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Case Report

Rapid onset obesity and ondine's curse: a deadly syndrome

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ABSTRACT

ROHHADNET syndrome is characterized by rapid-onset-obesity, hypoventilation, hypothalamic dysregulation, autonomic dysfunction and neural tumors. A 2.4-year-old girl presented with inability to be aroused from sleep. She was obese, obtunded, hypoventilating with severe hypercarbia. Non-invasive ventilation (NIV) was started following which her sensorium, hypercarbia normalized. History revealed hyperphagia, rapidly increasing weight after 1½ year of age with normal height centiles. Hormonal profile revealed hyperprolactinemia, central hypothyroidism, suboptimal growth hormone response and normal cortisol. She had presacral tumor, pain insensitivity, fluctuating blood pressure, constipation and strabismus. ROHHADNET syndrome was clinically diagnosed based on constellation of these features. She was discharged on nocturnal NIV. Over 8 months, her hypoventilation progressed requiring tracheostomy. She also underwent excision of the presacral tumor which proved to be ganglioneuroma. Whole exome sequencing was negative for CCHS and ROHHAD genes, which could be due to somatic mosaicism; variation in the genomic region not covered by the test; or large insertions, deletions, complex rearrangements. Arriving at the diagnosis is difficult due to its overlap with other hyperphagic obesity syndromes and lack of confirmatory genetic testing.

Keywords: Hypothalamic dysfunction, Hypoventilation, Neural crest tumor, Rapid onset obesity

INTRODUCTION

"Ondine's curse" is characterized by hypoventilation with normal respiratory rates and shallow breathing during sleep with adequate ventilation during wakefulness. Severely affected individuals hypoventilate also while awake. ROHHADNET syndrome is a rare disorder characterized by abnormalities of the endocrine system (hypothalamic dysfunction), autonomic nervous system, and respiratory control (ondine curse). These children appear "normal" until its onset between 1.5 and 10 years of age.[1-3] The acronym ROHHAD describes the typical sequence of symptoms experienced by most children, in order of their appearance. Often, the first sign is hyperphagia with dramatic weight gain. Hypoventilation develops few months later followed by hypothalamic dysfunction, diabetes insipidus, hyperprolactinemia, precocious/delayed puberty, growth hormone (GH) deficiency, adrenocorticotropic hormone (ACTH) deficiency, central hypothyroidism, autonomic dysfunction, light-nonresponsive pupils, constipation, temperature dysregulation, sweating disorders and reduced pain sensation.[4] Other features include developmental/behavioral disorders and seizures.[4]

CASE REPORT

A 2-years-4-months old girl presented with inability to be aroused from sleep. She was obtunded, hypoventilating (SPO2-85% in room air). Physical examination revealed facio-truncal obesity and adipomastia, pre-puberta sexual maturity rating with normal appearing female external genitalia.

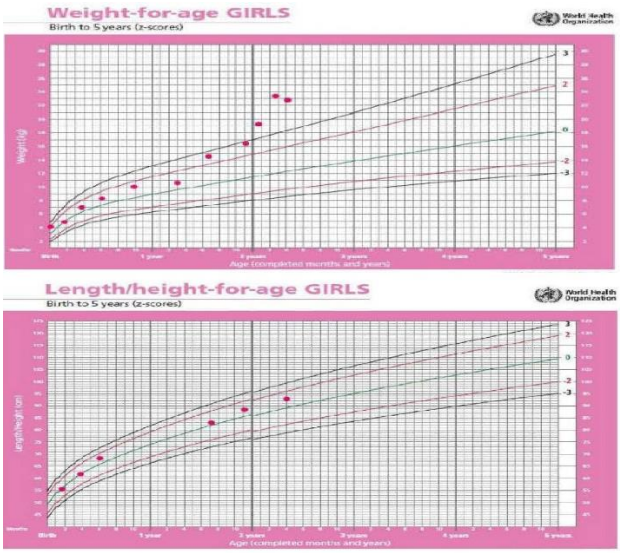

Figure 1: Growth chart depicting rapid weight gain after 1 ½ years of age and less than anticipated acceleration of height velocity in the setting of rapid weight gain.

