

PEDIATRICS

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A CLINICAL CASE OF SUCCESSFUL REHABILITATION OF A CHILD WITH UNDINE SYNDROME (CCHS-CONGENITAL CENTRAL HYPOVENTILATION SYNDROME, ONDINE SYNDROME, OMIM 209880)

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Abstract: The article describes a case of the combination of an orphan monogenic disease (Undine syndrome) with a disruption of methylation cycle (epigenetic status) and mitochondrial dysfunction. Correction of concomitant metabolic disorders has allowed improving the quality of life of the child.

KeyWords: Undine syndrome, synthropy, methylation, mitochondrial dysfunction



INTRODUCTION

Undine syndrome (central hypoventilation syndrome) is a rare orphan disease with an autosomal dominant type of inheritance. According to different authors, the incidence of the syndrome fluctuates [9, 41]. The syndrome was first described in 1962 by Severinghaus and Mitchell in three patients after surgical neurosurgical intervention [18]. Central hypoventilation syndrome is a disease of the respiratory system, which leads to apnea attacks during sleep. It may be congenital or acquired at a later age.

Possible causes include traumatic brain damage, particularly in the trunk. Congenital cases are rare and are associated with autonomous breath control deficiency [9,18]. The diagnosis can not be established immediately due to symptoms similar to pulmonary insufficiency [10].

Also there might be asymptomatic carriage among family members with a similar mutation. According to different authors, apnea develops mainly in sleep, but in severe cases it was noted during wakefulness.

Syndromes with late onset are very rarely described [13, 21, 40]. The authors do not bound the syndrome to a specific gender [10].

Furthermore, cases of sleep apnea are associated with neuroblastomas (tumors of sympathetic ganglia), Hirschsprung disease (partial agenesis of the enteric nervous system) [8], dysphagia (difficulty swallowing) are also described. Additional symptoms include darkening of the skin color which is associated with lack of oxygen, increased drowsiness, fatigue, headaches, and disturbance of night sleep (inability to sleep at night). Some patients may have sensitivity to sedatives and drugs. Reduced concentration of oxygen in erythrocytes also leads to hypoxia, which is caused by pulmonary vasoconstriction and hypertension, leading to pulmonary spasms [29]. Other symptoms comprise gastroesophageal reflux, ophthalmic disorders, convulsions, relapsing pneumonia, developmental delay, episodes of loss of consciousness and violation of temperature regulation [8].

As a rule, the syndrome results from congenital malfor-

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mation of the head or, more rarely, of the spinal cord. But it can also be caused by strokes, tumors, complications of neurosurgical interventions, consequences of neurodegenerative diseases, such as Parkinson's syndrome, multiple sclerosis [38]. Some patients develop the syndrome with impaired auditory potentials secondary to chronic alcoholism [20].

A genetic defect is associated with this syndrome, particularly a mutation in the PHOX2B gene (in 91% of cases) [21, 35], the 4p12 locus; this transcription factor is involved in the development of neurons [14, 15, 16, 19, 34]. This homeobox gene is important for the normal development of the autonomic nervous system. At the moment, the syndrome is characterized as a neurocristopathy or neural crest disease, from which a part of the autonomic nervous system occurs [18, 28].

As described in the literature, children develop episodes of apnea with cyanosis during the first months of life. Damage to the brain may not be present, but hypercapnia and hypoxia are noted. Polysomnography shows that a violation of ventilation is often noted during the slow-sleep phase. In extremely severe cases, the presence in other stages of sleep and wakefulness is described. Patients with Undine syndrome require constant monitoring of breathing, namely tracheostomy and ventilators and also oxygen therapy and agents for stimulating the respiratory system [19]. Recently, surgical correction of implanting the electrode into the diaphragmatic nerve has been carried out. Mortality among patients with this syndrome is high, unless breathing stimulation is used during sleep [40].

The American Thoracic Society established the following criteria for the diagnosis of Undine's syndrome [22]:

- adequate ventilation during wakefulness and hypoventilation with a normal respiratory rate and shallow breathing (decreased respiratory volume) during sleep, or hypoventilation, both during wakefulness and during sleep;
- absence or loss of reaction to hypercapnia and / or hypoxemia during wakefulness and sleep;
- absence of neuromuscular, pulmonary, cardiac diseases, as well as lesions of the brain stem;
- presence of a mutation in the PHOX2B gene;

- the presence of symptoms of autonomic nervous system dysregulation (decreased pupillary response to light, esophageal motility disorder, severe constipation even in the absence of Hirschsprung's disease, profuse sweating, lowering of basal body temperature, decreased perception of anxiety, etc.).

Taking into account that any monogenic or chromosomal syndrome is capable of some metabolic correction considering the revealed disorders, we performed a metabolic correction on the example of the presented clinical case and received a positive effect.

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose

To present a case of successful rehabilitation of a child with Undine's syndrome through normalization of concomitant metabolic disorders.

