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DIFFICULTIES IN DIAGNOSIS OF NEUROFIBROMATOSIS TYPE 1 IN A CHILD

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Summary. Neurofibromatosis type 1 is one of the most common genetic diseases. It can be inherited in an autosomal dominant manner, but in almost half of the cases it occurs de novo. Neurofibromatosis type 1 is associated with café au lait spots, freckles in the inguinal and axillary areas, neurofibromas, Lisch nodules of the iris or choroidal anomalies, optic pathway gliomas and characteristic bone anomalies. In the world, the pathology occurs with a frequency of 1:3500 newborns. Mutation in the NF1 gene, which is located on chromosome 17 q11.2, leads to the inability to synthesize the cytoplasmic protein neurofibromin. This latter protein acts as a modulator of cell growth and differentiation, starting from intrauterine life, it is expressed by cells of the nervous system, endothelium and smooth muscles near blood vessels. The mutated protein and associated changes in the cellular environment lead to a very high risk of cerebrovascular changes. Deficiency of the NF1 gene leads to hyperactivation of RAS, which triggers the AKT/mTOR and Raf/MEK/ERK proliferation signaling pathways. As a result, benign neoplasms are formed - neurofibromas, which have a high tendency to malignancy. The gold standard for diagnosing neurofibromatosis type 1 is molecular genetic testing. The article provides information on the prevalence, clinical picture, diagnostic and treatment options for neurofibromatosis type 1, as well as our own clinical observation. The presented clinical case is interesting due to the progressive course of the disease in a child and the formation of multiple plexiform neurofibromas. Currently, there are no methods for preventing this pathology, but early diagnosis and targeted therapy improve the quality of life of patients. Targeted therapy can have a great impact and slow the growth of neurofibromas. Selumetinib is a selective inhibitor of mitogen-activated protein kinase types 1 and 2 (MEK 1,2). It blocks MEK activity and the Raf/MEK/ERK signaling pathway, which helps suppress the proliferation of tumor cells in which this signaling pathway is activated.

Key words: neurofibromatosis type 1, neurofibromas, children.

ТРУДНОСТИ ДИАГНОСТИКИ НЕЙРОФИБРОМАТОЗА 1 ТИПА У РЕБЕНКА

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Резюме. Нейрофиброматоз 1 типа является одним из наиболее распространенных генетических заболеваний. Он может наследоваться по аутосомно-доминантному типу, но почти в половине случаев возникает de novo. Нейрофиброматоз 1 типа ассоциируется с пятнами цвета кофе с молоком, веснушками в паховой и подмышечной областях, нейрофибромами, узелками Лиша радужки или хориоидальными аномалиями, глиомами зрительного пути и характерными аномалиями костей. В мире патология встречается с частотой 1:3500 новорожденных. Мутация в гене NF1, который находится в хромосоме

17 q11.2, приводит к неспособности синтезировать цитоплазматический белок нейрофибромин. Этот последний белок действует как модулятор роста и дифференциации клеток, начиная с внутриутробной жизни, экспрессируется клетками нервной системы, эндотелия и гладких мышц вблизи кровеносных сосудов. Мутировавший белок и связанные с ним изменения клеточной среды приводят к очень высокому риску цереброваскулярных изменений. Дефицит гена NF1 приводит к гиперактивации RAS, что вызывает запуск сигнальных путей пролиферации AKT/mTOR и Raf/MEK/ERK. В результате формируются доброкачественные новообразования – нейрофибромы, имеющие высокую склонность к малигнизации Золотым стандартом диагностики нейрофиброматоз 1 типа является молекулярно-генетическое тестирование. В статье приведены сведения о распространенности, клинической картине, возможностях диагностики и лечения нейрофиброматоза 1 типа, а также собственное клиническое наблюдение. Представленный клинический случай интересен прогрессирующим течением заболевания у ребенка и формированием множественных плексиформных нейрофибром. В настоящее время не разработаны методы профилактики данной патологии, однако ранняя диагностика и таргетная терапия улучшают качество жизни пациентов. Таргетная терапия может оказать большое влияние и замедлить рост нейрофибром. Селуметиниб является селективным ингибитором митоген-активируемой протеинкиназы 1 и 2 типа (MEK 1,2). Он блокирует активность MEK и сигнальный путь Raf/MEK/ERK, что способствует угнетению пролиферации опухолевых клеток, в которых активирован данный сигнальный путь.