Her blood-pressure was labile and >95th centile. Blood gas showed respiratory acidosis (pH:7.21, pCO2:80 mmHg). She was started on non-invasive ventilation (NIV) after which her sensorium and hypercarbia normalized (PCO_2: 43 mmHg). On further interview, child had hyperphagia and significant weight gain in preceding 6 months. Review of her growth chart revealed rapidly increasing weight after 1½ year of age, while her height centile remained within the normal range (Figure 1). Her developmental milestones were normal. She had several episodes of hypoventilation during the hospital stay. An attempted sedation for CT abdomen resulted in hypoventilation, hypercarbia (PCO2:115 mmHg, pH:6.9), and seizures, requiring brief period of invasive ventilation. A conventional respiratory physiological study was attempted, but could not be performed in view of hypoventilation and desaturation during sleep. Cardiac ultrasound revealed moderate pulmonary hypertension, in keeping with hypercarbic respiratory failure.

MRI brain showed non-enhancing T2/FLAIR hyperintensity in bilateral centrum semiovale, fronto-parietal subcortical white matter and right peri-trigonal region, with diffusion restriction. EEG was normal. She was noted to have diminished pain sensitivity as evidenced by absence of grimace/cry during insertion of IV cannulas/arterial catheters. She had normal pupillary light reflex with bilateral alternating exotropia and normal fundus.

Table 1: Summary of endocrine evaluation.

Test	Result	Normal Range
TSH	0.64 micro IU/ml	(0.7 – 6.4)
T3	0.68 ng/ml	(0.9 – 2.4)
Free T4	0.89 ng/ml	(0.8 – 2.7)
Prolactin	27.82 ng/ml	(2.5 - 15)
Random Cortisol	48.44 micro g/dl	(0.49 to 58.6)
0.5 mg Dexamethasone suppression test	1.41 micro g/dl	(4.3 – 22.4)
IGF 1	123 ng/ml	(51-303)
IGF BP 3	3.45 micro g/ml	(0.8-3.9)
5 mcg/kg Clonidine stimulation	GH Basal: 1.92 ng/ml GH 30 min: 0.27 ng/ml GH 60 min: 1.2 ng/ml	Peak GH: > 10 ng/ml
Fasting Leptin levels	4.64 ng/ml	(3.63-11.09)
24 hour urine VMA	2 mg	(<13.6)
24 hour metanephrines	0.4 mg	(< 1)
24 hour epinephrine	6.04 µg/g creatinine	(4-32)
24 hour nor-epinephrine	89 µg/g creatinine	(20-108)
24 hour dopamine	1069 µg/g creatinine	(295-1123)
75 g Oral glucose tolerance test	Fasting 64 mg/dl post 1 hour 72 mg/dl post 2 hours 82 mg/dl	(60-90) (80-120) (80-120)
Total cholesterol	73 mg/dl	(< 200)
Triglyceride	61 mg/dl	(<150)
HDL (measured)	18 mg/dl	(35 - 70)
LDL (measured)	52 mg/dl	(< 100)
VLDL (calculated)	12.3 mg/dl	(< 40)

She was evaluated for endocrine and genetic causes of obesity. Hormonal profile (Table 1) revealed normal plasma cortisol, appropriately suppressed with low dose dexamethasone (0.5 mg); hyperprolactinemia; central

hypothyroidism; low IGF-1, and a sub-optimal GH response to 5 µg/kg of clonidine. Leptin levels were normal for age and weight. Oral 75 gm glucose tolerance test, lipid profile, creatine kinase, serum ammonia, lactate, liver function tests, renal function tests and chest X ray were normal. Her bone age corresponded to 2-3 years (Greulich-Pyle method).

Considering the constellation of symptoms, ROHHADNET syndrome was considered and screening thoracic and abdominal CT was performed to look for any neural crest tumor. CT revealed an FDG avid, homogenously enhancing mass in pre-sacral area on left side, posterior to rectum (Figure 2 and 3).

Figure 2: Contrast enhanced CT abdomen.

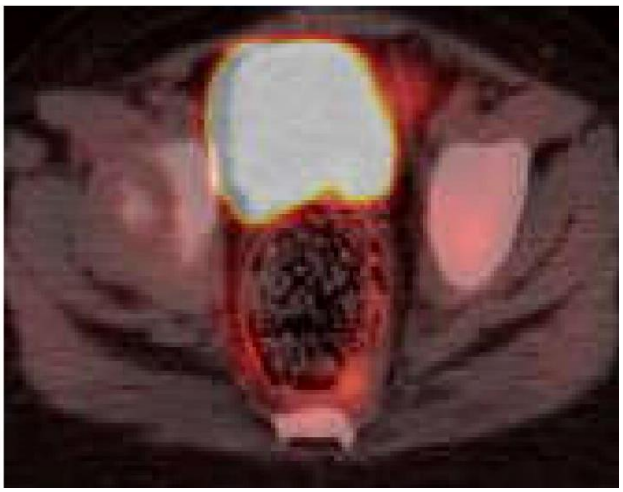

Figure 3: FDG-PET scan showing homogenously enhancing mass in pre-sacral region on left side posterior to rectum.

