CASE REPORT

Issues of diagnosing ROHHAD Syndrome in a 2-year-old girl : A Case Report and Review of Literature

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ABSTRACT

We present a clinical case of ROHHAD syndrome. In this article we discuss the rare occurrence of this pathology and, as a result, the issues encountered in the diagnosis and treatment of such children. Thus, in highlighting the problem, the team of Authors set the goal of emphasizing the importance of timely diagnosis, as well as correctly selecting comprehensive treatment for children with ROHHAD syndrome.

INTRODUCTION AND LITERATURE REVIEW

ROHHAD is an acronym for rapid-onset obesity (RO) with hypothalamic dysregulation (H), hypoventilation (H) and autonomic dysregulation (AD). According to the international classification of sleep disorders ICSD-3 2014, it is a type of sleeping- dependent hypoventilation and is a rare genetic disease that manifests after 2 years of life in previously healthy children [1-2]. There are about 100 clinical cases with this syndrome in the world [3]. The abbreviation ROHHAD describes a typical sequence of symptoms and stands for rapidly progressive Rapid-onset Obesity with hypothalamic dysregulation, Hypoventilation and autonomic dysfunction [1-3]. A dangerous manifestation of the disease is respiratory disorders in the form of sleep apnea, alveolar hypoventilation [3-4]. In contrast to the syndrome of congenital Central alveolar hypoventilation (Ondine's curse), ROHHAD-syndrome is characterized by late-onset, severe hypothalamic and autonomic disorders, the absence of mutations in PHOX2B gene, leading to a congenital syndrome [5-7].

From birth, children with ROHHAD-syndrome grow and develop physiologically, but at the age of 1.5–7 years, a sharp increase in body weight begins – rapidly progressing obesity, weight gain for 6-12 months, it can be from 10 to 20 kg- as a result of hypothalamic dysfunction and polyphagia [3, 8, 9]. After rapid weight gain, children develop respiratory disorders in the form of obstructive apnea and hypoventilation due to loss of vegetative control over the breathing process. Children with this syndrome develop alveolar hypoventilation with hypercapnia and hypoxemia (hypoxemia has an auxiliary diagnostic value) during sleep. However, the development of hypoventilation is not always obvious, since the child does not feel it, as in the syndrome of congenital Central alveolar hypoventilation. In more severe patients, hypoventilation may also occur while awake, which can lead to respiratory and cardiac arrest [4]. Hypothalamic dysfunction is manifested by fluid-electrolyte imbalances in form of Hypo - or

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hypernatremia as a result of vasopressin deficiency or reduced secretion of antidiuretic hormone; high levels of prolactin; low levels of thyroid hormones, cortisol, and somatotropic hormone; delay or early puberty; impaired glucose tolerance. Vegetative dysfunction manifests itself as eye changes (lack of response of the pupils to light, strabismus); violations of intestinal motility, which leads to constipation or diarrhea; episodes of increased body temperature, sweating; decreased pain sensitivity; bradycardia. Patients with ROHHAD-syndrome are also characterized by behavioral disorders, mood and mental retardation, obsessive disorders with episodes of psychosis, and autistic disorders. However, a surprisingly high percentage of children with ROHHAD syndrome have a normal or high level of intelligence. Some of them develop seizures, which may be caused by hypoxemia due to insufficient respiratory protection supports.

Approximately 40% of ROHHAD - syndrome Patients develop tumors that occur in the neural crest, such as ganglioneuroblastomas. In this regard, it was proposed to rename ROHHAD-syndrome to ROHHADNET-syndrome (Rapid-onset Obesity Hypoventilation Hypothalamic Autonomous Dysregulation Neural Endocrinological Tumor) to include these tumors in the diagnostic criteria, but this was accepted only for patients who develop these tumors. The development of tumors is associated with mutations in the PHOX2B gene.

To confirm ROHHAD-syndrome, the following criteria must be present: 1) the onset of rapid and extreme weight gain after 1.5 years (usually after 2-7 years) in a previously healthy child; 2) evidence of hypothalamus dysfunction; 3) alveolar hypoventilation; 4) features of vegetative dysregulation.