Ключевые слова: нейрофиброматоз 1 типа, нейрофибромы, дети.

Introduction. Neurofibromatosis is a group of heterogeneous disorders characterized by the formation of tumors of the central and peripheral nervous system, skin and bone lesions [1]. There are 3 types of neurofibromatosis: neurofibromatosis type 1 (NF1) - 96%, neurofibromatosis type 2 (NF2) - 3% and schwannomatosis (SWN) - 1% [2]. Neurofibromatosis type 1 is one of the most frequently diagnosed diseases of the nervous system predisposing to cancer. In the world, the pathology occurs with a frequency of 1:3500 newborns. The disease is inherited in an autosomal dominant manner, but in approximately 50% of individuals it is caused by a spontaneous de novo mutation [1,3].

The first sporadic descriptions of patients with skin tumors in neurofibromatosis type 1 appeared in 1642 in the treatise of the Italian scientist U. Aldrovandi "History of Monsters". In 1882, the German pathologist F.D. von Recklinghausen gave a complete scientific description of the clinical and morphological changes in a patient with neurofibromatosis [4]. Since this was long before the discovery of DNA, the disease began to bear his name - Recklinghausen's disease. Almost a hundred years later, in 1987, D. Berker conducted the first mapping and identified the gene for neurofibromatosis type 1 [3]. In 1988, the US National Institutes of Health held a conference on neurofibromatosis with the goal of developing consistent criteria for its diagnosis [5].

The cause of the disease is damage to the NF1 gene located on chromosome 17q11.2, encoding the tumor suppressor protein neurofibromin. This protein is a RAS-GTPase activator, produced in neurons, oligodendrocytes and Schwann cells [6]. Normally, neurofibromin interacts with the product of the RAS proto-oncogene, inhibiting its function and implementing dynamic control over cell growth. Deficiency of the NF1 gene leads to hyperactivation of RAS, which triggers the AKT/mTOR and Raf/MEK/ERK proliferation signaling pathways. As a result, benign neoplasms are formed - neurofibromas, which have a high tendency to malignancy [2,6].

The mutation rate of the NF1 gene is one of the highest in all known human diseases, which explains the variability of the clinical picture [3]. Skin manifestations in the form of "café au lait" spots are considered the most common changes in NF1, they are usually the first sign of the disease [5]. Freckles in the groin and axillary areas are characteristic, less often diffuse over the entire body [7]. Cutaneous neurofibromas are present in almost all patients with NF1, they appear in adolescence and are located on the trunk, then spread to the limbs, neck and face. Unlike cutaneous neurofibromas, plexiform neurofibromas are found in 50% of patients, often attract attention in early childhood and are considered congenital [2,5]. Gliomas of the optic pathway are observed in 15-20% of children [8]. Skeletal abnormalities associated with NF1 include macrocephaly, short stature, and osteopenia, as well as localized bone dysplasias (sphenoidal wing dysplasia, long bone dysplasia, and dystrophic scoliosis) [2]. Scoliosis may affect 10–26% of people with neurofibromatosis, making annual spinal

examinations essential during childhood and early adolescence. Approximately 50% of children with NF1 have learning disabilities, as well as increased susceptibility to autism spectrum disorders [7].

The diagnosis of NF1 is based on the clinical criteria recommended by the National Institutes of Health (NIH, 1987) Consensus, which include at least 6 café-au-lait spots, 2 cutaneous or subcutaneous neurofibromas, 1 plexiform neurofibroma, axillary or inguinal freckles, optic glioma, Lisch nodules (iris hamartomas), and characteristic bone lesions. A combination of at least 2 of these criteria is required to make a clinical diagnosis of NF1 [4,9].

