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CASE SERIES

ROHHAD-NET Syndrome: A Case Series

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Abstract

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysregulation and neural crest tumor (ROHHAD-NET) though a rare disease, is potentially fatal. It is of utmost importance to be understood and urgently diagnosed. We hereby report a series of three cases, the first of its kind from India. Children older than 18 months old usually exhibit rapid weight growth as a presenting symptom. Hypothalamic dysfunction could lead to endocrine issues, respiratory dysfunction and autonomic dysregulation. Over the years, with variable timing, one or more signs of hypothalamic dysfunction appear: hyperprolactinemia, growth hormone deficiency, central hypothyroidism, central adrenal insufficiency or Cushing syndrome, early or delayed puberty, water-electrolyte balance disorders. The diagnosis is difficult because there is no reliable test, and the treatment is mainly supportive. All the three children who were thriving well, presented with rapid weight gain and then developed symptoms of hypothalamic dysfunction. While in one a neural crest tumor was incidentally detected, the second had persistent hypernatremia and the third child presented with intestinal obstruction. The varied presentation and vague symptom spectrum exhibit a diagnostic challenge to the clinician and underscores the importance of creating awareness. An individualized strategic approach is needed as it is clinically difficult to distinguish ROHHAD syndrome from other obesity syndromes of genetic origin.

Key words: ROHHAD, obesity, central hypoventilation, neural crest tumor

INTRODUCTION

Rapid onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation and neuroendocrine tumor (ROHHAD-NET) is an uncommon polymorphic disorder involving the autonomic, respiratory and multiple other systems during childhood and carries a significant mortality risk. In 1965, the first case report was published[1] and and since then over the span of five decades only a couple of hundred cases have been reported world-wide.[2] Recognizing this syndrome continues to pose a significant challenge to the clinicians. At present, the criteria used to identify ROHHAD syndrome are clinical in nature and they include: 1) dramatic weight gain; 2) central hypoventilation appearing between age 1.5 and 7 years in a previously healthy child; 3) signs of hypothalamic dysfunction such as such as hyperprolactinemia, central hypothyroidism, erratic water balance, aberrant response to growth hormone (GH), adrenal insufficiency, or puberty disorders; 4) autonomic dysfunction.[3] The common tumors associated with ROHHAD NET are ganglioma, ganglioneuroblastoma, and rarely even neuroblastomas.[4]

Although their causes are still unknown, ROHHAD or ROHHADNET may exhibit hypothalamic-pituitary dysfunctions and mimic genetic obesity or syndromes such as Prader Willi Syndrome. Children experience a progressive loss of central respiratory control, which is frequently fatal.[5] In order to limit morbidity and death and to offer timely respiratory assistance, prompt diagnosis based on early identification is crucial. We report three children with a probable diagnosis of ROHHAD NET who presented at our tertiary care centre.

Early onset obesity is commonly encountered and it is important to keep this rare diagnosis in mind and appropriately investigate a child with rapid weight gain. Early diagnosis improves the clinical management and prognosis in ROHHAD syndrome, and it has a strong association with neural crest tumors.

