ROHHAD Syndrome – Focus on Endocrine Abnormalities and Precocious Puberty

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Background: ROHHAD (rapid-onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation) syndrome is a rare disease, with around 200 cases described worldwide. Other clinical manifestations may be pulmonary hypertension, cough, recurrent upper respiratory tract infections, metabolic disorders. **Objective:** The aim of this article was to present a case of ROHHAD syndrome, a very rare disorder with multisystemic involvement and an unknown etiology. **Case report:** We present the case of an 11-year-old girl with ROHHAD syndrome. The disease was diagnosed at the age of 3.5 years when she was hospitalized due to obesity, adynamia, hyponatremia, and a convulsion. An electroencephalogram (EEG) recording showed epileptic brain activity, and antiepileptic therapy was initiated. Diagnostic tests revealed the presence of a tumor mass in the abdomen, which was surgically removed. Histopathology confirmed malignant ganglioneuroblastoma. The girl received chemotherapy according to the protocol. Genetic analysis of the patient showed no genetic predisposition to the onset of the disease. At the age of 8.5, she was hospitalized again due to vaginal bleeding. Endocrinological evaluation revealed precocious puberty, absolute growth hormone deficiency (although growth was at the 25th percentile), and hypothyroidism. Growth hormone, luteinizing hormone-releasing hormone (LH-RH) analogue, and Levothyroxine were included in therapy. The precocious puberty episodes have been stopped, and she no longer receives LH-RH analog. Levothyroxine, growth hormone, and antiepileptic drugs are continued in the therapy. The girl has no cognitive disorders, achieves good results in school, and her current growth chart values are within the reference values for her age. **Conclusion:** ROHHAD syndrome is a rare disease, with around 200 cases described worldwide. The disease can lead to severe complications, including intellectual impairment and death. The diagnosis is made on the basis of clinical manifestations, and the therapy requires a multidisciplinary approach.

Keywords: Obesity, hypothalamic dysfunction, precocious puberty, rare disease.

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1. BACKGROUND

ROHHAD (rapid-onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation) syndrome is a rare disease, with around 200 cases described worldwide. Other clinical manifestations may be pulmonary hypertension, cough, recurrent upper respiratory tract infections, metabolic disorders (1). The etiology of ROHHAD syndrome is still unknown. Mutations in PHOX2B, the gene that is the cause of congenital syndrome of central hypoventilation and dysfunction of the hypothalamus and the autonomic nervous system, are mentioned as possible etiological factors (2). A certain number of patients with ROHHAD syndrome had detected antihypothalamus and antipituitary antibodies in the cerebrospinal fluid (3), and specific antineural autoantibodies in the serum (4). Prognosis depends on clinical manifestations and timely recognition and treatment of the disease.

2. OBJECTIVE

The aim of this research is to present the case of an 11-year-old girl with ROHHAD syndrome, which was clinically manifested by endocrine abnormalities and precocious puberty.

3. CASE PRESENTATION

The girl is now 11 years old. She was born at term, with a birth weight of 3650 g, a length of 51 cm, and she was developing properly. In the age of 3.5 years she was hospitalized due to loss of consciousness, rapid obesity with adynamia, hypoventilation, hyponatremia

An electroencephalogram (EEG) recording showed epileptic brain activity, and antiepileptic therapy was initiated. Diagnostic tests revealed the presence of a tumor mass in the abdomen, which was surgically removed. Histopathology confirmed malignant ganglioneuroblastoma. On the basis of clinical manifestations,

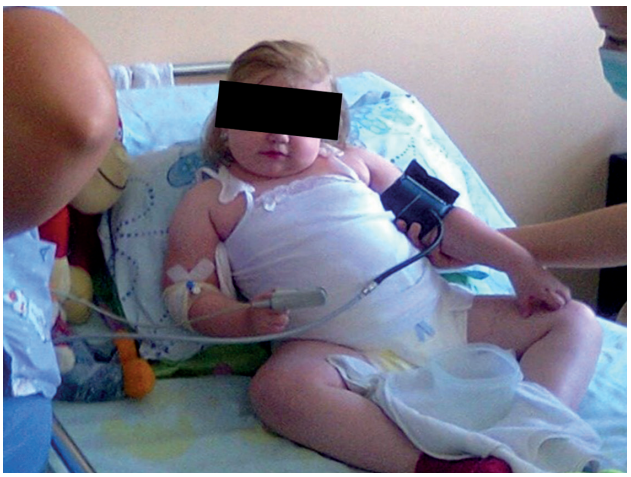

Figure 1. Preoperative (private archive)