Surgery is the main treatment for neurofibromas, but it has a high recurrence rate because plexiform neurofibromas are difficult to remove entirely due to interdigitation into normal tissues and peripheral nerves. Persistent pain at the site of a plexiform neurofibroma may indicate malignancy. It is important to note that plexiform neurofibromas have a lifelong risk of malignant transformation [2,9]. Chemotherapy is a potential therapeutic option for plexiform neurofibromas.

Targeted therapy can have a great impact and slow the growth of neurofibromas. In April 2020, the US Food and Drug Administration (FDA) approved the use of selumetinib (KOSELUGO, AstraZeneca) for children with NF1 from 2 years of age with inoperable plexiform neurofibroma [10]. Selumetinib is a selective inhibitor of mitogen-activated protein kinase types 1 and 2 (MEK 1,2). It blocks MEK activity and the Raf/MEK/ERK signaling pathway, which helps suppress the proliferation of tumor cells in which this signaling pathway is activated. Other MEK inhibitors, such as trametinib and binimetinib, have also shown positive preliminary results [8,10].

The aim of the work was to describe our own clinical observation of the course of neurofibromatosis type 1 in a 13-year-old child.

A clinical case. Patient I., born in 2011. From the anamnesis it is known that the child is from the 2nd pregnancy (1st pregnancy - miscarriage, 3rd pregnancy - healthy child), which proceeded with gestosis and ureaplasmosis in the 2nd trimester. The first term labor, spontaneous. Body weight at birth is 3100 g, body length is 51 cm, head circumference is 34 cm, chest circumference is 33 cm, Apgar score is 8/9 points.

The boy grew and developed in accordance with his age. Past illnesses - acute respiratory viral infection, chickenpox. Preventive vaccinations were carried out according to the national calendar. The allergological anamnesis is not burdened.

It is known from the anamnesis that at the age of 3, pigment spots of the color "coffee with milk" appeared on the child's body, but the parents did not contact a pediatrician with this complaint. At the age of 5, the boy was operated on at the State Budgetary Institution of the Rostov Region "N.V. Dmitrieva Regional Children's Clinical Hospital" (Ryazan) for fibroma of the occipital region.

At the age of 7, the parents noted complaints of swelling in the chin and neck area, the child was examined by a pediatric oncologist and geneticist at the consultative and diagnostic center of the State Budgetary Institution of the Rostov Region "N.V. Dmitrieva Regional Children's Clinical Hospital".

According to medical records, an objective examination of the child revealed a “coffee with milk” colored spot measuring 15.0 x 8.0 cm on the anterior surface of the body, as well as multiple pigment spots measuring from 1.0 x 0.5 cm to 3.0 x 3.0 cm on the skin of the trunk and limbs (Figure).

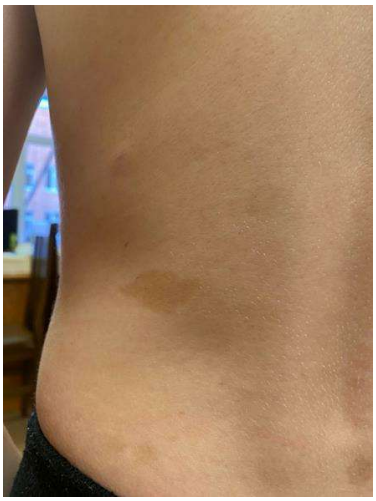

Figure. Multiple pigmented spots of the color "cafe-au-lait spots" on the skin of the back.

According to the results of ultrasound examination of soft tissues of the neck (03.03.20), subcutaneous formations with a heterogeneous structure were found symmetrically on both sides in the area of the sternum and the upper posterior surface of the neck.

