CLINICAL CASE

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CASES OF SYNDROME OF CONGENITAL CENTRAL HYPOVENTILATION (VTSG, CCHS, UNDIN SYNDROME) IN YAKUTIA

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Congenital central hypoventilation syndrome (CCHS, OMIM: 209880; CHS, ICD Q99, or "Ondine's curse syndrome") is a rare form of central sleep apnea, characterized by a loss of automatic and voluntary control of ventilation that causes apnea at sleep. The frequency of occurrence of the syndrome 1: 50000 - 200000 newborns [2]. This article presents 2 clinical cases of CCHS in children in the Republic of Sakha (Yakutia).

The first case of a child born in 2016, the diagnosis was confirmed at the age of 7 months. The second case is a child born in 2018, the diagnosis is confirmed up to 1 month of life. Both children were examined and treated in the perinatal center of "Republican Hospital No. 1 - National Medical Center" ("RH №1 – NCM"). The diagnosed congenital central hypoventilation syndrome was later confirmed by genetic studies in central clinics in Moscow and St. Petersburg. In clinical practice, hypodiagnosis of a given disease often occurs, which explains the rarity of its definition. Taking into account the clinical manifestations and depending on the degree of their intensity, early diagnosis prevents the undesirable effects of episodes of hypoxia and hypercapnia, ensures proper control of episodes of asphyxia and determines the prognosis of the disease. Since CCHS usually manifests itself in the neonatal period and mimics a variety of diseases, differential diagnosis requires the exclusion of various conditions involving alveolar hypoventilation, including congenital myasthenia, a number of myopathies, diaphragm dysfunction, and various lung and heart malformations.

Keywords: congenital central hypoventilation syndrome, Ondine's curse syndrome, hypoventilation, respiratory failure, PHOX2B gene.

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Introduction. Congenital central hypoventilation syndrome (CCHS, OMIM: 209880; CHS, ICD Q99, or "Ondine's curse syndrome") is a rare form of central sleep apnea, characterized by a loss of automatic and arbitrary control of ventilation, which causes apnea when falling asleep. This pathology was first described in 1962 by J. Severinghaus and R. Mitchell [6]. People with this disease are not able to breathe on their own during sleep. Along with apnea, the symptoms of this pathology include persistent cyanosis and emerging pulmonary hypertension.

The frequency of occurrence of the syndrome 1: 50000 - 200000 newborns [7]. Around 1,000 cases of CCHS have been described worldwide. In Russia there are registered 21 cases of this disease.

In the Republic Sakha (Yakutia) with a population of 964,330 people, 2 cases of CCHS were identified. The article presents these clinical cases. Congenital central hypoventilation syndrome is a genetic disease most often associated with the PHOX2B mutation in the 4p12 locus (in 93-100% of patients). Very rarely, the molecular genetic cause of the disease can be mutations in the *RET, GDNF, EDN3, BDNF* and *ASCL1* genes.

The classic CCHS syndrome is characterized by hypoventilation with normal respiratory rate and shallow breathing during sleep or during wakefulness and sleep, impaired autonomic nervous system, decreased sensitivity to hypoxia and hypercapnia, and the presence of neurocristopathy in some patients. After giving birth to a child with CCHS, this leads to the need for artificial ventilation. With age, there is a need to connect to the device during sleep. Genetic testing is required to confirm the diagnosis. Specialists from the Paris Hospital "Hospital des Enfants Malades" found that a special gene, called *Phox2B*, is associated with respiratory arrest. The analysis of the genes of 43 people with the syndrome of "the curse of Ondine" in comparison with 250 healthy people. At the same time, their parents did not have this defect, that is, the mutation was not inherited, but originated in the genetic set of germ cells.

