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Case Report

D-dimer Changes in a Patient with ROHHAD Syndrome: A Case Report

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Abstract Rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation (ROHHAD) syndrome is a rare, but life-threatening disease. The value of monitoring D-dimer levels in ROHHAD syndrome cases remains to be determined. Here, we present a 9-year-old boy with ROHHAD syndrome who had a high level of D-dimer before surgery for an adrenal tumour but fell to normal following surgical excision. ROHHAD syndrome patients may be at risk of thrombosis. Changes in D-dimer level may be used as a marker to help predict the development of neural crest tumour in ROHHAD syndrome patients.

Key words *D-dimer; Hypercoagulable state; Neural crest tumour; ROHHAD syndrome*

Introduction

Rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation (ROHHAD) syndrome is a rare, but life-threatening disease. It is a kind of hypothalamic obesity that manifests in the endocrine, autonomic nervous, cardiovascular, and respiratory systems.[1] The following characteristics serve as the diagnostic criteria: (1) rapid-onset paediatric obesity and alveolar hypoventilation during sleep; (2) signs and symptoms of hypothalamic dysfunction and autonomic abnormalities; and (3) exclusion of other conditions generating comparable symptoms, such as congenital central hypoventilation syndrome (CCHS). About 40-56% of patients are at risk of developing neural crest tumours (ganglioneuromas and ganglioneuroblastomas), some specialists suggest that ROHHAD syndrome with neural crest tumours is called rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, neuroendocrine tumour (ROHHADNET).[2] ROHHAD syndrome has a 50-60% mortality rate, therefore, it is critical to make an early diagnosis.[3] To date, there have been around 100 cases of ROHHADS reported, and this boy may be the first reported case of ROHHADNET in China.

Previous reports of ROHHAD syndrome cases rarely mentioned the manifestation of coagulation disorders. Herein, we describe a ROHHADNET with elevated D-dimer level, the level of D-dimer was high before surgery but fell to normal following surgical excision of an adrenal tumour. The changes in D-dimer level may be used as a marker to help predict the development of neural crest tumour in ROHHAD syndrome patients.

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Case Presentation

A 9-year-old boy was evaluated for poor height growth (about four centimeters per year), rapid-onset obesity (rapid weight gain approximately 12 kg per year), frequent diarrhoea, excessive sweating, and hypalgesia. He did not have polyuria or urge to drink. Physical examination revealed that his height was 121.8 cm (<-2SD), weight at 34.5 kg (BMI>97%). He had a typical moon face, a buffalo back, a micropenis (approximately 2 cm), and small testis (about 0.5 mL each). A complete laboratory assessment revealed hypernatraemia (161.1 mmol/L), high plasma renin (>500 pg/mL), and urinary-osmolality (939.00 mOsm/kg). Although there was no sign of tachypnea or dyspnoea, the arterial blood gas revealed an increased PCO_2 and decreased PO_2, indicating he had central hypopnea with obstructive apnoea which was confirmed on polysomnography monitoring. The increased NSE (neuron-specific enolase) and hyperprolactinaemia were the other test findings. Brain magnetic resonance imaging revealed a tiny pituitary gland. Adrenal ultrasonography and enhanced magnetic resonance imaging both revealed a left adrenal mass.

After admission, the boy was noted to have a low grade fever, with a daily temperature ranging from 36°C to 37.8°C. The growth hormone stimulation test was positive (peak of 0.08 ng/mL), and IGF1 level was 51.4 ng/mL (<-2SD) (Table 1). The 24-hour Holter electrocardiogram revealed sinus arrhythmia with sinoatrial node movement and atrial premature beats on occasion. The average blood pressure was 108/67 mmHg based on 24-hour ambulatory blood pressure measurements. His serum sodium levels gradually returned to normal after he was hydrated by drinking plenty of water (approximately 2000 mL/day). The boy underwent adrenal tumour surgery in our hospital. The pathology of tumour revealed ganglioneuroma. D-dimer levels (>20 μg/mL) was high during the preoperative period. Interestingly, D-dimer level returned to normal after adrenal tumour was removed. Genetic testing revealed that he did not have a *PHOX2B* gene mutation for congenital CCHS, nor a methylation anomaly in 15q11.2- q13 region for Prader Willi syndrome. The patient was eventually diagnosed to have a ROHHAD syndrome (rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation) with neuroendocrine tumour or ROHHADNET. There were no abnormalities observed in the specified ROHHAD genes. The boy was treated with hydration, a rigorous diet, and intense exercise. During the night, he was placed on bi-level positive airway pressure (BiPAP). However, He was not compliant for follow up regularly after being discharged. He even had repeated syncope as a result of his worsening hypopnoea.