Additional screening for ROHHAD syndrome includes nighttime polysomnography to determine any signs of obstructive sleep apnea. Daytime hypoventilation can be diagnosed by monitoring levels of carbon dioxide (PaCO2) and blood oxygen saturation (peripheral saturation, SpO2) during the day. Detection of the level of PaCO2>50 mm Hg and SpO2<95% and allows to establish the diagnosis of "awake" hypoventilation [4]. In the development of sudden obesity, a targeted assessment of ventilation by pulse oximetry and capnography is necessary during sleep and when awake. It is recommended to conduct a comprehensive examination: a detailed physiological assessment of breathing when awake as well as during sleep, a comprehensive cardiological assessment, including 72-hour Holter monitoring of electrocardiography, veloergometry (physical tolerance or exercise test) and echocardiography (with the determination of pressure in the pulmonary artery due to the possibility of developing pulmonary hypertension due to hypoxemia), neurocognitive testing to assess intellectual development as a marker of neurological status. It is also necessary to examine the endocrine system to determine the symptoms of hypothalamic dysfunction and/or pituitary pathologies. It is also important that if hypercalcemic dehydration is noted, one should determine the secretion of the antidiuretic hormone before assuming the diagnosis of "diabetes insipidus ". Obesity can alter the secretion of growth hormone and the level of insulin-like growth factor-1 (IGF-1), which should be taken into account when evaluating the function of growth hormone. It is necessary to take into account such complications of obesity as fatty liver dystrophy, impaired lipid metabolism or diabetes mellitus. It is important to conduct computer tomography of the chest and abdominal organs to detect tumors of the neural crest [10].

Treatment of ROHHAD-syndrome is currently symptomatic. Obesity is extremely difficult to control through diet and exercise, and measures are needed to prevent further weight gain. Since patients with ROHHAD-syndrome do not improve their breathing adequately during exercise, it is important to recommend moderate loads whose safe parameters are based on monitoring the PaCO2 level and pulse oximetry during training.

Hypothalamus dysfunction observed in these patients should be evaluated and treated by a pediatric endocrinologist. Treatment methods may include hormone replacement therapy, a strict fluid intake regime, and other measures. It is shown that the introduction of growth hormone improves body composition, and the use of dopamine agonists to normalize prolactin levels does not change the clinical course of the disease [11].

One of the main problems in patients with ROHHAD syndrome is a violation of respiratory control. It is important to remember that the isolated supply of oxygen does not eliminate hypoventilation. Alveolar hypoventilation requires invasive or non-invasive ventilation to ensure adequate ventilation, prevent atelectasis and attachment of lower respiratory tract infection, as well as due to the risk of apnea and acute cardiorespiratory insufficiency, while CPAP therapy (Constant Positive Airway Pressure, continuous positive airway pressure) is effective for obstructive sleep apnea syndrome, respiratory disorders due to upper respiratory tract obstruction [13].

Some children with ROHHAD syndrome may initially need invasive ventilation only during sleep, and then there is a need for constant support both during sleep and when awake. In children who need ventilation only at night, mask ventilation with two-levels (bi-level) positive pressure can be performed. Those children who require a ventilator for 2 hours a day are given ventilation through the tracheostomy [12].

For adequate development, children receiving ventilation should be at home, but need to have a ventilator at home, which has a provision for the availability of a backup ventilator, pulse oximeter, capnograph for transcutaneous PaCO2 monitoring and an energy generator. Specialized service is needed to control home ventilation, which is not yet developed in Russia. In recent years, it has become possible to patronize children by visiting hospice services. In many countries, such families are provided with night care staff [13].

Other assisted breathing techniques, such as diaphragm stimulation, may have limited success due to obesity-associated with ROHHAD-syndrome, but they should be considered in some patients.

Patients with ROHHAD syndrome are at risk of bradycardia, which can be eliminated only after the installation of a pacemaker. The lack of temperature control requires careful regulation of the ambient temperature and attention to low body temperatures. For chronic constipation due to impaired motility of the gastrointestinal tract, laxatives are prescribed.