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CASE 1

A 6.5 year old female student presented with recent weight gain. Her mother reported that the child consumed a high caloric diet, but she did not report diet high in calories and she did not report snoring, sleep disturbances or constipation. Her exposure to screen time was not significant and the mother reported that she did not play as she did previously. She was born at term with a birth weight of 3.25 kg, with an uneventful neonatal period and had normal developmental milestones. Her weight was 35 kg (z score +2.4 SD), height 125 cm (z score +1.4 SD) and Body Mass Index (BMI) 22.5 kg/m^2 (+3 SD). She had acanthosis nigricans over the neck, axilla and groin, she did not appear cushingoid and no striae were noted. Investigations revealed her fasting blood sugar to be 5.7 mmol/L, fasting lipid profile showed elevated triglycerides 5.4 mmol/L and LDL 3.7 mmol/L and normal thyroid function test (Free T4 15.4 pmol/L [NR: 10.9-22.5 pmol/L], TSH 3 mIU/ml [NR: 0.6-5.5 mIU/ml]). Her bone age was 7 years. She was considered to be a child with exogenous obesity and was advised lifestyle modifications. Two months later, she was admitted to the pediatric intensive care unit with complaints of difficulty in breathing and features of intestinal obstruction. She was found to have hypertension (BP 150/92 mm Hg) and low potassium (2.2 mEq/L). Computed Tomography (CT) scan abdomen revealed an adrenal mass; her 24-hour urine vanillylmandelic acid and metanephrines were normal. She was started on amlodipine and alpha blockers; her BP was controlled however the hypokalemia persisted. Her midnight serum cortisol was 206 nmol/L, overnight dexamethasone suppression test showed a cortisol level of 524 nmol/L. The possibility of Cushing's syndrome was considered. The pediatric surgeon advised removal of the tumor. A large mass was removed; however, she went into shock post-operatively and expired. Histopathology revealed an adrenal ganglioneuroma. On retrospection, we consider the possibility of ROHHAD-NET in her case. Another possibility we considered was Ectopic ACTH secretion from ganglioneuroma but the postoperative severe hypotension and hypoventilation which did not respond to steroid treatment makes the diagnosis of ROHHAD syndrome more likely. The cause of death could be respiratory depression which could be a part of ROHHAD syndrome in retrospect.

CASE 2

A 4 year and 9 month-old-female presented with acute onset of rapid weight gain for the last 3 months. She had gained almost 10 kg in 3 months. The mother reported an increased appetite, she ate a lot of fried food and simple sugars. Her dietary intake of fruits and vegetables were negligible. She was apparently very active previously and was now less interested in play. She was not interacting well with others and spent a lot of time lying in the bed. Her exposure to screen time was only 15-30 minutes per day. Mother had also noticed that she had started snoring recently, but did not report day time sleepiness or breathing difficulty. She did not complain of headache, vomiting, frequent urination or excessive thirst. She had no history of prolonged intake of corticosteroids or any other medications. On probing further regarding the diet, she was taking double the quantity of food that she was consuming previously. She was a second born child of a non-consanguineous marriage with an uneventful antenatal period. Her birth weight was 3.2 kg with and the postnatal period was uneventful; she was exclusively breastfed for 6 months. Family history was unremarkable except for maternal grandfather who had type 2 Diabetes Mellitus. On examination, she appeared alert, blood pressure was 126/72 mm Hg, at the 95th centile. She appeared to have moon facies, a buffalo hump and acanthosis nigricans over the neck. Her weight was 23.5 kg (z score +1.85 SD), height 97 cm (z score -2.33 SD) and BMI 24.9 kg/m^2 (+4.45 SD). She was short, obese and prepubertal, with no signs of virilization (Figure 1). Her systemic examination was unremarkable.

A complete hemogram done was normal. Renal and liver function tests were normal. Free T4 was 21.8 pmol/L [NR: 10.9-22.5 pmol/L], TSH- 6.2 mIU/ml [NR: 0.6-5.5mIU/ml]. Random blood sugar, glycated hemoglobin and serum electrolytes were normal. Initial 8 am serum cortisol was 262 nmol/L [NR: 110-606 nmol/L] and ultrasonography of the abdomen done in another health centre was reported as normal. Her bone age corresponded to chronological age. A repeat 8 am serum cortisol was 634 nmol/L [NR: 110-606 nmol/L], and ACTH 36.7 pg/ml [NR: 6-48 pg/ml]. An overnight dexamethasone suppression test was done,

Figure 1. Child described in Case 2. She was short, obese and was prepubertal, with no signs of virilization.

