ROHHAD syndrome requires a multidisciplinary approach, and the outcomes may be unpredictable.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published, and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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