

ROHHADNET Syndrome Presenting as Major Behavioral Changes in a 5-Year-Old Obese Girl

abstract

Behavioral issues are a frequent problem in the pediatric population. Often, these are evaluated and considered to be psychiatric in origin. We report on a pediatric patient who presented with severe behavioral disturbance and developed organic symptoms including hypoventilation and dysautonomia and who was ultimately diagnosed with ROHHADNET syndrome, a syndrome of rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation associated with a neuroendocrine tumor. Autopsy findings revealed novel findings of the syndrome, including hypothalamic encephalitis. *Pediatrics* 2014;134:e586–e589

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KEY WORD

ROHHADNET

ABBREVIATIONS

ROHHAD—rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation

ROHHADNET—rapid-onset obesity, hypothalamic dysfunction, hypoventilation, autonomic dysregulation, and neuroendocrine tumor

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Rapid-onset obesity, hypothalamic dysfunction, hypoventilation, autonomic dysregulation, and neuroendocrine tumor (ROHHADNET) syndrome is increasingly recognized in the literature as a cause of late-onset hypoventilation in pediatric patients. Although the behavioral component of this syndrome is well known, it is rarely considered in the differential of behavioral disturbances. We report on a patient who presented with severe behavioral disturbance and who developed organic symptoms consistent with ROHHADNET syndrome.

PATIENT PRESENTATION

Our patient was a developmentally normal 5-year-old girl with no past medical history. Three months before admission, she had a dramatic change in her behavior evidenced by violent outbursts, talking to herself, and a decline in her school performance. She gained 30 pounds over this period due to hyperphagia. She was taken to see a psychiatrist, who admitted the patient for psychosis and started risperidone treatment. Despite initiation of the medication, she continued to have extreme anxiety, anger, and intense eruptions. During the time she was being evaluated for her mental health issues, she developed high fevers and abdominal pain with eventual prolapsing rectum. She was admitted to the general pediatric service for evaluation.

The physical examination of the patient demonstrated an obese, combative African-American female with a BMI of 27.8 (99th percentile for age; weight, 37.2 kg) compared with a premonitory BMI of 14.3 (22nd percentile for age; weight, 25 kg). Her pupillary examination was significant for tonic pupils bilaterally (5 and 6 mm, respectively). Her cardiorespiratory and abdominal examinations were unremarkable. She had full-thickness rectal prolapse. Her genitourinary examination revealed Tanner II pubic hair and breasts.

During the initial course of her hospitalization, she was noted to have multiple episodes of self-induced rectal prolapse, fever, and hypoxia. Her metabolic panels during this time revealed a worsening metabolic alkalosis with hyponatremia and hypochloremia. Her aggressive behavior escalated, necessitating treatment with benzodiazepines and antipsychotic medications. Her profound personality changes became the focus of her initial workup. There were episodes of mania and hypomania, auditory hallucinations, major anxiety, and combativeness. A multispecialty evaluation to investigate the cause of her altered mental status was undertaken, which started with psychiatric evaluations and progressed to include cerebrospinal fluid analysis, HIV testing, a paraneoplastic panel (Carcinoma antigen-125, alpha-fetoprotein, carcinoembryonic antigen), arsenic and lead testing, and screening for infectious (New York State encephalitis panel) and autoimmune (N-methyl-D-aspartate encephalitis); these were all negative. At this time, a primary psychiatric diagnosis was considered the most likely cause of her behavior disturbance.

During the evaluation for her fever and gastrointestinal complaints, a computed tomographic scan of her chest, abdomen, and pelvis revealed a 4 × 4 cm right adrenal mass. Screening laboratories were significant for a slightly elevated Ca-125 level, minimally elevated dehydroepiandrosterone, and borderline elevated plasma metanephrine and normetanephrine (but not at a level concerning for a pheochromocytoma), luteinizing hormone, follicle-stimulating hormone, and estradiol levels were in the prepubertal range along with normal thyroid function, free and total testosterone and, 17-OH progesterone and dehydroepiandrosterone sulfate levels. Two weeks after admission, the patient suffered a respiratory arrest requiring endotracheal intubation and transfer to

the PICU. Initial arterial blood gas analysis revealed a pH of 7.30, Pco₂ of 75 mmHg, Po₂ of 69 mmHg, and an HCO₃ of 37 mEq/L on 100% oxygen, demonstrating acute on chronic respiratory failure. Her hemodynamic status was unstable with severe hypotension and significant tachycardia (>200 beats per minute at times, which was out of proportion to her hypotension) refractory to fluid resuscitation and a lactic acidosis requiring vasoactive medications and stress dose steroids. She eventually stabilized and was extubated days later but with respiratory difficulty evident by tachypnea, small tidal volumes, and hypercarbia on arterial blood gases, which ultimately required reintubation and ventilation. During this time, she remained combative.