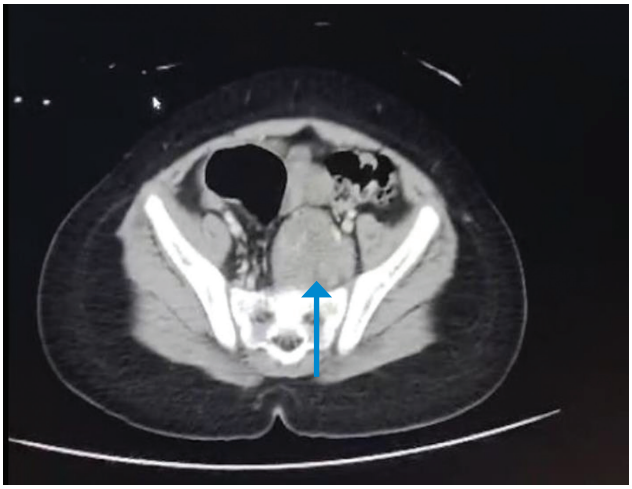

Figure 2. Heterogeneously enhancing lesion with defined soft tissue density lesion in the pelvis with sacral foraminal extension with a possibility of a neurogenic neoplasm.

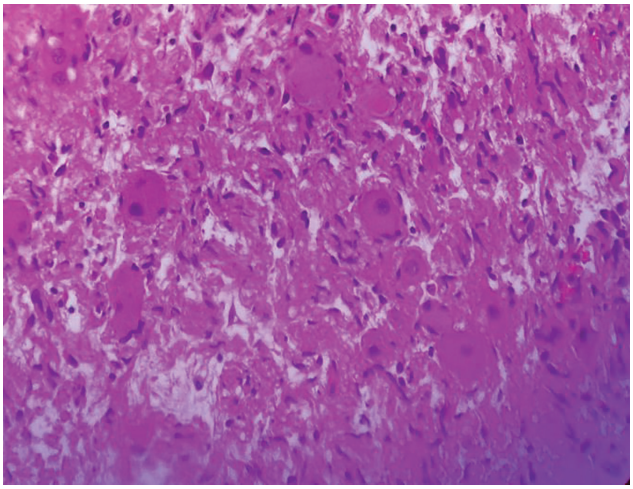

Figure 3. Histopathology revealed an admixture of ganglion cells and Schwann cells with no blastemal component which was suggestive of ganglioneuroma.

serum cortisol was 44 nmol/L [NR <50 nmol/l]. In view of further suspicion, a CT scan of the abdomen was done which showed a heterogeneously enhancing lesion with fairly defined soft tissue density lesion in the pelvis with sacral foraminal extension with a possibility of a neurogenic neoplasm (Figure 2). She was tested for tumor markers which were negative. Urinary vanillylmandelic acid was 26.4 µmol/day [NR:0-38.5 µmol/day], serum AFP 1.62 ng/ml [NR: 5-10ng/ml], β HCG <0.1 IU/L [NR:0.02-0.8 IU/L], carcinoembryonic antigen 3 mcg/L [NR: <3 mcg/L], serum testosterone 0.21 nmol/L [NR: 0.08-0.34 nmol/L] and dehydroepiandrosterone sulphate (DHEAS) 0.14 µmol/L [NR: 0.5-3.8 µmol/L]. Tumor excision was done. Post laparotomy, histopathology revealed an admixture of ganglion cells and Schwann cells with no blastemal component which was suggestive of ganglioneuroma (Figure 3). She was discharged post recovery. We considered the possibility of ROHHAD-NET, weight gain as a part of paraneoplastic syndrome with ectopic ACTH production or simple exogenous obesity with incidentally detected tumor. Genetic testing was not done due to financial reasons. We plan to monitor her closely for symptoms of hypoventilation.

CASE 3

A 3-year and 8 month-old female was referred to our tertiary care centre with prolonged fever, seizure and hypernatremia. She had already been on ventilatory support for 15 days at the time of presentation (Figure 4). On admission to the Pediatric Intensive Care Unit (PICU), her Glasgow Coma Scale score was 3 requiring high ventilatory support (SpO_2 87-90%, with FiO_2 100%), febrile, high-volume pulse and normal blood pressure. Arterial blood gas showed metabolic alkalosis and chest X ray ruled out pneumothorax. Bedside echocardiogram showed good contractility and was normal. Hemogram showed hemoglobin of 8.5 g/dl, total leucocyte count of 19,400 cells/µL (neutrophils 69% and lymphocytes 26%), Erythrocyte