Figure 2. The girl at the age of 11

the diagnosis of ROHHAD syndrome was established. The genetic analysis of the patient's parents showed no genetic predisposition to the onset of the disease. The girl received chemotherapy according to the protocol, and he was monitored by a neuropediatrician and a hemato-oncologist on an outpatient basis. At the age of 8.5 years she was admitted in hospital due to menstrual bleeding. Her weight was 34 kg which correspond to weight-to-age percentile (p) of 75-90 p and her height was 128 cm (25-50 p). Analyzes by an endocrinologist showed an absolute deficiency of the growth hormone, low values of gonadotropin, and hypothyroidism. Growth hormone, luteinizing hormone-releasing hormone (LH-RH) analogue, and Levothyroxine were included in therapy. The precocious puberty episodes have been stopped, and she no longer receives LH-RH analog. At regular check-ups over the period of 2 years, the hormonal therapy showed adequate response, and hergrowth charts were recalculated. Levothyroxine, growth hormone, and antiepileptic drugs are continued in the therapy. The girl is now 11 years old, weight 48.9 kg (75-90p), and height 145.6 cm (50p). The girl has no cognitive disorders, she achieves good results in school.

4. DISCUSSION

ROHHAD syndrome is a new, rare and complex disease that requires a multidisciplinary diagnostic and therapeutic approach. Following the diagnostic criteria by Harvengt et al. the main criterion of the disease is the onset of rapid weight gain that appeared at the age between 2.5-4 years. Hypoventilation occurs in the first five years after the onset of obesity, as central hypoventilation, apneic pauses, cyanotic episodes. Autonomic dysregulation is the third criterion (1). Hypothalamic dysfunction may manifest as growth hormone deficiency, diabetes insipidus, precocious puberty, hypothyroidism, corticotrophin deficiency, dysnatremia (5). Studies of the prevalence of the disease in relation to gender have shown that it is twice as common in girls (1, 5). Neuroendocrine tumors (NET) are found in about 50% of cases within two years of the onset of obesity. Patients with ROHHAD syndrome who develop a neuroendocrine tumor such as ganglioneuroma or ganglioneuroblastoma are described as ROHADNET syndrome (5). Psychiatric manifestations are often present, from behavioral changes to psychosis (1). Difficulties with breathing can be of different degrees from snoring during sleep, apneic pauses, tendency to respiratory infections in which they may require mechanical ventilation. Hypoventilation can lead to neurological impairment, respiratory failure and death (6).

We presented the case of an 11-year-old girl with ROHADNET syndrome, symptoms manifested at the age of 3.5 years. At the age of 8.5 years, she had symptoms of endocrine abnormalities (absolute deficiency of the growth hormone, low values of gonadotropin, and hypothyroidism).

Systematic review on ROHHAD/NET by Bougneres et al. including 46 studies with 158 patients, showed various forms of endocrine disorder; growth hormone deficiency in 25% of cases, diabetes insipidus in 19%, and central precocious puberty in 15% cases (5). Obesity is an increasingly common problem among children, in combination with other disorders the differential diagnosis should exclude ROHHAD, Prader-Willi, Cushing's disease and similar disorders (1). In ROHHAD syndrome, obesity is difficult to regulate with diet and exercise, but is well regulated with treatment of hypothalamic dysfunction and endocrine abnormalities. A special challenge in these patients is the treatment of breathing disorders and hypoventilation, which sometimes require a positive pressure ventilation or mechanical ventilation in home conditions (7).

Cooperation among specialties is important for early establishment of the correct diagnosis. For physicians it is very important to have information about rare cases in order to be able to establish a diagnosis more quickly and ensure a better prognosis for the patient (8). Treatment requires a multidisciplinary approach depending on clinical manifestations.

5. CONCLUSION

ROHHAD syndrome is a new and still insufficiently researched disease, and the prognosis and life expectancy are uncertain. Every new case presented and new research in the world contributes to the easier recognition and timely treatment of this disease, with the aim of providing the best neurocognitive outcome.

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