Tumors from the neural crest require surgical removal, however, to date, surgical removal of neural crest tumors has not reduced the deployment of the ROHHAD syndrome phenotype and has not caused recovery from the disease. An interdisciplinary team of specialists, including an endocrinologist, pulmonologist, cardiologist, intensive care doctor, respiratory specialist, otorhinolaryngologist, surgeon, oncologist, gastroenterologist, neurologist, ophthalmologist, psychologist, psychiatrist, speech therapist, and special education specialist, working together with the child and family to optimize care and quality of life, is crucial for the successful management of patients with ROHHAD-syndrome [12].

CLINICAL CASE

Anamnesis vitae: a female child from II pregnancy, II spontaneous vaginal delivery at 39 weeks gestation age. Bodyweight at birth 3560 g, length 53 cm. From the age of 2, the child began gaining weight significantly: (for 6 months, the increase in body weight was 5 kg). At the same time, there were complaints of dry cough, enuresis, and sweating. No medical help was sought. In September 2018 (at 2 years 7 months old), after contact with a patient with an acute respiratory viral infection, the girl developed a low-grade fever and a dry cough. After 4 days, the body temperature increased to 38-41 0C, while the state of health decreased slightly. On an outpatient review, after two courses of antibacterial

therapy (azithromycin, cefixime), there was no improvement, so she was admitted to the hospital with the diagnosis: "Acute respiratory viral infection. Community-acquired pneumonia?"

Upon admission, the condition became severe due to intoxication and fever. A subcutaneous fat layer developed excessively and was evenly distributed. On auscultation of the lungs, wheezes and rhonchi were heard. Tachypnea up to 64 breaths per minute. SpO2 was 86-88% in room air and 99-100% when oxygen was provided through nasal cannulas. The child's condition deteriorated: she developed lethargy, confusion, and shortness of breath. Laboratory results of acid-base state and biochemical analysis of blood were as follows: blood pH 7.23–7.27, BE-12.3-10.4 mmol/l, sodium 144-159 mmol/ l, potassium 3.35–4.52 mmol/l, chlorine 135-130 mmol/ l, glucose 4.6–5.9 mmol/l, calcium 1,8-2,1 mmol / l. in the General analysis of urine: specific gravity 1025-1030. According to a chest X-ray done on admission, pneumonia was excluded. The child was treated with oxygen therapy, infusion, diuretics, and symptomatic therapy. With treatment, the indicators of the acid-base state of the blood, sodium, and chlorine normalized, but there was no significant improvement in the condition of the child. Fever persisted, and episodes of O2 desaturation at night. Due to a history of long-term continuous use of antipyretic drugs, fever, electrolyte disorders, respiratory failure, and background of significant weight gain, a preliminary diagnosis was made: "systemic hypothalamic-pituitary Pathology? Hyperosmolar syndrome. Decompensated metabolic acidosis, hyperthermic syndrome, ROHHAD-syndrome?".

She underwent a comprehensive examination. According to the results of laboratory tests, adrenocorticosteroid hormone, cortisol, thyroid hormones, thyroid-stimulating hormone, insulin, C-peptide, human chorionic gonadotropin in the blood serum were all within the normal range. A significant increase in the level of prolactin (up to a maximum of 32 ng/ml, the norm is 1.2–19.5 ng/ml) was detected during repeated blood tests, while there were no clinical manifestations of hyperprolactinemia. Diabetes insipidus was excluded. In the analysis of urine according to zimnitsky's test, the relative density of urine from 1005 to 1020, isosthenuria was absent. Indicators of the acid-base state of blood and blood gases were monitored twice daily, PaCO2 increased to 88 mm Hg. PaO2 decreased to 25.2 mmHg. However, hypernatremia remained up to 156.2 mmol /l. Markers of bacterial infection were not increased. MRI examination of the brain with intravenous contrast showed no signs of structural pathology. Based on the conducted examinations, volume formations of the hypothalamic-pituitary region (MRI of the brain with intravenous contrast), volume formations of the thoracic cavity, abdominal cavity and retroperitoneal space (CT with contrast) were excluded. Echocardiography- showed no structural changes of the heart and hemodynamics were normal, the pressure in the pulmonary artery was also normal. On daily Holter monitoring, ECG and blood pressure (BP), the heart rate and blood pressure were within normal range. EEG-signs of epileptiform activity was not detected. Infectious causes of fever (toxoplasmosis, yersiniosis, salmonellosis, herpesvirus infections, HIV, syphilis, hepatitis B and C) were excluded. Blood cultures for sterility, showed no growth. Tuberculosis was excluded (based on the results of the Mantoux reaction, Diaskintest). Oncohematological diseases were also excluded (based on the results of bone marrow puncture, alpha-fetoprotein – within the normal range). There were no neuro infections (cerebrospinal fluid was normal, PCR and seeding for flora were negative. A genetic study was conducted. There were no mutations in the PHOX2B gene, indicating the syndrome of congenital Central alveolar hypoventilation. ROHHAD-syndrome was diagnosed based on the patient history, clinical picture and results of laboratory and instrumental findings (significant weight gain over 6 months, persistent fever without