The existence of an isolated dysfunction of autonomic centers, in the brainstem and hypothalamus, expressed by a decrease in the activity of adrenergic neurons, is shown in the structure of apnea. At the biochemical level, a decrease in the activity of adrenaline-synthesizing enzyme - phenylethanolamine-N-methyltransferase in different parts of the medulla oblongata, but most significant in the dorsal-median C2 field, which includes the nucleus gelatinosus, belonging to the nucleus tractus solitarius, and the posterior vagal nucleus was found. The cause of hypoventilation lies in the disorder of information integration at the level of the brain stem and is manifested in a violation of the transmission of impulses from the brain, setting in motion the respiratory muscles (diaphragm and muscles of the chest) [5]. Patients CCHS do not respond

to changes in the concentration of oxygen and carbon dioxide in the blood. This is due to the fact that the receptors in the blood vessels of the neck and brain do not send the correct impulses to the brain stem. The brainstem does not respond with increased respiratory stimulation when necessary. Patient CCHS does not feel, both consciously and unknowingly, that his breathing is insufficient, so that the breaths he makes remain superficial and the breathing rate is low. As a result, the supply of oxygen and the release of carbon dioxide are not sufficient. Clinical manifestations of CCHS are already in the neonatal period.

In foreign and domestic literature, polysomnography using specialized computer complexes is considered the "gold standard" for diagnosing sleep disorders [3]. Standard polysomnography allows you to reliably establish the type, type, severity, zone of localization of respiratory disorder.

Pending the results of testing *PHOX2B* genes, other causes of hypoventilation should be excluded. For differential diagnosis, an examination is necessary, including: chest X-rays; diaphragmatic fluoroscopy; electrocardiography and echocardiography; magnetic resonance imaging and / or computed tomography of the brain and brainstem; tests for metabolic disorders; comprehensive neurological assessment; polysomnography to establish the presence of hypoventilation and sleep-related breathing disorders.

The purpose of this study is to present a clinical case of CCHS syndrome, to examine the problem of diagnosing and treating patients with this very rare disease.

Materials and research methods. A pro- and retrospective analysis of the medical records of children with CCHS examined on the basis of the GAU RS (Ya) RH №1 - NCM was carried out.

Results and discussion.

Description of the first CCHS case. We happened to observe for a long time a boy who was born from a second pregnancy from a mother of 29 years old, somatically healthy, and a father of 28 years old, somatically healthy. It is known that the child's own and cousin's fathers died in infancy for an unclear reason.