With her constellation of symptoms, physical examination findings, and adrenal mass, additional diagnoses were considered as a cause for this child's symptoms. To evaluate a central cause of her altered mental status and hypoventilation, an MRI of the brain and brainstem was completed and found to be normal. To rule out a central congenital syndrome of hypoventilation, the *PHOX2B* gene was analyzed and was negative.

Because of concerns of a hormonally active adrenal lesion causing her behavior changes, an adrenalectomy was performed and found to be an adrenal ganglioneuroblastoma. Her aggressive behavior and hypoventilation did not improve after tumor resection. With the diagnosis of a neural crest tumor and the above-mentioned symptoms, we diagnosed the patient with ROHHADNET, a syndrome of rapid-onset obesity, hypothalamic dysfunction, hypoventilation, autonomic dysregulation, and neuroendocrine tumor.

Her hospital course was long and complicated. Despite corroboration by centers with experience with patients with ROHHADNET, the family was not willing to

accept this diagnosis and pressed to continue all aspects of care. A tracheostomy was placed for chronic ventilatory support. Severe hypotension, tachycardia, and temperature dysregulation (severe hyperpyrexia with temperatures $>41^{\circ}\text{C}$ or hypothermia with temperatures $<35^{\circ}\text{C}$) occurred intermittently throughout her hospitalization, often requiring hemodynamic support. Her behaviors continued to be problematic but she responded somewhat to clonidine and lorazepam.

Approximately 90 days into her hospitalization, she developed septic shock due to diffuse pneumatosis of the small and large intestines. Surgical intervention was not offered at that time because of extremely poor prognosis. With hemodynamic support and broad-spectrum antibiotics, she survived for 6 weeks but ultimately acutely decompensated after developing multiorgan system failure and died.

An autopsy with examination of the brain and spinal cord was completed. The patient was obese with a weight of 38 kg, height of 117 cm, and a BMI of 27.8 (99th percentile for age). Figure 1 details the autopsy findings. There was hypothalamic encephalitis with a perivascular and mild parenchymal chronic inflammatory infiltrate of CD3 T cells without vascular necrosis and numerous CD68 immunoreactive microglia and rare microglial nodules (Fig 1C). Gliosis demonstrated elongated GFAP (glial fibrillary acidic protein)-immunoreactive processes. No viral inclusions were found, and there was no herpes simplex 1 and 2 or cytomegalovirus immunoreactivity. There were remote infarctions in the caudate nucleus and cerebellum, watershed infarctions, and diffuse spinal cord hypoxic injury (polidystrophy) thought to be secondary to respiratory dysfunction. There was bilateral pneumonia with early hyaline membrane disease thought to be secondary to aspiration, and there were bilateral pleural effusions.

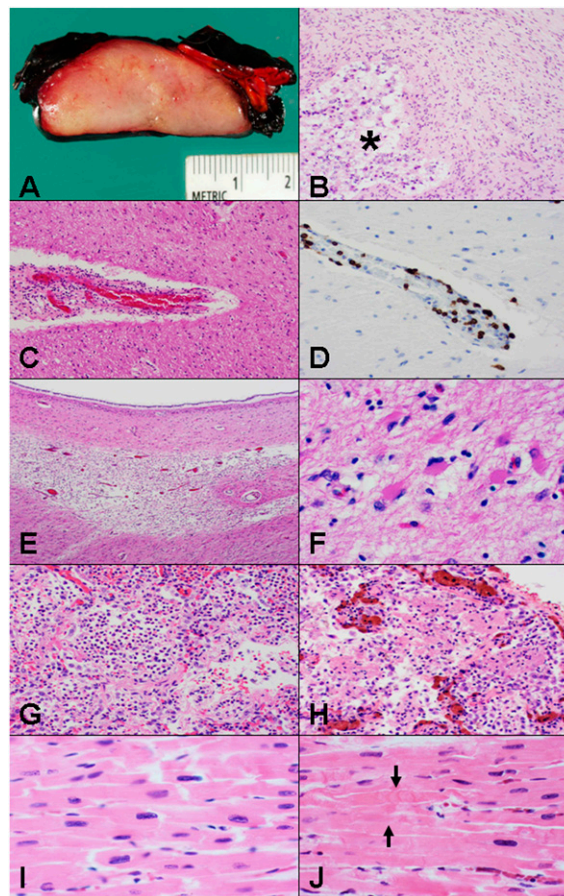


FIGURE 1

A, Ganglioneuroblastoma has a fleshy cut surface. B, A neuroblastic focus (*) is seen adjacent to Schwannian stroma with maturing ganglion cells. C, Hypothalamic encephalitis with a perivascular CD3-positive T-cell infiltrate. D, CD3 immunostain. E, Remote infarction in the right basal ganglia with (F) reactive astrocytosis. G, Aspiration pneumonia with intraalveolar acute inflammation and (H) early hyaline membrane disease. I, Myocardial hypertrophy with myocyte enlargement of left ventricle and (J) focal contraction bands (between the arrows). (Original magnifications: B and C, $\times 100$; D, G, and H, $\times 200$; E, $\times 40$; F, I, and J, $\times 400$.)

