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Pitt–Hopkins syndrome clinical case

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ABSTRACT

Pitt–Hopkins syndrome is a rare pathology of the nervous system caused by a mutation in the *TCF4* gene, located in the 21st locus of the 18th chromosome. The incidence rate is currently unknown. The main phenotypic manifestations of the syndrome are facial dysmorphisms: a beak-shaped nose, short nasal passages, a wide mouth with an upper lip in the form of a "Cupid's bow", widely spaced teeth, deep-set eyes, upturned palpebral fissures, a single palmar crease and fetal finger pads. Also, in addition to external changes, patients have intellectual disabilities. Many patients are characterized by a delay in psychomotor development, noted already in the first year of life. Over time, the behavior of patients is often associated with autistic disorders, which complicates the diagnosis of this syndrome. We have described a clinical case of a girl who had complaints of delayed psychomotor development, which was noted from 4 months, sleep disorders, rare sudden paroxysmal states in the form of excitement, crying. During an in-depth examination, Pitt–Hopkins syndrome was suspected, which was later confirmed molecularly genetically. We performed direct Sanger sequencing, which resulted in the discovery of a mutation chr18:55228987C>T c.2045G>A (p.Arg682Gln) in the *TCF4* gene in a heterozygous state. The article reflects the theoretical aspects of Pitt–Hopkins syndrome, clinical features and requirements for diagnosing the syndrome using the example of a diagnostic search in a young child.

Keywords: Pitt–Hopkins syndrome, epilepsy, *TCF4*, apnea, hyperventilation, children

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Клинический случай пациента с синдромом Питта–Хопкинса

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АННОТАЦИЯ

Синдром Питта–Хопкинса — редкая наследственная патология нервной системы, причиной которой является возникновение патогенного варианта в гене *TCF4*, расположенном в 21 локусе хромосомы 18. Частота встречаемости в настоящее время неизвестна. Основными фенотипическими проявлениями синдрома являются лицевые дисморфии: клювовидный нос, короткие носовые ходы, широкий рот с верхней губой в виде «лука Купидона», широко расставленные зубы, глубоко посаженные глаза, птоз, поперечная ладонная борозда, фетальные пальцевые подушечки. Также, помимо внешних изменений, у пациентов отмечается тяжелая умственная отсталость. Для многих пациентов характерна задержка психомоторного развития, отмечаемая уже на первом году жизни. Со временем поведение пациентов часто ассоциируется с аутистическими расстройствами, что осложняет диагностику данного синдрома.

Описан клинический случай девочки, наблюдавшейся в связи с задержкой психомоторного развития, которую отмечали с 4 месяцев, нарушения сна, редкие внезапные пароксизмальные состояния в виде возбуждения, плача. В ходе углубленного обследования был заподозрен синдром Питта–Хопкинса, который в дальнейшем был подтвержден молекулярно-генетически (у ребенка выявлен патогенный вариант chr18:55228987C>T c.2045G>A (p.Arg682Gln) в гене *TCF4* в гетерозиготном состоянии). Таким образом, в статье отображены теоретические аспекты синдрома Питта–Хопкинса, клинические особенности и требования к его диагностике на примере диагностического поиска у ребенка раннего возраста.

Ключевые слова: синдром Питта–Хопкинса, эпилепсия, *TCF4*, апноэ, гипервентиляция, дети

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INTRODUCTION

Pitt–Hopkins syndrome is a rare hereditary disorder of the nervous system caused by a pathogenic variant in the *TCF4* gene located at locus 21 on chromosome 18, most often occurring sporadically.

This syndrome was first described by D. Pitt and I. Hopkins in 1978 in two unrelated children with similar external changes, abnormal breathing patterns, and psychomotor developmental delays [15]. In 2007, molecular karyotyping revealed that the clinical picture of Pitt–Hopkins syndrome is caused by a microdeletion of the long arm of chromosome 18.

Some patients with the clinical picture of Pitt–Hopkins syndrome appeared to have pathogenic variants in the *CNTNAP2* gene at 7q35.36 or in the *NRXN1* gene at 2p16.3. The inheritance pattern is autosomal recessive. These findings were subsequently named Pitt–Hopkins Like Syndrome 1 (PTHLS1) and Pitt–Hopkins Like Syndrome 2 (PTHSL2). Common features of PTHLS are mental retardation, absence of speech, and respiratory disorders, but in both PTHLS1 and PTHLS2, motor skills are normal or only slightly delayed. Facial features differ: the nose in PTHLS1 remains normal, and the upper lip is not curved [1, 2].