The first pregnancy of the mother ended with the birth of a healthy boy. This pregnancy proceeded pathologically (the threat of termination in the second trimester, placental insufficiency, chronic hypoxia of the fetus, polyhydramnios). The boy was born in the conditions of the central regional hospital from the second spontaneous birth at the 37th week of gestation, in the head previa, body weight 3420 g, length 46 cm, rated on a Apgar scale 3/7 points. The state of birth is extremely severe, depression of consciousness was noted, reduced motor-reflex activity, progressive apnea, primary resuscitation measures were held in the delivery room, the child was transferred to a ventilator. On the 5th day at stabilization, the child was extubated, breathing in the NCPAP mode. Respiratory failure increased in dynamics, the boy was re-intubated and reconnected to the ventilator. As a child, an absentee consultation with specialists from the Yakutsk Republican Clinical Hospital (YRCH) was held. On the eighth day of his life, the boy was transferred to the resuscitation department of the YRCH in a very serious condition, caused by hypoxic-hemorrhagic damage to the central nervous system, respiratory insufficiency (RI), 3rd degree, and depressed consciousness. According to the results of the neurosonogram (NSG), on the eighth day of life, diffuse changes in the brain parenchyma, ventricular dilatation on the right, intraventricular hemorrhage (IVH), 2-3 degrees on the right, expansion of the third ventricle were detected. In the course of 22 days, internal and external hydrocephalus, echo signs of brain atrophy, and cystic leukomalation were revealed according to the NSG data. Radiography of the chest from the first day was observed hypoventilation. Based on the clinical picture, the data of laboratory and instrumental diagnostics, a clinical diagnosis was made: perinatal damage of the central nervous system of a hypoxic-hemorrhagic genesis of a severe degree. Syndrome of motor disorders. Complications: Cystic leucomalacia of the brain. Cortical atrophy. Internal, external hydrocephalus. Related diseases: ventilation-associated pneumonia. Pulmonary hemorrhage in history (on the 20th day of life). The child is transferred to neonatal reanimation unit of Perinatal Center of "RH №1 - NCM". During their stay in reanimation unit, the respiratory insufficiency of the 2–3rd degree remained in dynamics. When attempting to translate for independent breathing, episodes of apnea and bradycardia were noted. It was noted the absence of spontaneous breathing during sleep. At the age of 2 months, the child had generalized convulsions, in connection with which he was prescribed anticonvulsant therapy (depakin). When examined in a clinical blood test without inflammatory changes, CRP is negative. According to the results of radiography of the chest in the first 2 weeks revealed hypoventilation of the lungs, then without pathology. An echocardiography determined aneurysm of the secondary part of the interatrial septum with a discharge (0.33-0.35 cm), signs of pulmonary hypertension of 1 degree, tricuspid valve regurgitation of 1 degree, slight right ventricular myocardial hypertrophy (0.36 cm), separation of pericardial leaves, dilation of the right ventricle (1.0-1.1 cm), right atrium (2.0 cm), expansion of the pulmonary artery (0.92-0.93 cm). According to the results of Holter ECG monitoring, episodes of sinus bradycardia were noted at night. According to ENMG, the syndrome of impaired conduction along the median and peroneal nerves on both sides of moderate degree according to the axonal type. Signs of primary muscle damage was not detected. On MRI of the brain (in the age of 4 months.), The traumas of hypoxic-hemorrhagic brain injury in the perinatal period, internal triventricular hydrocephalus, cerebrospinal fluid normotension, periventricular hemorrhage foci in the anterior horns of MR signs of perinatal encephalopathy, retrotserebellyarnaya arachnoid cysts. According to MRI of the brain at the age of 8 months, a moderately pronounced internal occlusive triventricular hydrocephalus caused by a supracellular arachnoid cyst, cerebrospinal hypertension was described. The effect of arachnoid cyst on the third ventricle, interventricular orifices, on the chiasm, the pituitary stalk, on the pituitary gland, and on the brain legs was revealed. Compared with the previous study, an increase in the suprasellular cyst is determined, leading to occlusive hydrocephalus. At the age of 8 months, the patient has a ventriculo-peritoneal shunt (HPS).

A blood test was conducted at the Center for Molecular Genetics, aimed at finding private mutations in the *PHOX2B* gene. As a result of DNA analysis, an increased number of copies of the GCN-repeat with localization in the *PHOX2B* gene was revealed, which made it possible to confirm the diagnosis of CCHS syndrome. The boy continued to be in the neonatal reanimation unit on a ventilator, whose parameters changed in accordance with the dynamics of his condition. After a complete examination of the child, the final clinical diagnosis is made: Congenital central hypoventilation syndrome. Perinatal CNS lesion of mixed genesis severe. Occlusive hydrocephalus. Condition after HPS. Syndrome of motor disorders of the type of tetraparesis. Bulbar syndrome. Rough delay of psychomotor development. Partial atrophy of the optic nerves in both eyes. Complication: respiratory insufficiency II-III degree. The carrier tracheostomy. Related diseases: Iron

deficiency anemia 1 degree. Symptomatic epilepsy, generalized form, with primary-generalized seizures. Congenital heart defect: atrial septal defect. Regurgitation on TC 1 degree. Pulmonary hypertension 1 degree. Gastroesophageal reflux with esophagitis.

During the period of inpatient treatment (1 year, 1 month), the child repeatedly suffered from ventilation associated pneumonia. Since the disease is based on a congenital genetic defect and the boy needed constant mechanical ventilation in the future, and his hospital stay threatened with the constant development of hospital infections, it was decided to organize respiratory support at home. For this purpose, a detailed discussion was conducted with the parents of the child about possible complications in patients who were on long-term ventilation. He explained the conditions necessary to provide respiratory support at home. The parents agreed to the proposed treatment plan. At the moment, the boy is 2 years old, while awake, he can do without mechanical ventilation.

The presented observation demonstrates a complex case of diagnosis of congenital central hypoventilation syndrome, in which the diagnosis was established at 7 months of a child's life.