In view of hypertension and neurogenic tumor, urinary catecholamines and metanephrines were done, which were normal (Table 1). She was discharged on thyroxine and nocturnal NIV. Parents were trained to provide basic life support. Eight months later she collapsed while receiving nebulisation (? Hypoxia induced seizures) for respiratory illness at a nearby clinic where she was intubated. MRI Brain showed chronic infarcts in watershed areas with gliotic foci. Interim history revealed that the hypoventilation episodes have worsened (clinically and also evident with portable SP02 probe showing frequent desaturations) necessitating NIV support even for short naps during daytime and sometimes while awake also. She was extubated to BIPAP once awake. However, she developed hypoventilation soon after requiring re-intubation. She had 3 unsuccessful extubation attempts due to poor respiratory effort. Due to constant risk of apparent life threatening event, tracheostomy was planned. MRI Abdomen and pelvis showed mild interval increase in size and extension of the pre-sacral mass (Figure 4).

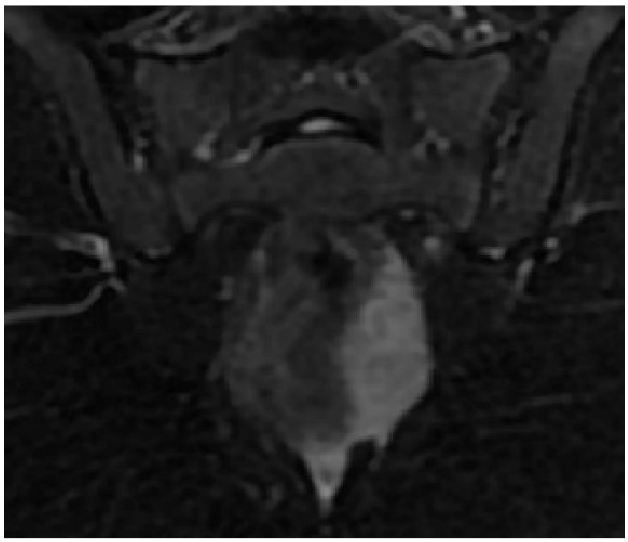

Figure 4: MRI Pelvis showing ill-defined presacral mass abutting rectum anteromedially, extending upto left mesorectal fascia and levator ani muscle laterally and inferiorly respectively.

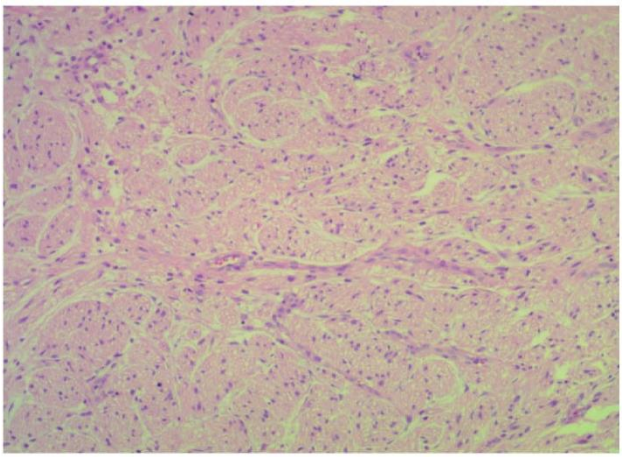

Figure 5: Histology of the presacral tumour showing monomorphic population of small, round cells with finely granular cytoplasm.

She underwent tracheostomy and excision of the pre-sacral mass at the same setting. HPE of the pre-sacral mass showed maturing ganglioneuroma (Figure 5).

Whole exome sequencing was done and 18 genes associated with CCHS and ROHHAD (ADCYAP1, ASCL1, BDNF, CD36, CD5, EDN3, GDNF, GFRA1, HTR1A, NDN, NTRK2, PDE11A, PHOX2B, RAI1, RELN, RET, TAF1, WDFY4) along with 'pathogenic' and 'likely pathogenic' variants were analysed, all of which were negative. She was discharged on BIPAP support via tracheostomy on need basis.