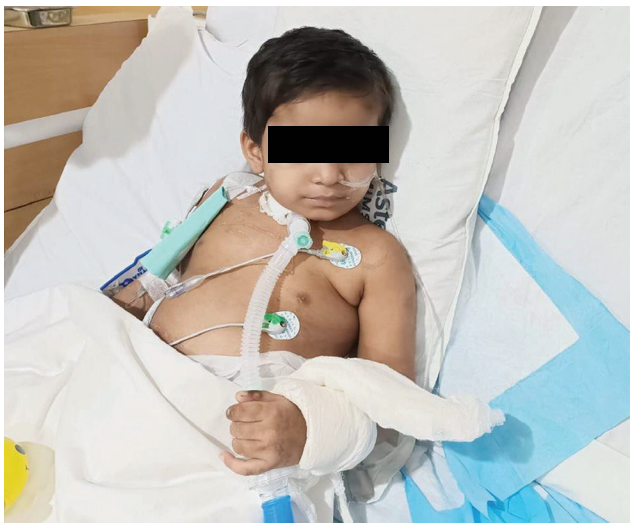

Figure 4. Case 3. Three-year-8-month-old referred with prolonged fever, seizure and hypernatremia. She had already been on ventilatory support for 15 days at the time of presentation to our center.

Sedimentation Rate 73 mm/hour, C-reactive protein – 15 mg/L, serum electrolytes showed hypernatremia (158 mmol/L and hypokalemia (3.2 mmol/L). Liver and renal function tests were normal. Chest X ray showed bilateral infiltrates. She was started on hypernatremia correction and broad-spectrum antibiotics after sending blood and urine cultures. She had hypotension and mild ventricular dysfunction which was stabilized with multiple inotropes, also required high ventilatory support and hence lung protective measures were initiated; inotropes were tapered and stopped by day 4 of admission. MRI brain was done considering the possibility of meningoencephalitis. It showed leptomeningeal enhancement in bilateral occipital and frontal region, hemorrhagic changes in the right pons and cerebellar hemisphere. Cerebrospinal fluid (CSF) examination was normal and Electroencephalogram (EEG) showed mild cerebral dysfunction. She continued

to have serially increased sodium levels up to 176 mmol/L with borderline low potassium levels (3.1-3.7 mmol/L), low urine sodium (<10 mmol/L), normal renal function and normal urine output. The paired serum osmolarity was 290 mosm/kg and urine osmolarity was 200 mosm/kg. We suspected a dysfunction in the renin angiotensin aldosterone pathway; however, PRA and aldosterone were normal. In view of persisting hypernatremia, an adrenal pathology was suspected and CT scan abdomen was done which showed right adrenal mass and thrombus involving bilateral external and common iliac veins. She was started on desmopressin, spironolactone and hemodialysis was done in view of persisting hypernatremia and failure of conventional methods; serum sodium levels dropped to 159 mmol/L, free water correction was continued according to sodium levels. Pediatric endocrinology consultation was sought, the possibilities of adrenocortical carcinoma, aldosterone secreting adenoma and pheochromocytoma were entertained, but evaluation showed normal DHEAS level- 0.005 µmol/L [NR: 0.5-3.8 µmol/L], normal cortisol level-468 nmol/L [NR: 110-606 nmol/L], normal ACTH-18 pg/ml [NR: 6-48 pg/ml], testosterone-0.08 nmol/L[NR: 0.08-0.34 nmol/L] and urine vanillylmandelic acid and plasma metanephrine levels. IVC filter placement was done in view of an iliac thrombus to avoid a catastrophe of pulmonary thromboembolism in a patient who had just recovered from shock. She was started on prazosin for pre-operative stabilization. Laparotomy and right adrenalectomy was done (Figure 5), biopsy showed a ganglioneuroblastoma, bone marrow biopsy was negative for N-myc and Positron Emission Tomography (PET)- CT scan was normal.