The prevalence of Pitt–Hopkins syndrome is currently unknown, however, in 2009, a study by J.A. Rosenfeld was published. The study screened 13,186 patients for mutations in the *TCF4* gene and microdeletions affecting *TCF4* regions, and analyzed the literature. The results suggest that the syndrome occurs from 1 in 34,000 to 1 in 41,000 people [16].

The *TCF4* gene encodes a protein that acts as a transcription factor [3, 4]. It initiates neuron differentiation by participating in the development of the fetal nervous system during pregnancy. In the embryo, the *TCF4* gene is expressed in the brain, retina, and internal organs, and postnatally in lymphocytes, fibroblasts, intestines, and muscles. The presence of pathogenic variants in the *TCF4* gene disrupts differentiation of the nervous system [13, 20]. Disruption of *TCF4* function leads to a decrease in signal transmission along one of the main signaling pathways responsible for embryogenesis and cell differentiation (the WNT pathway). As a result, neuronal precursor cells have reduced proliferation activity and the ability to differentiate into neurons [14].

Clinical phenotype. The main phenotypic manifestations of Pitt–Hopkins syndrome are facial dysmorphisms: beak-like nose, short nasal passages, wide mouth with a Cupid's bow-shaped upper lip, widely spaced teeth, deep-set eyes, ptosis, transverse palmar crease, and fetal finger pads. External changes are accompanied by intellectual disability. Many patients experience psychomotor retardation, which is already noticeable in the first year of life. Over time, the behavior of patients is often associated with autistic disorders: elevated mood accompanied by clapping, spinning, waving movements of hands, stereotypy [1, 2, 20].

Paroxysmal hyperventilation patterns followed by apnea, sometimes leading to cyanosis, are one of the most severe clinical manifestations of this syndrome. Symptoms usually begin between the ages of 3 and 7, but there are cases of later onset. This condition is characterized by short episodes of heavy breathing, followed by a period of breath holding with possible loss of consciousness. The pathophysiology remains unclear, but it is assumed that this type of pathology is caused by a dysfunction of the proteins which are responsible for brainstem formation as a result of defective *TCF4* [1, 2, 5, 17, 20].

In addition to specific symptoms, patients may have congenital developmental abnormalities: urogenital malformations, finger abnormalities (syndactyly, polydactyly), gastrointestinal tract pathologies (constipation, Hirschsprung's disease, reflux), ophthalmological problems (myopia, strabismus), scoliosis [1, 5, 20]. Magnetic resonance imaging (MRI) of the brain in patients with suspected Pitt–Hopkins syndrome may reveal changes such as corpus callosum dysplasia, bulging of the caudate nucleus heads, small hippocampus size, cerebellar cortex and vermis hypoplasia [7].

Epilepsy. Epileptic seizures occur in more than 40% of patients with Pitt-Hopkins syndrome [5, 7, 17]. They can debut at any age. There are virtually no detailed descriptions of electroencephalograms (EEG) in the literature. However, both focal and generalized abnormalities can be seen in EEG recordings. The EEG may be normal at an early age and acquire changes in the form of epileptiform activity as a patient matures [7].

Diagnosis. There are no specific tests for diagnosing Pitt-Hopkins syndrome, except for molecular genetic analysis in conjunction with clinical presentation.

To suggest a diagnosis, there is a specialized scale developed independently by S. Whalen (2012) and G. Marangi (2012) [11, 19].

The Whalen scale identifies several groups of signs. Frequent features, rated at +1 point: deep-set eyes; protruding middle or lower parts of the face; broad bridge of the nose; broad or beak-like nose; flared nostrils; large mouth; upper lip in the form of a "Cupid's bow"; everted lower lip; ataxic gait; convulsive states with hyperventilation; hypotonia; good-natured, smiling appearance; anxious behavior; strabismus. The following signs are scored at 2 points: severe motor development delay up to 3 years of age or the onset of independent walking after 3 years of age; absence of speech; stereotypical movements of the hands or head.

Signs that are not characteristic of Pitt–Hopkins syndrome are also indicated, for which 1 or 2 points are

deducted. These include microcephaly, tall stature, malformations of internal organs, and loss of previously acquired skills. When the final score is obtained, the number is evaluated according to the values acceptable for the patient's age. Up to 3 years of age, a score equal to or greater than 10, and after 3 years of age, a score of 15, suggests the presence of Pitt-Hopkins syndrome and warrants referral of a patient for screening to detect pathogenic variants in the *TCF4* gene.