According to MRI data of soft tissues of the neck (06.03.20), an MR picture of a solid formation of subcutaneous fat tissue of the craniovertebral region and soft tissues of the neck with spread to the anterior chest wall, as well as to the upper mediastinum and spinal canal at the level of the C1-C2 segment is noted.

Complete blood count (03.03.20): erythrocytes – 4.68×1012/l, hemoglobin – 132 g/l, MCV – 78.6, MCH – 28.2, platelets – 409×109/l, leukocytes – 6.35×109/l, eosinophils – 8%, band cells – 1%, segmented cells – 46%, lymphocytes – 34%, monocytes – 11%, erythrocyte sedimentation rate – 5 mm/h.

Blood biochemistry (11.04.20): C-reactive protein is negative, LDH is 442.7 U/L, AST is 23.7 U/L, ALT is 16.0 U/L, total bilirubin is 12.1 μmol/L, total protein is 74.1 g/L, urea is 3.0 mmol/L, creatinine is 45.4 mmol/L, Na is 143.1 mmol/L, K is 3.82 mmol/L, Ca is 2.33 mmol/L, P is 1.02 mmol/L, ferritin is 7.7 μg/L.

MRI of the brain (06.03.20) shows a picture of isolated focal changes in the brain tissue, as a manifestation of dysmyelination in NF1. The child was given a preliminary diagnosis of neurofibromatosis type 1.

In August 2020, to confirm the diagnosis, the boy underwent a molecular genetic study at the Dmitry Rogachev National Medical Research Center for Pediatric Hematology and Oncology (Moscow): a deletion of one nucleotide c.7009delG in a heterozygous state was found in the NF1 gene in exon 47, leading to a shift in the reading frame and the formation of a premature stop codon p.Glu2337LysfsTer38.

Results of the histological examination dated 08/15/20: plexiform neurofibroma of the occipital region on the right, has expression of EMA, GLUT1, S100, CD34. The child was clinically diagnosed with neurofibromatosis type I, histologically verified plexiform neurofibroma of the occipital region on the right.

In August 2022, in order to search for a known mutation, a study of the biological material of the nuclear family was conducted at the N.P. Bochkov Research Center for Medical Genetics (Moscow) using DNA sequencing: the boy was found to have a heterozygous deletion in exon 47 of the NF1 gene: NM 000267.3: c.7009del, NP 000258.1: p.Glu2337fs, chr17:29670035.

The mother was also found to have a heterozygous deletion in exon 47 of the NF1 gene: NM 000267.3: c.7009del, NP 000258.1: p.Glu2337fs, chr17:29670035. The father and younger brother did not have a heterozygous deletion in exon 47 of the NF1 gene.

The boy was recommended pathogenetic therapy with the drug "Koselugo" (Selumetinib). The issue of its provision is currently being resolved.

Conclusions. Thus, this clinical case demonstrates the heterogeneity of the manifestations of neurofibromatosis type 1. The first signs of the disease are nonspecific, appear after birth and usually progress over time. Therefore, for timely diagnosis and optimal tactics of managing patients with neurofibromatosis type 1, specialists should be aware of the various clinical features of this disorder. Children with this pathology require an interdisciplinary approach and continuity in therapy throughout their lives.

According to the literature, the prognosis of the disease is ambiguous. Complications of neurofibromatosis are diverse and include blindness due to optic nerve glioma, vascular disorders associated with NF1-specific vasculitis, pathological bone fractures, attention deficit hyperactivity disorder, cosmetic defects [1,2]. In addition, patients with NF1 have an increased susceptibility to the development of pheochromocytoma, sarcoma, melanoma and breast cancer [8,11].

Neurofibromatosis type 1 has a high degree of variability in clinical presentation, which complicates clinical diagnosis, especially in early childhood. Accurate diagnosis of NF1 is important for individualized clinical care, multidisciplinary approach and genetic counseling. Pediatricians play a crucial role in improving the diagnosis of this disease. All patients with NF1 require careful periodic monitoring to minimize the risk of serious complications.

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