clinical and laboratory signs of bacterial infection, water-electrolyte disorders, desaturation when the child was awake (up to 88%) and during sleep-up to 78% without O2 (in room air), hypercapnia and absence of mutation in the PHOX2B gene).

Although the background of treatment was complex, there were a few positive dynamics like the normalization of body temperature, correction of the blood electrolyte imbalance, and an improvement in the severity of respiratory failure. In December 2018, the child was discharged with recommendations of oxygen therapy at night due to normal PaCO2 indicators at discharge and compliance of a diet with limited volume and caloric content of food taken.

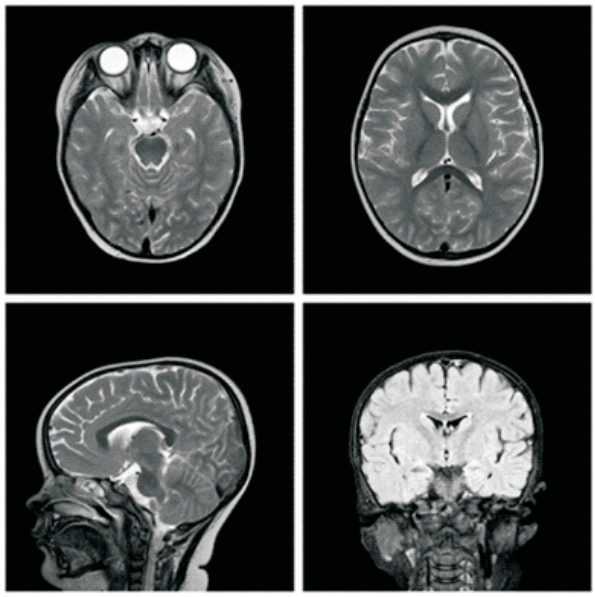
On review as an outpatient, the child's condition remained stable for 3 months. The level of SpO2 during the day remained within the normal range (95-99%), at night she was on oxygen support. With parent's adherence to diet changes, the child's body weight was controlled. However, during this period, fevers up to 38.5 C were noted three times. They were controlled at home.

On March 12, 2019, the patient presented to our hospital with a fever of up to 40,0*C. After 3 days, respiratory failure increased (SpO2 reduced to 50%), and she had noisy breathing. The child was admitted to the intensive care unit. Although she had a constant supply of O2, SpO2 was 78%. On examination, she was sluggish, in a state of stun and not fully oriented. On auscultation of the lungs generalized dry and moist rales were present. She also had pronounced shortness of breath and tachycardia. Due the weakening of the swallowing reflex a nasal gastric tube was inserted, and the patient received enteral nutrition. Taking into account the long-lasting fever up to 40.0 and to exclude sepsis blood tests were performed (procalcitonin <0.5 ng / ml). According to an acid-base blood test - she had compensated metabolic acidosis, hyponatremia 118 mmol/l, and hypokalemia up to 2.4 mmol/l. At night (during sleep) and during the day (when awake) a study was conducted on acid-base balance of the blood (see table), which was evidence of hypoxemia and hypercapnia. On chest x-ray, community-acquired pneumonia was diagnosed.

