E.A. Tkachuk, T.A. Astakhova, L.V. Rychkova, O.V. Bugun, T.A. Belogorova, T.V. Taskaeva

A CLINICAL CASE OF HUNTINGTON'S DISEASE

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The article presents a clinical case of Huntington's with the aim of analyzing the causes of difficulties in making a diagnosis. The etiopathogenetic basis of the disease is given. It is noted that Huntington's disease is a disease caused by the expansion of tandem microsatellite repeats. It has been shown that as a result, a mutant huntingtin protein is synthesized, which plays an important role in the formation of the nervous system in the embryo.

A clinical case is described in a child diagnosed with Huntington's disease (Westphal form), confirmed by molecular genetic research: CAG repeats were detected in the first allele of the HTT gene. It is noted that during diagnosis, an important point is to determine the type of inheritance and determine the Sherman effect and anticipation.

Keywords: Huntington's disease, Huntingtin, Sherman effect, anticipation.

Introduction. The prevalence of neurodegenerative diseases is of great concern to scientists worldwide, and the study of the course and clinical prognosis is highly relevant.

Huntington's disease (HD) is a severe hereditary degenerative disease of the nervous system, which is characterized by a progressive course, inherited diseases of the nervous system, motor, cognitive and psychiatric disorders. The striking clinical manifestation of HD is extrapyramidal hyperkinesias. The disease is transmitted by autosomal dominant type of inheritance and is characterized by complete penetrance, antisense, and the effect of paternal transmission [3].

The disease is based on an increase in trinucleotide repeats of the CAG of the HTT gene, located on chromosome 4 in exon 1 (4p.16.3). The gene encodes a protein called gentingtin, which plays an important role in the formation of the nervous system in the embryo. Gentingtin is a large protein with a molecular mass of 348 kD and consists of several domains. It is believed that gentingtin provides cell signaling, supports vesicular transport, synaptic transmission, and is involved in the regulation of cellular autophagy and apoptosis, association and dissociation of intracellular proteins [1]. Gentingtin expression is predominant in the brain (neurons of striatum, pale globe, thalamus, cerebral cortex, glial cells). It is also expressed in testes, heart, liver and lungs [6]. In the cell, the protein is localized predominantly in the nucleus and cytoplasm surrounding the nucleus. However, gentingtin is considered a poorly studied protein and its functions are poorly described.

The gentingtin protein in the first exon normally contains up to 35 CAG repeats, each of which encodes glutamine as part of the protein. An increase in CAG repeats over 35 leads to an increase in the glutamine content of the polyglutamine portion of the protein. Abnormally elongated due to glutamine, gentingtin loses its normal properties, loses its quaternary structure, and forms intracellular amyloid-like inclusions due to polyglutamine aggregation. As a result, the altered protein penetrates into cell nuclei, initiating neurodegeneration. The mechanisms of neurodegeneration are oxidative stress, microglial activation, excitotoxicity (glutamine toxicity), mitochondrial dysfunction, apoptosis, disorders of morphology and physiology of neuronal transport systems, dysregulation of transcription, and dysfunction of proteins aggregating with mutant gentingtin [6].

As a result of neglected molecular genetic mechanisms, severe clinical manifestations develop, which are largely determined by the amount of glutamine residues of gentingtin and the quality of available compensatory mechanisms.

Materials and Methods. Clinical case

A child (boy), 13 years old, complains of speech, memory and concentration disorders (with a tendency to worsen), slowness, involuntary and irregular movements in various muscle groups (mainly in the hands), "rotational" body movements. Low motivation for learning, prolonged falling asleep, bruxism (rare) are also noted.

With the above complaints has been observed by a neurologist since 2021 after hospitalization in November 2021 in the neuropsychiatric department of OGKUZ IODKB (Irkutsk Regional Children's Clinical Hospital). He was examined by a geneticist. After hospitalization, the diagnosis was made: unspecified encephalopathy with cognitive impairment. Associated diagnosis: mild mental retardation without pronounced behavioral disorders; motor disorders; high degree myopia; complex myopathic astigmatism.