The Marangi scale is partially similar to the previous version. It also includes a list of common phenotypic features of this syndrome, which are scored as 1, 2, or 4 points. In addition, the scale includes features of instrumental diagnostic results. The interpretation of age differences in the results is the same as in the Whalen scale.

With a final score of 10 or more out of 16 on the Marangi scale, a patient is also recommended to undergo screening for pathogenic mutations in the *TCF4* gene.

Differential diagnosis. The differential diagnosis includes Angelman, Mowat–Wilson, and Rett syndromes. Many patients with unsteady gait, lack of speech, and stereotypical behavior were diagnosed with Pitt–Hopkins syndrome after receiving the results of whole-genome sequencing using high-throughput next-generation sequencing (Next Generation Sequencing, NGS), where no data for differential pathologies were identified, but a pathogenic variant in the *TCF4* gene was detected [12, 17].

Treatment. The main focus in treating children with Pitt–Hopkins syndrome is symptomatic therapy based on physical therapy, speech therapy, and work on cognitive and motor disorders. Given the presence of psychomotor development disorders as well as pathologies of other systems, surgeons, gastroenterologists, pulmonologists, neurologists, and ophthalmologists may be involved in comprehensive therapy.

For older children, it is necessary to develop an individualized education plan, paying particular attention to the early mastery of alternative means of communication and behavior management strategies [5, 17].

CLINICAL CASE

Patient V., 2 years and 10 months old, has been under observation by a neurologist and pediatrician for 2.5 years due to psychomotor development delay, which could be traced back to the age of 4 months, as well as sleep disorders, and rare sudden paroxysmal states of agitation and crying.

Medical history: the child is from the second pregnancy (the first pregnancy in the same marriage resulted in a healthy girl, now 5.5 years old), which proceeded without complications. Parents deny consanguineous marriage. The second girl was delivered by cesarean section at 40 weeks. Apgar score — 7/8 points, birth weight 3400 g, body length 53 cm. The child and the mother were discharged from the maternity hospital on the 6th day. The neonatal period proceeded without complications. From an early age, she showed delays in motor and speech development. She has been able to hold her head up for 4 months and follow objects with her eyes since 6 months of age. Since 6.5 months of age, she has been able to roll over, pull herself up when her hands are pulled, coo and smile, pick up toys on her own, and transfer them from one hand to the other. The ability to sit independently appeared at 1.5 years of age, and at 2 years of age, she learned to stand and step over a support.

Medical history and examinations performed. At 9 months, due to developmental delay, a neurologist recommended an MRI of the brain, which revealed a small area of hyperintensity in the periventricular white matter of the right parietal region of the brain, probably of post-hypoxic nature, and moderately expressed mixed hydrocephalus. At 2 years of age, a repeat MRI was performed, which showed no significant changes compared to the previous MRI.

Phenotype characteristics. During an objective examination of the child at 1 year and 10 months of age, attention was drawn to the presence of abnormalities such as epicanthus, deep-set eyes, convergent strabismus, dysplastic auricles, a protruding long bridge of the nose and a rounded tip, a short philtrum, a large mouth with plump lips resembling "Cupid's bow". There are hemangiomas in the forehead and occipital regions, and two light brown spots on the left shin and right thigh, and flat-valgus foot posture. Taking into account the phenotypic characteristics, a karyotype study was performed: 46, XX — normal female.

At 2 years and 6 months, the child was consulted by a geneticist. Taking into account the previously described phenotypic features, delayed statical and motor and speech development, and changes in the MRI image of the brain, a hereditary pathology was suspected. When comparing clinical signs with the Whalen scale for assessing Pitt–Hopkins syndrome, the total score was 11. The child had signs rated at 1 point: deep-set eyes, prominent nasal bridge, broad nose, large mouth, hypotonia; as well as signs rated at 2 points: severe motor development delay, absence of speech, stereotypy. When considering the signs on the Marangi scale, the girl received 1 point for normal birth weight, motor discoordination, and MRI abnormalities; 2 points for intellectual disabilities and lack of speech; and 4 points for facial dysmorphia. Thus, the total score was also 11 points. According to the interpretation of the results, the child had indications for testing for pathogenic variants in the *TCF4* gene. At 2 years and 6 months, molecular genetic testing (whole-genome sequencing using NGS) was performed.