Table; Studies of acid-base balance of the blood at night and in the morning according to our results.

Indicators	Time			Standards
	00:33	01:58	08:24	
pH (acidity)	7,37	7,34	7,33	7,35-7,45
pO_2 (partial oxygen pressure)	45,9	49,9	133,5	83-108 mm Hg. st.
PCO_2 (partial pressure of carbon dioxide)	59,5	55,7	53,5	32-48 mm Hg. st.
cO_2 (CT) (the concentration of oxygen) (venous)	11,3	10,9	13,7	37-42 mm Hg. st.
cBE (base excess)	7,9	3,9	1,6	-2,9-0 mmol/l
HCO_3-c ((concentration of bicarbonate ions) bicarbonate - vein	33,2	29,6	27,5	24-28 mmol/l

On 17.04.2019 there was deterioration in the acid-base balance of the blood (decreased pH, increased hypercapnia), increased respiratory failure, and fever – Respiratory support and antibacterial therapy were started. The child's condition continued to deteriorate. Medical sedation with (diazepam, rocuronium)was done. On inspection, tactile stimuli were negative. Fever was up to 41.0*c. The child was on ventilation through a nasotracheal intubation tube in the form of synchronized intermittent mandatory ventilation (SIMV) with FiO2 45%, positive end- of-expiration pressure (PEEP) +6 cm of water. On tracheal sanitization, an abundant amount of Muco-purulent sputum was noted. Hemodynamics were stable. Blood pressure was 110/57 mm Hg. heart rate 162 per minute. Repeated MRI examinations of the brain were performed in the hospital to exclude ROHHADNET syndrome. No pathologies were detected, and there were no volume lesions (see picture 1). In an extended genetic study, mutations in SWAG candidate genes - RET, GDNF, EDN3, BDNF, ASCL, PHOX2A, GFRA1, BMP 2, ECE1 – were not detected.



Picture 1. MRI of the child's brain (description in the text).

During the treatment, multicomponent therapy of respiratory failure was performed. Hypothalamic syndrome with vegetative-vascular disorders and thermoregulation disorders, psychasthenic syndrome, negativism, and emotional hyper-reactivity persisted. Gradually with therapy, neuropsychological symptoms regressed and clear consciousness was restored, she had adequate independent breathing when awake and fever subsided, speech functions were restored, was able to swallow, small and large motor skills were restored, she was able to walk independently, but had a wide gait and psychoneurological development of large motor skills were partially delayed. Taking into account the nature and specifics of the underlying disease, the child continued on non-invasive respiratory support during sleep with the following parameters: ST mode (Spontaneous-Timed, spontaneous-synchronized), peak inhalation pressure (PIP) 16 cm h. for example, positive end-expiratory pressure (PEEP) +5 cm of water. V., frequency of 20 breaths per minute. In July 2019, the child was discharged home in a satisfactory condition with recommendations for non-invasive ventilation during sleep and to continue diet changes. At present, the child's condition is satisfactory. There have been no fevers or episodes of desaturation when awake. During sleep, the child is on a non-invasive ventilator through a nasal mask with the above parameters. In General, therapy was positive. There have been satisfactory dynamics in growth rates and a decrease in the rate of weight gain due to diet changes.

CONCLUSION

ROHHAD-syndrome is currently a rare but actively studied disease. Due to the versatility of clinical manifestations, which often do not allow doctors to identify the main clinical symptom of the disease. The lack of reliable genetic criteria for ROHHAD-syndrome is a serious diagnostic problem for pediatricians, along with other sleep disorders. This clinical presentation demonstrates the need to take a good history and a thorough and comprehensive examination. Joint examination and management of such patients by a team of specialists is vital. The diagnostic criteria must include the detection of PaCO2 during daytime and at night (when child is awake and when asleep) – a key marker is a hypoventilation. Dynamic monitoring and management of patient data provide ventilation and oxygenation using invasive or non- invasive ventilation with mandatory monitoring of relevant indicators (PaO2, PaCO2); with exception of ROHHADNET-syndrome and pulmonary hypertension, which was carried out in this patient.

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