He was examined and treated in OGKUZH IOKPB No. 1 (Irkutsk Regional Clinical Psychiatric Hospital No. 1). Diagnosis: Mild mental retardation with persistent pronounced disorders

TKACHUK Elena Anatolievna – MD, Professor, Department of Pathological Physiology and Clinical Laboratory Diagnostics, FSBEI HE Irkutsk State Medical University MH RF; senior researcher, Laboratory of Psychoneurosomatic Pathology of Childhood, FSBSI Scientific Center for Family Health Problems and Human Reproduction, Irkutsk, Russia; e-mail: zdorowie38@gmail.com, ORCID: 0000-0001-7525-2657; **ASTAKHOVA Tatiana Alexandrovna** – MD, PhD, Research Associate, Laboratory of Cardiovascular Pathology, Pediatrics Department, FSBSI Scientific Center for Family Health Problems and Human Reproduction, Irkutsk, Russia. e-mail: tatjana_astahova@mail.ru, ORCID: 0000-0003-1427-4734; **RYCHKOVA Lyubov Vladimirovna** – MD, corresponding member RAS, Director, FGBNU Scientific Center for Family Health Problems and Human Reproduction, Irkutsk, Russia. e-mail: rychkova.nc@gmail.com, ORCID: 0000-0003-2910-0737; **BUGUN Olga Vitalievna** – MD, chief physician of the Clinic of FSBSI Scientific Center for Family Health Problems and Human Reproduction, Irkutsk, Russia. e-mail: clinica_zam1@inbox.ru, ORCID: 0000-0001-7716-014X; **BELOGOROVA Tatiana Albertovna** – head of the neurological department of the Clinic of the FGBNU Scientific Center for Family Health Problems and Human Reproduction. e-mail: belogorova.tat@gmail.ru, ORCID: 0000-0001-7429-7992; **TASKAEVA Tatyana Vladimirovna** – neurologist of the neurological department of the Clinic of the FSBSI Scientific Center for Family Health Problems and Human Reproduction, e-mail: taskaeva50@gmail.ru, ORCID: 0000-002-0310-5612

of asthenic, passive-dependent types, with pronounced mental infantilism, pronounced emotional-volitional disorders on the background of residual organic insufficiency of the CNS (dysontogenetic, neurodegenerative genesis) with motor stereotypes.

For further observation he was sent for hospitalization to the Clinic of the Scientific Center for Family Health Problems and Human Reproduction.

Child from 3 pregnancies. The first pregnancy - a boy of 22 years old (healthy), the second pregnancy was a medical abortion. Pregnancy proceeded against the background of threatened termination of pregnancy. The labor was independent at the term of 40 weeks. Apgar score 7-8 points. Birth weight 3686 g, height 53 cm. Discharged from the maternity hospital with the diagnosis of perinatal lesion of the central nervous system (CNS) of mixed genesis. He was breastfed until the age of 1 year. Neuropsychiatric development was delayed. The genealogical anamnesis on the paternal side (father and grandfather) shows Huntington's disease.

Objective. At the time of examination, no disorders on the part of somatic organs were detected. There is a decrease in body weight (at height 156.3 cm, weight 40.2 kg, body mass index (BMI) 16.5 units), but according to WHOAnthroPlus body weight is normal.