There was myocardial hypertrophy (weight, 140 g; expected, 94 g) with early left ventricular ischemia (Fig 1 I and J). In addition, there were ascites and multiple intraabdominal bowel adhesions after her multiple bowel resections with evidence of ongoing bowel ischemic injury. In addition, there were signs of iron overload from blood transfusions with hepatic and splenic hemosiderosis, pancreatic islet hyperplasia, and marked thymic involution.

DISCUSSION

The constellation of symptoms of rapid-onset obesity, hypothalamic dysfunction,

hypoventilation, and autonomic dysregulation was first described in 1965¹ and has been increasingly reported in the literature over the past 2 decades. Late-onset central hypoventilation with hypothalamic dysfunction was described by clinicians at Johns Hopkins after evaluating case reports of 10 patients in the literature at the time.² Most of the patients presented with hyperphagia, similar to our patient. The cause of hyperphagia has been reported as a causative mutation disrupting the function of hypothalamic integrative centers, which correlates with the finding of hypothalamic encephalitis in our patient. Patients presented with

a variety of endocrine manifestations (obesity, glucocorticoid deficiency, and adrenal tumors being the most marked presentations) with electrolyte abnormalities noted such as hypernatremia and hyperprolactinemia. Our patient had the most prominent endocrine features but did not present with the common electrolyte derangements. Respiratory manifestations are typically alveolar hypoventilation or altered respiratory control, but all patients had some form of hypoventilation, differing only whether it was present while they were asleep, awake, or both. Patients often had abnormal temperature and cardiovascular control with significant dysautonomia. Neurobehavioral disorders were common and presented in a myriad of ways, including personality changes such as in our patient. Behavioral disturbances were present in approximately half of patients and were manifested by depression, Tourette's, obsessive-compulsive disorder, and episodes of psychosis. Patients often died of cardiorespiratory arrest; approximately half of the patients analyzed died of cardiorespiratory arrest.³ Ize-Ludlow et al⁴ first used the acronym, ROHHAD, evaluated 21 patients and found that all of the patients had rapid-onset obesity and alveolar hypoventilation. They found that more than half of the patients had gastrointestinal dysmotility and

thermal dysregulation, similar to our patient. The mean age for presentation of hypothalamic dysfunction was 3 years of age, autonomic dysfunction at 3.5 years of age, behavioral disturbance at 4.8 years of age, and respiratory symptoms at 6.1 years of age. Our patient presented at 5 years of age. Bougnères et al² expanded to acronym to ROHHADNET to describe those patients with ROHHAD who develop neuroendocrine tumors. It is not established yet that the 2 syndromes share the same etiology.

Our patient had signs and symptoms (behavior changes, weight gain, and self-induced rectal prolapse) suggestive of a psychiatric diagnosis. The importance of this case is to highlight that even when behavioral changes are prominent, if they are accompanied by physical examination findings the etiology is organic. The behavior changes, tonic pupils, and anisocoria (likely due to dysautonomia) in our patient were prominent findings that, coupled with hypoventilation, helped make the diagnosis of ROHHADNET syndrome.

The pathophysiology of ROHHADNET syndrome has been difficult to elucidate. There has not been identification of a specific autoantibody or clear immunologic mechanism to explain the features of ROHHADNET syndrome, but some centers are treating this syndrome with immunosuppressive

regimens assuming there is an autoimmune component. A recent case report by Paz-Priel et al⁵ reported the successful use of cyclophosphamide to treat symptoms of ROHHADNET after an exhaustive immunotherapy regimen. The mechanism behind this treatment is still unclear. There had been no evidence of central nervous system inflammation on imaging or cerebrospinal fluid examination until our patient's evaluation. The autopsy of our patient revealed brain abnormalities, including hypothalamic encephalitis, which could explain some of the dysautonomic and hyperphagic symptoms in these patients. The noted injury to the caudate nucleus could be implicated as a reason for her emotional outburst; its cause was likely due to ischemia. In addition, there was diffuse damage to the cortex and spinal cord consistent with ischemic insults likely due to the multiple arrests and dysautonomia she had during her hospitalization.⁴ North et al⁶ described 2 cases of children with bilaterally unresponsive pupils; the autopsy results of 1 of the cases described pathology findings similar to ours, with changes noted in the hypothalamic region.

Though rare, ROHHADNET should be considered in the differential for patients with rapid weight gain, hypoventilation, dysautonomia, and most importantly, behavior disturbance.

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