Table 1 The results of the patient's labs

Item	Value	Reference range
IGF-1 (ng/ml)	51.40	84-350
GH stimulation testing with arginine and clonidine (ng/ml)	GH peak 0.08	＞10
Prolactin (ng/ml)	24.04	2.1-17.7
Direct renin concentration (pg/ml)	>500	4-38
Serum Na (mmol/L)	161.1	135-145
Plasma osmolality (mosm/kg)	336	275-305
Morning cortisol (nmol/L)	561.09	118.68-618.24
1mg dexamethasone suppression test (nmol/L)	30.36	<138
TSH (mIU/L)	4.176	5.09-9.66
FT3 (pmol/L)	4.43	3.31-4.81
LH (IU/L)	<0.07	0-0.5
FSH (IU/L)	1.28	0.4-2
NSE (ng/ml)	50.40	0-16.3

Discussion

ROHHAD syndrome was firstly reported by Fishman LS, which was described as "delayed central hypopnoea with hypothalamic dysfunction". It was renamed as ROHHAD syndrome by Ize-Ludlow and colleagues in 2007. They tried to distinguish this syndrome from CCHS and late-onset central hypoventilation syndrome (LO-CHS).

The primary symptom of ROHHAD syndrome is rapid weight gain in childhood during the first 1.5-10 years of life (mainly 2-8 years), but the height increases slowly. The rapidly weight gaining (6-10 kg in 6-12 months) leads to severe obesity. The patient gradually suffers from endocrine disorder, hypopnoea and neurological symptoms. Unlike simple obesity, the patient of ROHHAD syndrome continue to gain weight despite strict dietary control and regular exercise. Severe obesity leads to metabolic syndrome, including hyperglycaemia, hyperlipidaemia, and hyperuricaemia.

Hypothalamic dysfunction mainly affects the hypothalamic pituitary functional axis, which can lead to hyperprolactinaemia, growth hormone deficiency, central hypothyroidism, precocious puberty, hypogonadism, and adrenal insufficiency. In addition, patients may experience diabetes insipidus, syndrome of inappropriate secretion of antidiuretic hormones, or water balance disorders (hypernatraemia or hyponatraemia) caused by decreased thirst. Hypothalamic dysfunction can also lead to disorders of the Autonomic nervous system, including abnormal thermoregulation (high or low temperature), eye abnormalities (strabismus, abnormal pupillary light reflex), irregular heart rate, abnormal blood pressure, gastrointestinal dysfunction (constipation or diarrhoea), hyperhidrosis, cold extremities, pale hands or feet (Raynaud's phenomenon), and abnormal pain sensation.

The aetiology of ROHHAD syndrome remains unclear. Three major etiopathogenetic hypotheses have been proposed: genetic, epigenetic, and autoimmune.[4,5] The notion of ganglioneuroma-mediated paraneoplastic syndrome explains why ROHHADNET patient has hypernatraemia due to diabetes insipidus and adipsia. NSE and Chromogranin A (CgA) are highly specific biomarkers for neuroendocrine tumours, the value of monitoring D-dimer levels in ROHHAD syndrome cases remains to be determined. Although elevated D-dimer level is relatively common in obese patients, previous reports of ROHHAD syndrome cases rarely mentioned the manifestation of coagulation disorders. Recently, Tian et al. described a case of ROHHAD syndrome without a neural crest tumour who had cerebral venous thrombosis.[2] This patient's D-dimer was likewise high, and the authors attributed thrombosis to hem-concentration (dehydration), reduced plasma osmotic pressure (hyponatraemia), or changed intracranial pressure (long-term hypoventilation). In our case, the boy's D-dimer was significantly elevated before tumour removal, but it recovered to normal after surgery. He did not have evidence of thrombosis. As a result, we believe that ROHHAD syndrome is at risk of thrombosis due to hypercoagulability. To evaluate the state of a ROHHAD syndrome patient, the level of D-dimer should be monitored. D-dimer may be used as a marker to predict tumours in ROHHAD syndrome patients and tumour recurrence in ROHHADNET patients.

The surveillance protocol for patients with ROHHAD should include monitoring of weight and height growth, serum electrolyte levels, signs of metabolic syndrome, hypophyseal hormone levels, cardiac abnormalities, hypoventilation, and tumour recurrence. These clinical manifestations can develop from months to years after the onset of rapid-onset obesity. Additionally, cognitive and behavioural abnormalities are observed in some patients, necessitating psychological assessments. It is estimated that 50-60% of patients succumb to complications such as hypoventilation, cardiopulmonary failure, and cardiopulmonary arrest.

In conclusion, the child with rapid-onset obesity and poor height growth should be evaluated for evidence of hypoventilation, endocrine dysfunction, and autonomic dysregulation for early identification of ROHHAD syndrome and to lower the risk of mortality through active management. Furthermore, owing to their hypercoagulable status, ROHHAD syndrome patients may be at risk of thrombosis. Changes in D-dimer level may be used as a marker to help predict the development of neural crest tumour in ROHHAD syndrome.

Declaration of Interest

No conflict of interest involved.

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