A pathogenic variant chr18:55228987C>T; c.2045G>A (p.Arg682Gln) was detected in the *TCF4* gene in a heterozygous state, which is associated with Pitt–Hopkins syndrome with an autosomal dominant pattern of inheritance. During confirmatory diagnosis using direct Sanger sequencing of the *TCF4* gene in the parents and child, the pathogenic variant chr18:55228987C>T c.2045G>A (p.Arg682Gln) in the *TCF4* gene in a heterozygous state was detected only for the child, confirming its *de novo* occurrence.

At 2 years and 9 months, video EEG monitoring was performed: no epileptiform activity or epileptic seizures were detected.

Physical examination at 2 years and 10 months of age revealed an average severity of the disease due to neurological deficits, with no impact on well-being. The skin was clear, except for the previously described hemangiomas and light brown spots, and the mucous membranes were clear and moist. The subcutaneous fat layer is evenly distributed; tissue turgor is sufficient. Physical development: weight 12 kg (z-score: –1.31), height 90 cm (z-score: –1.34), development is harmonious, below average. Auscultatory breathing is puerile, no wheezing, respiratory rate (RR) 23 per minute. Heart tones are rhythmic, heart rate (HR) 118 per minute. The abdomen is soft, accessible to palpation. The liver and spleen are not enlarged. Stool is formed, once every 2 days.

Neurological status at 2 years and 10 months: the girl reacts calmly to the examination. Stereotypical movements of the arms and legs are noticeable. The patient babbles, does not speak consciously, and does not understand spoken language. She does not follow simple commands and has not developed self-care skills. There is truncal ataxia. Muscle tone is diffusely reduced, without asymmetry. Tendon reflexes are lively, without asymmetry.

Final diagnosis. Based on complaints of paroxysmal states of phenotypic features combined with severe mental and speech development delays, delayed verticalization and independent walking, movement disorders (stereotypy, trunk ataxia), and the detection of a *TCF4* gene mutation, a diagnosis of Pitt-Hopkins syndrome was made.

Medical interventions. In this clinical situation, the girl needs to regularly attend rehabilitation activities and sessions with a speech therapist. Dynamic video EEG monitoring is also required for timely detection of epileptiform activity.

The prognosis for patients with this pathology is unfavorable, as the rehabilitation potential of existing intellectual and speech disorders is very low, with the possible subsequent development of epilepsy.

Analyzing the patient's clinical phenotype in comparison with the literature data, the following features can be noted. The presence of pronounced psychomotor development delay from the first months of life in the absence of data on asphyxia at birth or other intrauterine anomalies that could be the cause of these disorders (uncomplicated pregnancy, birth of a child with normal weight and height indicators and APGAR score) should lead a clinician to consider the possible presence of a genetic pathology. However, differential diagnosis of Pitt-Hopkins syndrome in the first year of life is not possible, even in combination with multiple stigmata and developing paroxysmal conditions, as the main clinical symptoms manifest at the age of 3–7 years. However, in this case, it was possible to assume the presence of a hereditary pathology based on the patient's medical history and phenotype, which allowed for timely molecular genetic testing. The detection of a pathogenic variant in the *TCF4* gene and the diagnosis of Pitt–Hopkins syndrome in a girl aged 2 years and 10 months allows us to develop a treatment and care strategy for the patient, as there is a risk of developing epilepsy with paroxysmal respiratory patterns of hyperventilation with apnea up to cyanosis.

A possible promising direction in treatment is gene therapy, but its achievements have only been described in mouse models. The methods are based on the use of histone deacetylase (HDAC) negative regulators [8, 9, 18], regulation of the signaling pathway responsible for embryogenesis and cell differentiation (WNT pathway) [8], regulation of ion channels [6], and the use of viral gene therapy [10].

CONCLUSION

The presented clinical case demonstrates a variant of Pitt–Hopkins syndrome, confirmed by molecular genetic testing. Treatment of disorders associated with this syndrome is currently very difficult. The patient requires comprehensive treatment involving a neurologist, psychotherapist, and speech therapist. Complete correction of this disease is not possible.

ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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Competing interests. The authors declare that they have no competing interests.

Consent for publication. The authors obtained written informed voluntary consent from the patient's legal representatives to publish personal data, including photographs (with face covering), in a scientific journal, including its electronic version.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный и равный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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