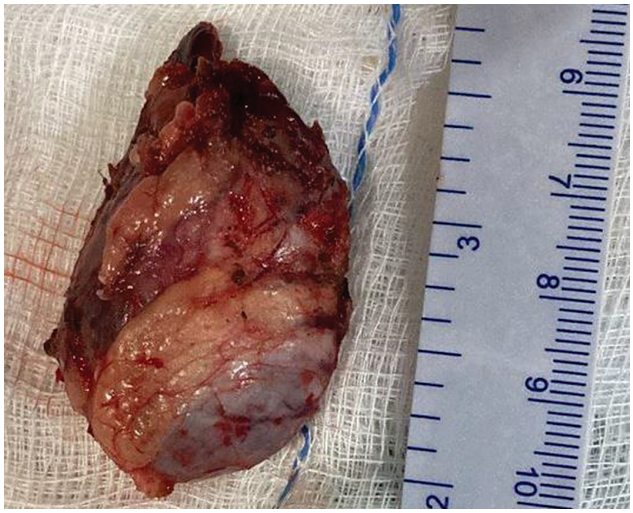

Figure 5. Case 3. Laparotomy and right adrenalectomy were done. Biopsy showed ganglioneuroblastoma.

Post surgery she continued to have hypernatremia and hypertension which responded to vasopressin and clonidine. A final diagnosis of ROHHAD-NET was considered, in view of rapid weight gain, persistent sodium disturbance, the hypoventilation, autonomic instability and the presence of a ganglioneuroma. She needed a tracheostomy and weaned off to a portable Bilevel Positive Airway Pressure (BIPAP). Table 1 summarizes the investigations done in the three cases discussed. Table 2 compares the three cases with respect to clinical symptoms, investigations, management and outcome.

Table 1. Summarizing the blood and urine investigations in our 3 cases

	Case 1	Case 2	Case 3
Hemoglobin (g/dl)	11	11.2	8.5
Total leucocyte count (cells/µL)	6600	8,000	19,400
Platelet count (lakh/mm^3)	4	3.8	3.5
ALT (IU/L) [NR: 7-45]	45	43	55
AST (IU/L) [NR: 8-33]	32	32	60
Serum sodium (mmol/L) [NR: 135-145]	4.1	138	158-176
Serum potassium (mmol/L) [NR: 3.5-5.5]	2.2	4.7	3.2
Serum osmolarity			290
Urine osmolarity			200
Urine sodium			<10
Fasting blood sugar (mmol/L) [NR: 3.9-11.1]	5.7	5	6
Fasting lipid profile (mmol/L)	TG – 5.4 mmol/L LDL – 3.7 mmol/L		
Free T4 (pmol/L) [NR: 10.9-22.5 pmol/L]	15.4	21.8	16
TSH (mIU/ml) [NR: 0.6-5.5mIU/ml]	3	6.2	5
Serum prolactin (µg/L) [NR: <25 µg/L]	150	138	Not done
8 am serum cortisol [NR: 110-606 nmol/L]	206 (midnight)	262-634	468
ACTH	Not done	36.7	18
Dexamethasone suppression test [NR <50 nmol/L]	524	44	
DHEAS (µmol/L) [NR: 0.5-3.8]		0.14	0.005
Serum testosterone (nmol/L) [NR:0.08-0.34)		0.21	0.08
Urine metanephrines mcg/day [57-210 mcg/day]	90	120	100
Urine VMA µmol/day [NR:0-38.5 µmol/day]	6	26.4	20
Serum Alpha fetoprotein [NR: 5-10 ng/ml]		1.62	
Humam chorionic gonadotropin (IU/L) [NR: 0.02-0.8]		0.1	
Carcinoembryonic antigen 3 (mcg/L) [NR <3 mcg/L]		3	

DISCUSSION

We describe 3 cases characterized by rapid onset obesity and investigations confirmed the presence of an adrenal neuroendocrine tumor. The diagnosis was delayed in the first two cases and by the time the third child presented, we were more aware and equipped to diagnose ROHHAD.