The main severity of the disease is determined by neurological pathology. Olfaction is not impaired, he can see. Pupil reaction to light is alive, eyeball movement is in full volume, convergence is weakened. Eye slits D=S. Trigeminal points are painless. The face is symmetrical. Sensitivity on the face is preserved. Chewing muscles tense enough, chews slowly. Hearing is preserved. No nystagmus. The pharyngeal reflex is positive. Low standing of the wishbones of the soft palate. Head movements in full volume. Tongue along the center line, with a slight deviation to the left. Movement in full. Muscle tone is altered by extrapyramidal type in the muscles of the hands. Fine motor skills are insufficient. Muscle strength is sufficient. Tendon and periosteal reflexes from the hands are enlivened D=S, from the legs are enlivened D=S. No pathologic reflexes. Meningeal signs are negative. Dermographism is red, persistent. In Romberg's pose sTable. Coordination tests: paltsenosovaya, patellofemoral test performs slowly, does not miss. Palpation of paravertebral points and percussion of spinous processes are painless. Gait is not grossly disturbed. Walking on heels, toes, jumps. Dermographism is red, persistent, hyperhidrosis of palms and feet is noted. Sensory disorders are not revealed. The function of pelvic organs is controlled. Involuntary and unregulated movements in the hands are noted. He is oriented in place, time and identity. She reacts positively to the examination, enters into verbal contact, responds in one-word answers. There is a violation of sound pronunciation. Instructions are carried out after repetition. There is a decrease in intellectual functions.

Consulted by an endocrinologist: no endocrine system disorders were found. Ultrasound (ultrasound examination) of the thyroid gland and ultrasound of the adrenal glands without peculiarities.

An interference EMG (electromyogram) of the tibia muscles was performed: at rest, spontaneous activity of fibrillation potentials on the right side was recorded; after tonic tests, fibrillations and pseudomyotonic discharges were noted (Fig. 1).

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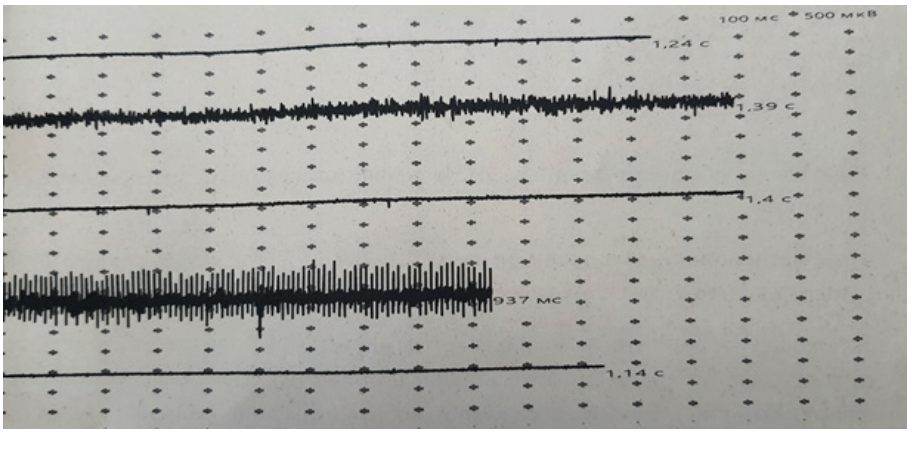

Electromyography of the child's lower leg muscles (fibrillations and pseudomyotonic discharges)

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EEG (electroencephalogram) shows moderate changes in bioelectrical activity, alpha rhythm is significantly disorganized, predominant in the right occipital region, frequency 9.6-11.4 Hz and amplitude up to 41 μV. No epileptiform activity was registered.

Magnetic resonance imaging (MRI) revealed an MRI picture of external, open, moderately pronounced hydrocephalus, diffuse signals from the heads of caudate nuclei and shell on both sides. Indirect signs of intracranial hypertension were detected.

The child has been counseled by a geneticist. Presumptive diagnosis of Huntington's disease, Westphal's form. Referred for genetic testing in the HTT gene.

A genetic examination for Huntington's disease revealed CAG repeats in the first allele of the HTT gene 77 (corresponding to a pronounced expansion) and 15 in the second allele (corresponding to the norm). The diagnosis of Huntington's disease, Westphal form, was confirmed. Treatment has been prescribed.