Description of the second case. A child from a mother of 28 years old with words practically healthy, second pregnancy, second birth. From the anamnesis, it is known that the first pregnancy in 2013 ended in operative childbirth on time, a healthy boy was born with a weight of 3940g, and a child from his first marriage. This pregnancy proceeded in the first half without features, in the second half a woman received amoxiclav about sore throat and by the end of pregnancy, lower limb edema was noted. Childbirth was operational in time, in the head previa, in a medical institution of the first level. Heredity through the mother of the child is not burdened. There is no information about hereditary diseases on the father's side.

A girl was born weighing 3730 g, height 55 cm, head circumference 36 cm, breast circumference 35 cm, with Apgar score of 8/9 points. At 40 minutes of life, the child had a worsening condition in the form of respiratory arrest. The child needed moistened oxygen. On the second day of life, the girl was transferred to a ventilator for a long apnea, bradycardia. On the fourth day, air ambulance entered the newborns reanimation unit of Perinatal Center of the "RB № 1-NCM" with a preliminary diagnosis: Hypoxic-ischemic damage of the central nervous system of the II degree, depression syndrome. Apnea newborn. Respiratory insufficiency III degree. During the initial examination, the condition is extremely serious, due to respiratory failure, neurological symptoms. She was conscious, motor activity, unconditioned reflexes were reduced, muscle tone was dystonic. Hemorrhagic syndrome was noted in the form of a small amount of hematomesis. Hardware breathing, auscultation of wired wheezing. Heart tones are rhythmic, clear. Soft abdomen, leaning. Liver and spleen are not enlarged. Peristalsis is sluggish. Transitional chair. Diuresis is sufficient.

A day after admission, the girl had episodes of apnea, bradycardia when trying to switch to independent breathing, according to ABS analyzes - decompensated acidosis, she was transferred back to mechanical ventilation. When examined, in a clinical blood test without inflammatory changes, in the analysis of the cerebrospinal fluid without features, the CRP is negative. According to radiography of the chest in the first 2 weeks described hypoventilation, then without pathology. When performing tracheobronchoscopy, the pathology of the structure of the bronchial tree is excluded. Neurosonography showed no structural changes. On echocardiography, a functioning arterial duct of 0.2 cm was described. According to the results of ECG monitoring, episodes of pronounced sinus bradycardia were noted at night. Additionally, MRI, CT scan of the brain, which did not detect structural changes in the brain, were performed.

In the dynamics persisted respiratory insufficiency II-III degree. It was noted the absence of spontaneous breathing during sleep, while waking was able to briefly disconnect from the ventilator. The child suspected CCHS syndrome. On day 25, DNA analysis was sent to the Center for Molecular Genetics in Moscow, where an increased number of copies of a GCN repeat located in the PHOX2B gene was detected in one of the chromosomes, which allowed to confirm the diagnosis of "central congenital hypoventilation syndrome". For further examination and treatment, the child on the ventilator has been transferred to the Federal State Budgetary Institution "V.A. Almazov Science Center" in St. Petersburg.

Presented observation demonstrates the case of early diagnosis of CCHS syndrome.

Conclusion. It should be remembered about the possibility of variability of the clinical picture, which can complicate the diagnosis of CCHS. Genetic counseling is necessary if a child is born with suspected CCHS. Early diagnosis of CCHS and timely initiated respiratory support avoid chronic hypoxia, irreversible damage to the central nervous system and ensure an adequate quality of life for the patient.

The problem of treating and monitoring patients with rare diseases is the lack of standards of care. The exact prevalence of this pathology in children is also unknown, which is primarily due to hypodiagnosis. The examples of children with CCHS clearly demonstrate the possibility of a positive prognosis in the case of timely recognition of the disease. Many successfully ventilated patients today are more than 20 years old, which suggests a normal life expectancy, despite the genetic defect. Lethal outcomes in patients with CCHS are associated with the inability to provide optimal ventilation. A child requiring round-the-clock fan support needs a tracheostomy and a home ventilator system. In order to increase mobility and improve the quality of life in the future, such children need implantation of a phrenic nerve stimulator, which is currently performed thoracoscopically when they reach the age of 18 months.

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