Dramatic weight gain between the ages of 2 and 4 accompanied by excessive eating is usually the presentation of ROHHAD.[3] Prior to the onset of the above symptoms these children were reportedly healthy. In the months and years that follow, hypothalamic and autonomic dysfunction can manifest.[6] Endocrine disorders such as hypothyroidism or precocious puberty may be early signs for recognition. However, a study done by Desse et.al, have reported four cases who presented with autonomic dysfunction at first, followed by hypothalamic dysfunction and these subset patients developed ROHHAD without obesity.[7] The intensity and timing of these patients' clinical presentations vary. Some individuals show clear behavioral abnormalities, while others show clear endocrine involvement. Electrolyte imbalance, especially dysnatremia, was present in a majority of the patients, requiring attention. Polydipsia or diabetes insipidus leads to water imbalance and dysnatremia secondary to hypothalamic dysfunction. ROHHAD is now also called ROHHAD-NET as 40% of the cases are accompanied by ganglioneuroma in the abdomen and lungs and neuroendocrine tumors such as ganglioneurobalstoma.[8] Most children recorded a short period of around two years between the onset of obesity and the diagnosis of neural crest origin tumor.[4]

The prognosis is poor as alveolar hypoventilation often results in a cardiac arrest in these children. All the three children had a normal chest X ray and 2D echocardiography, metabolic and neurological disorders were also ruled out, hence, central hypoventilation was considered.[5] Three main etiopathogenetic hypothesis have been postulated: genetic, epigenetic, and autoimmune. Extensive screening and chromosomal analysis have failed to uncover any genetic alteration, despite the fact that an underlying genetic component has been hypothesized for the pathophysiology of ROHHAD due to its similarities with Congenital Central Hypoventilation Syndrome (CCHS). However, in order to rule out a *PHOX2B*, genetic testing is advised for all suspected cases of ROHHAD. We could not carry out genetic testing in our cases due to financial constraints.[4] *PHOX2B* mutations are absent, as is the case for other candidate genes, like *ASCL1*, *BDNF* and *HCRT*. *ASCL1* gene is required for the generation of ventral neuroendocrine neurons which acts as a modifier gene for *PHOX2B* and

Table 2. Summarizing the clinical manifestations, investigations, management and outcome of the 3 cases

	Case 1	Case 2	Case 3
History			
1. Age of presentation	6.5 years old girl	4-year-9-month-old girl	3-year-8-month-old girl
2. Presenting symptom	Recent onset weight gain, within two months developed difficulty in breathing, abdominal distension and vomiting.	Rapid onset weight gain 3 months, snoring	Prolonged fever, seizures, hypernatremia, prolonged ventilation
Examination	Body Mass Index (BMI) 22.5 kg/m^2 (+3 SD). Acanthosis nigricans + Hypertension +	BMI 24.9 kg/m^2. (+4.45 SD). She appeared to have moon facies, a buffalo hump and acanthosis nigricans over the neck. Blood pressure at the 95th centile	Prolonged fever, seizures, Hypotension Prolonged ventilation
Investigations			
1. serum electrolytes	Hypokalemia(2.2 mmol/L)	Normal	Hypernatremia (176 mmol/L), low potassium levels (3.1 mmol/L)
2. Serum cortisol	206 nmol/L	593 nmol/L	468 nmol/L
3. Dexamethasone suppression test	serum cortisol 524 nmol/L	serum cortisol was 44 nmol/L	Not done
4. Serum prolactin	150 µg/L	138 µg/L	Not done
5. CT abdomen findings	An adrenal mass	A heterogeneously enhancing lesion with fairly defined soft tissue density lesion in the pelvis with a possibility of a neurogenic neoplasm.	Right adrenal mass and thrombus involving bilateral external and common iliac veins.
Management			
1. Surgery	Laparotomy done and a large mass was removed.	Tumor excision was done.	She was started on desmopressin, spironolactone and hemodialysis. Laparotomy and right adrenalectomy was done.
2. Histopathology	Adrenal ganglioneuroma.	Ganglioneuroma	Ganglioneuroblastoma
Outcome			
1. Immediate post-operative	Succumbed	Discharged	Post surgery continued to have hypernatremia and hypertension. She needed tracheostomy.
2. Long term		She had gained 5 kg on follow up after 2 months.	Gaining weight