Discussion of results. The clinical manifestations of Huntington's disease are well and thoroughly described. Characteristic clinical symptoms, autosomal dominant type of inheritance and progressive course of the disease allow to assume with high accuracy that the patient has HD. The effect of paternal transmission, the Sherman effect (the possibility of increasing the number of repeats in each subsequent generation) and, as a consequence, anticipation (the effect of aggravation of clinical manifestations of the disease) are not unimportant additional features that allow to suspect HD. However, the "gold standard" of diagnosis verification is DNA diagnosis with determination of the number of CAG repeats in HTT gene alleles [2]. The diagnostic value is more than 36 copies of trinucleotide CAG repeats.

The important role of gentingtin in living organisms is emphasized by the fact that homologous proteins encoded by homologs of the HTT gene have been found in many animals, starting with protozoa. It is a large protein with a molecular mass of 348 kD, consisting of several domains. Its main functions are currently known. Gentingtin is required to maintain the clonal potential of neural stem cells during the process of neural induction (in the experiment HTT gene knockout mice died before the development of the nervous system); Gentingtin controls the interaction between neuroepithelial cells. Gentingtin participates in the formation of the protein framework by interacting with b-tubulin and binds to microtubules, localizes at the poles of the spindle during mitosis (controlling the orientation of the spindle), and regulates the processes of intracellular transport (by interacting with the dynein/dynactin complex). It is known that gentingtin is a regulator of transcription, affecting brain-derived neurotropic factor (BDNF) through regulation of the transcription factor REST/NRSF, which negatively affects the regulation of BDNF. The interneuronal function of genentigtin is important for the proper formation of

excitatory synapses of the cortex and striatum [7,8].

Formation of mutant gentigntin causes proteolysis and formation of toxic glutamine fragments of gentigntin that aggregate in the cell, transcription is impaired due to inhibition of histone acetyltransferase activity, chromatin condensation and BDNF (neurotrophin that stimulates and supports neuronal development), protein homeostasis and mitochondrial function are disturbed, ATP production is reduced, axonal transport, synaptic transmission and transport of organelles (mitochondria, autophagosomes and synaptic vesicles) are disturbed, synaptic plasticity is disturbed and excitotoxicity is formed, and neuroglia dysfunction occurs due to disruption of glutamate capture by astrocytes [5].

All this leads to severe neurological changes. In this clinical case, the detected 77 trinucleotide CAG repeats caused severe neurological changes at an early age. The first clinical manifestations could be seen immediately after birth, which was recorded as perinatal CNS lesions and delayed neuropsychiatric development. However, until the age of 10, neurodegenerative changes developed relatively slowly, the child attended a general education school and only in the 7th grade was transferred to a remedial school.

Despite the fact that the child was repeatedly examined, the diagnosis could be esTableished only by the age of 13 years. This is due to difficulties in determining the type of inheritance [4] due to the fact that the family lives without the father and has no information about the father's health status and the health status of relatives on the father's side. After repeated examinations by specialists, the mother still managed to recall some abnormalities in the neuropsychiatric condition of the father and grandfather on the father's side. It was noted that the grandfather's neuropsychiatric state was less disturbed than the child's father's. This made it possible to suspect the presence of tandem microsatellite repeat expansion disease and eventually make a diagnosis.

Conclusion. Timely diagnosis of Huntington's disease is an important aspect of patient care. Tandem microsatellite repeat expansion diseases are often difficult to diagnose, as are neurodegenerative diseases. The main tool to help esTableish the correct diagnosis is the determination of the type of inheritance. However, an obstacle in its determination is the difficulty in collecting (or inability to collect) genealogical anamnesis, which significantly increases the time of diagnosis of the disease. The fundamental signs that allow to suspect expansion diseases are the Sherman effect and anticipation, and it is these that should be paid attention to in the first place in the diagnosis. An important point in the diagnosis of hereditary pathology is the timely consultation of the patient by a geneticist and his examination in a specialized department of hereditary pathology.

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