DISCUSSION

ROHHAD was first described in 1965 and was re-named in 2007 when it was shown to be distinct from congenital central hypoventilatory syndrome (CCHS) by absence of CCHS-related PHOX2B mutations.[5,1] The disease is now called ROHHADNET because of the accompanying ganglioneuroma in abdomen and lungs and neuroendocrinal tumors such as ganglioneuroblastoma in about 40% of the patients.[6,7]

Symptoms develop after 1½ year of age, with dramatic weight gain, hyperphagia; followed by hypoventilation. Before diagnosing central hypoventilation, it is important that diseases of lung and heart are ruled out.[8] Other hypothalamic abnormalities include diabetes insipidus and hyperprolactinemia.[3,5] Autonomic dysfunction include altered pupillary light reflex, strabismus, altered gastrointestinal motility, temperature dysregulation, decreased pain sensation. Few develop seizures, though this feature may be related to hypoxemia. About 40% develop neural crest tumors like ganglioneuromas or ganglioneuroblastomas.[4] 50% to 60% children ultimately suffer cardiac arrest.[9]

Differential diagnosis includes Prader-Willi syndrome in which hyperphagia and obesity is associated with hypotonia, mental retardation, short stature, GH deficiency, hypogonadotropic hypogonadism, and sleep apnea. Bardet-Biedl syndrome is charecterised by obesity, mental retardation, dysmorphic extremities, pigmentary retinopathy, hypogonadism, renal abnormalities. Leptin deficiency, POMC gene mutation, and MCR4 gene mutation also have to be considered among monogenic causes of early-onset obesity.[8,10,11] Normal levels of leptin and cortisol ruled out these causes in our patient. In contrast to most cases of exogenous obesity.[2,9] where growth velocity and IGF-1 levels are high normal, in ROHHAD patients IGF-1 levels are depressed with sub-optimal GH response to stimulatory tests.

Searches for a neuroanatomical pathology to explain symptoms of ROHHAD have not yielded consistent findings. Reported MRI pathologies include bilateral basal ganglia hypodensities, Rathke's cleft cyst and hypointensities in pons, midbrain.[1,2] Hypothalamic inflammation with lymphocytic infiltrates were found in two cases.[12,13] MRI brain in our patient showed hyperintensity in bilateral centrum semiovale, frontoparietal subcortical white matter and right peri-trigonal region with diffusion restriction, which is probably related to hypoxemia.

Sedation induced respiratory arrest is quite common.[13,15] All children with ROHHAD require some form of ventilatory assistance. Few reports have suggested that early intervention with nocturnal artificial ventilation may improve daytime ventilation.[14] Ventilator management must be targeted to the child's specific needs. The goal is to maintain adequate oxygenation and ventilation. Assistive breathing techniques like diaphragm pacing may have limited success due to associated obesity.

Previous studies postulated eight genes as candidate ROHHAD genes, but failed to identify any disease associated variants among their cohorts.[1,2,9] There has been a report of "Retinoic acid Induced-1" gene (RAI-1) receptor mutation in one case.[16] It was later confirmed that none of these 8 genes or RAI1 gene were major ROHHAD genes.[17] In our case, none of the tested genes were positive. A negative test could be due to variation in the genomic region not covered by the test; or due to large insertions, deletions, duplications, inversions, complex rearrangements which cannot be detected. As somatic mosaicism represents major mechanism, the major tissue carrying the mutation would not have been sampled. Use of patients' neuroendocrine tumour represents one approach to address this challenge.[17] Hence unambiguous identification of ROHHAD syndrome has been challenging; confirmatory laboratory testing is not yet available, and the patient population may represent heterogeneous group of underlying etiologies. Hence emphasis on diagnosis based on clinical findings.

CONCLUSION

ROHHADNET syndrome mimics genetic obesity syndromes and several endocrine disorders. Because of high prevalence of cardiorespiratory arrest and the probability of accompanying tumors, early diagnosis is important. Negative genetic test could be due to somatic mosaicism; variation in genomic region not covered by the test; or due to large insertions, deletions, complex rearrangements which cannot be detected. Unambiguous identification of ROHHAD syndrome is challenging; confirmatory laboratory testing is not yet available. Hence emphasis on diagnosis based on clinical findings. Multidisciplinary care and aggressive intervention is critical to optimise the neuro-developmental outcomes and to ensure a good quality of life.

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