Table 3. Key differentiating features between ROHHAD syndrome, PWS and CCHS

	ROHHAD syndrome	PWS	CCHS
Rapid onset obesity	Yes	Yes	No
Hypoventilation	Yes	Sometimes	Yes
Growth Hormone deficiency, Hypothyroidism, Adrenal dysfunction, precocious puberty, hypogonadism	Sometimes	Sometimes	No
Hyperprolactinemia	Yes	No	No
Disturbance in water balance	Yes	No	No
Bradycardia	Sometimes	No	Sometimes
Gastrointestinal dysmotility	Yes	No	Yes
Thermal dysregulation	Yes	Yes	Yes
Cold extremities, increased sweating	Yes	No	Yes
Altered pain perception	Yes	Yes	Yes
Behavioural disorders	Sometimes	Yes	Sometimes
Sleep abnormalities	No	Yes	Sometimes
Neural crest tumors	Yes	No	Yes
Neonatal hypotonia	No	Yes	No
Delayed motor and cognitive skills	No	Yes	Yes
Dysmorphic facial features	Sometimes	Yes	Sometimes
Genetic testing	No candidate genes	Parent specific DNA methylation	PHOX2B mutation

BDNF gene has a role in neuronal development. Epigenetic hypothesis is supported by report of discordant presentation of ROHHAD syndrome in monozygotic twins.[6] Numerous authors who have described patients with clinical presentations consistent with ROHHAD and whose CSF fluid analysis revealed intrathecal secretion of oligoclonal bands as well as the detection of anti-hypothalamic and ant pituitary antibodies have proposed the immune-mediated etiology.[9] The possibility of a genetic etiology is slowly losing value and newer possibilities like the epigenetic theory, paraneoplastic syndrome, an autoimmune syndrome or the need for a trigger seems more promising.[10] Table 3 highlights the key differentiating features between ROHHAD, Prader Willi Syndrome (PWS) and Congenital Central Hypoventilation Syndrome (CCHS).

Due to phenotypic similarities, patients with ROHHAD syndrome are usually missed for Prader-Willi syndrome, a disorder characterized by early childhood obesity. In the absence of low birth weight, infantile hypotonia and feeding difficulties during early infancy, this differential was excluded.[11] A potential overlap between ROHHAD and Smith–Magenis syndrome (SMS) has also been suggested.[12] CCHS secondary to PHOXB2 mutation can be a differential for central hypoventilation, however as our cases presented with other clinical features of ROHHAD, this diagnosis was ruled out.

Sixteen individuals of ROHHAD syndrome have been recorded to have died from respiratory or cardiac issues, or from an underlying NET such as neuroblastomas or ganglioneuromas.[2] It is believed that paraneoplastic involvement of the hypothalamus may result from these malignancies.[1] Dysautonomia is an additional prevalent ROHHAD syndrome presentation that can result in arrhythmias, sudden cardiac arrest, sleep apnea, and/or narcolepsy, among other potentially fatal occurrences.[13]

CONCLUSION

ROHHAD/NET is an uncommon illness that primarily affects females and manifests in childhood. The early indicators that can be identified are rapid obesity and hypothalamic dysfunction. Early detection and prompt respiratory support administration may avoid serious complications that could result in untimely death.

LESSONS LEARNED

1. 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.
2. All patients with ROHHAD syndrome should be screened for neuroendocrine tumors by imaging and biomarkers.
3. ROHHAD syndrome is a potentially fatal disease that requires timely diagnosis and management by a multidisciplinary team.

Ethical Consideration

Patients' consents were obtained before submission of the manuscript.

Statement of Authorship

All authors certified fulfilment of ICMJE authorship criteria.

CRediT Author Statement

DS: Conceptualization, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing; **MSI:** Investigation, Resources, Writing – draft preparation; **JG:** Investigation, Resources, Writing – review and editing; **VMV:** Writing – review and editing, Supervision; **PR:** Writing – review and editing, Supervision; **KMR:** Investigations, Resources; **BA:** Investigation, Resources, Writing – review and editing; **AM:** Supervision

Author Disclosure
The authors have no conflict of interest.

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