2.2 Subjects & Methods

The process of the child's examination involved administration of clinical-genealogical, syndromological, biochemical, molecular-genetic and instrumental methods of investigation.

3 RESULTS AND DISCUSSION

Proband N., a 3-year-old girl attended a medical appointment. On examination she was diagnosed with Undine syndrome (confirmed molecularly at 5 months, a mutation in the gene PHOX-2B).

Presentation: delayed psycho-motor and speech development (the child does not speak), weight deficit, episynrome, alopecia areata, stereotypes (strokes with brushes), atopic dermatitis, lack of attention, does not chew when tired, repeats head movements from side to side and beats her head.

Past history: she has been considered disabled since birth, when she had seizures with a frequency of 5-7 episodes a day and respiratory depression (was on ALV). She was diagnosed with intrauterine infections of unspecified

etiology, perinatal hypoxic-ischemic CNS lesion, oppression syndrome and motor disorders syndrome in the form of muscle hypotension. For a month she was on mechanical ventilation. At the age of 2 months her condition worsened due to respiratory failure, and she again was rendered auxiliary ventilation. During wakefulness breathing was independent, at night on ventilator. EEG was normal. There was an epipresence against the background of the cohitum (her mother also noted an increase in episcasis in the hot season).

Life history: a child from the third pregnancy (complicated by chronic pyelonephritis, ureaplasmosis, anemia), 2nd physiological birth in gestation period of 40 weeks. Weight at birth was 3380 g, height 51 cm. Apgar score was 5/6 points.

Features of the phenotype: blonde hair, foci of alopecia in the parietal and occipital areas, blue sclera, short filter.

Family history: cases of oncopathology, epilepsy, blindness of unspecified genesis.

On examination:

- biochemical blood assay: moderately reduced level of alpha-amylase, sodium; increased level of direct bilirubin;
- moderate hyperhomocysteinemia in the metabolites of methylation cycle;
- increased level of lactate when assessing metabolites of energy metabolism;
- moderately elevated level of magnesium and reduced level of copper when assessing trace elements in blood;
- hypermethioninemia in the case of nonspecific hypoacidemia when assessing amino acids.

MTHFR 677 T / T mutation was detected in the study of polymorphic variants of the genes of folate-methionine cycle enzymes.

Gas chromatography / mass-spectrometry of urine showed a change in metabolites indicating a violation in the Krebs cycle.

Assessment of presentation, history taking, phenotype features, clinical genealogy, as well as the results of additional diagnostic methods, allowed to establish **final diagnosis:**

Undine Syndrome. Insufficiency of methylene tetrahydrofolate reductase (polymorphism MTHFR 677 T / T). Disruption of the exchange of sulfur-containing amino acids. Moderate hyperhomocysteinemia. Mitochondrial dysfunction.

Metabolic status assessment showed a decrease in the level of amylase in the blood, moderate hyperbilirubinemia indicating a disruption of the gastrointestinal tract function (pancreatopathy, cholestasis), which must be taken into account when choosing therapeutic strategy.

Increased levels of magnesium may indicate its admission to the analysis, as well as a violation of the system of detoxification. The decrease in the level of copper indicates its insufficient intake in the body triggering a disruption of myelination of nerve fibers.

The presence of polymorphism MTHFR 677 T / T (pathological homozygote) in combination with a moderate increase in the level of homocysteine and methionine in the blood indicates a violation of the epigenetic status (disturbance of the methylation process), which, according to E.Ya. Grechanina et al. [2], on the one hand, increases the course of the underlying disease, and on the other hand, determines the possibility of therapeutic correction, including, the appointment of cofactor and diet therapy.

The increase in lactate level in the blood, the presence of disorders in the Krebs cycle (according to gas chromatography / mass-spectrometry of urine) suggests the presence of mitochondrial dysfunction, which requires a course of electro-tropic therapy. Replenishment of amino acids, including alanine (amino acid directly related to mitochondrial activity) makes it possible to regulate the energy capabilities of the body.

Thus, a complex therapy was prescribed, which included the correction of nutrition (hypomethionine diet, enrichment of the diet with foods high in copper, restriction of digestible carbohydrates and the introduction of whole grains cereals), as well as drugs normalizing the level (P-5-P, TMG) and stimulating energy metabolism (L-carnitine, coenzyme Q10, riboflavin, biotin, succinic acid). In the course of treatment within a month the child stopped cramping and reached the talking stage.

4 CONCLUSIONS

This case demonstrates the effect of synthropy, which is a combination of a rare orphan monogenic disease and metabolic disorders. Correction of the association of disrupted methylation cycle and mitochondrial dysfunction improved the quality of life of the child and led to stable positive changes. Thus, diagnosis and correction of metabolic disorders in monogenic and chromosomal syndromes gives a possibility to provide successful rehabilitation of patients.

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Received: 31-Mar. - 2017

Accepted: 23-Jun. - 2017