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DIFFICULTIES IN DIAGNOSING HEREDITARY NEURODEGENERATIVE DISEASE IN A CHILD

N.A Belykh[1*], Yu.B. Starodubtseva[2], M.A. Sologub[1***], I.V. Piznyur[1****]**
[1]Ryazan State Medical University named after Academician I.P. Pavlov
(Rector - MD, Prof.Kalinin R.E),
Ryazan, Russian Federation
[2]Kolomna Central District Hospital (Chief Physician - Mitin O.V.),
Kolomna, Russian Federation

nbelyh68@mail.ru
*https://orcid.org/0000-0002-5533-0205
dokstarodub@gmail.com
**https://orcid.org/0000-0003-2361-9925
mihailsologub99@gmail.com
***https://orcid.org/0000-0001-9268-2325
innaabramova@yandex.ru
****https://orcid.org/0000-0002-9267-439X

Summary. Neurodegenerative diseases represent a wide range of diseases of different nature, caused by the gradual death of individual groups of nerve cells and characterized by steadily progressive neurological deficits, including motor disorders, psychoemotional and cognitive (up to dementia) disorders and epileptic seizures. The most common neurodegenerative pathology in children is neuronal ceroid lipofuscinosis. The article describes data on the prevalence, features of the therapy of this pathology, and also presents a clinical case with the onset of the disease in a child aged 2 years 11 months. The clinical case demonstrates the difficulties of diagnosing this pathology due to the rarity of this pathology, a wide range of differential diagnostics, the duration and high cost of molecular genetic studies. An early examination would make it possible to explain the nature of epilepsy, to choose a rational therapy for this disease in a timely manner.
Key words: neuronal ceroid lipofuscinosis, child, epilepsy.

ТРУДНОСТИ ДИАГНОСТИКИ НАСЛЕДСТВЕННОГО НЕЙРОДЕГЕНЕРАТИВНОГО ЗАБОЛЕВАНИЯ У РЕБЕНКА

Н.А. Белых[1], Ю.Б. Стародубцева[2], М.А. Сологуб[1], И.В. Пизнюр[1]
[1] Рязанский государственный медицинский университет имени академика И.П. Павлова (ректор- д.м.н., проф. Калинин Р.Е),
г. Рязань, Российская Федерация
[2] Коломенская центральная районная больница
(главный врач- Митин О.В.),
г. Коломна, Российская Федерация

Резюме. Нейродегенеративные заболевания представляют собой широкий спектр различных по своей природе болезней, обусловленных постепенной гибелью отдельных групп нервных клеток и характеризующихся неуклонно прогрессирующим неврологическим дефицитом, включая двигательные расстройства, психоэмоциональные и когнитивные нарушения и эпилептические приступы. Наиболее частой нейродегенеративной патологией у детей является нейрональный цероидный липофусциноз. В статье описаны данные о распространенности, особенностях терапии данной патологии, а также представлен клинический случай с дебютом заболевания у ребенка в возрасте 2-х лет 11 месяцев. Клинический случай демонстрирует трудности диагностики данной патологии вследствие редкости данной патологии, широкого круга дифференциальной диагностики, длительности и высокой стоимости молекулярно-генетических исследований. Раннее обследование позволило бы объяснить природу эпилепсии, своевременно подобрать рациональную терапию данного заболевания.

Ключевые слова: нейрональный цероидный липофусциноз, ребёнок, эпилепсия.

Introduction. Neuronal ceroid lipofuscinosis (NCL), or Batten disease or Spielmeyer-Vogt disease, are a group of monogenic hereditary neurodegenerative diseases. The diseases have similar clinical manifestations: seizures, visual impairment, cognitive decline [1].

NCL is morphologically characterized by cellular lipopigment inclusions, neuronal damage, and progressive neurodegeneration. When manifested in childhood, in the clinical picture of the disease, progressive mental and motor disorders and loss of vision are noted. At the onset of the disease in adults, cognitive impairment (dementia) predominates [2].

To date, 14 genetically distinct forms of NCL have been identified. All forms are characterized by the accumulation of abnormal lipofuscin-like material in the lysosomes of nerve cells, progressive and selective destruction of neurons, especially in the cerebral cortex, cerebellum, and retina [2].

The first description of neuronal ceroid lipofuscinosis in the medical literature was given by Otto Christian Stengel in the early 19th century. He described a juvenile disorder with blindness and progressive dementia. In 1903, Frederick Batten described a similar clinical picture as "cerebral degeneration with macular changes." The German neurologists W. Spielmeye and H. Vogt also reported a similar disorder in 1905. Subsequently, juvenile neuronal ceroid lipofuscinosis was named Batten-Spielmeyer-Vogt disease. European neurologists J. Janský (1908) and M. Bielschowsky (1913) described a similar disorder, but with a "late infantile" onset. This form became known as late infantile neuronal ceroid lipofuscinosis or Jansky-Belshovsky disease. In 1925, H. Kufs described a disease in adults with similar pathological characteristics, but without loss of vision, which occurred in juvenile ceroid neuronal lipofuscinosis and late infantile ceroid neuronal lipofuscinosis. This condition is called ceroid neuronal lipofuscinosis in adults or “Kufs disease”. Fifty years later, in 1973, M. Haltia and P. Santavuori described a distinct infantile form. Today, this pathology (classic infantile neuronal ceroid lipofuscinosis) is also known as “Haltia-Santavuori disease” [3].

In 1969, based on the ultrastructural pattern of lipofuscin or ceroid accumulation (a feature that helped distinguish this group of diseases from similar neurological disorders), the term neuronal ceroid lipofuscinosis was proposed. Prior to the discovery of genomic mutations, NCL was classified by a combination of the age of disease onset and ultrastructural patterns of neuronal deposition.

For the first time, a gene mutation associated with Batten's disease was discovered in 1995 with the help of the method of genetic examination, and in 2012 an updated classification was proposed considering the characteristics of the genetic background of patients and biochemical and clinical phenotypes. In the proposed version, the classification of disorders has been simplified and codified numerically according to the affected gene (for example, Batten's disease CLN1) [4]. The classification was structured along 7 diagnostic axes: 1) affected gene; 2) mutation; 3) biochemical phenotype; 4) clinical phenotype; 5) ultrastructural characteristics; 6) the level of functional disorders; and 7) other remarks (additional genetic, environmental or clinical traits). Due to the cumbersomeness of its use in clinical practice, some authors (Mink, Augustine, Adams, Marshall, & Kwon, 2013) suggested combining axes 1) and 4) for routine use [5].

To date, the lack of models of the disease limits a comprehensive understanding of the pathological factors that lead to its progression. Batten's disease is classified into 5 main types:

1. Congenital NCL, when children are born with microcephaly, due to the intrauterine onset of the disease.

2. Infantile NCL, when symptoms such as seizures and loss of motor function appear between the ages of 6 and 18 months and are accompanied by loss of psychomotor and speech skills. A child has signs of regression, accompanied by epileptic seizures and gradual loss of vision, hyperexcitability, anxiety, and sleep disturbance. At the age of 15 to 20 months, symptoms worsen with the formation of microcephaly, truncal ataxia, dystonic features, choreoathetosis, and myoclonic jerks. By the age of 2, children completely lose their sight, lose all cognitive and motor skills. Death usually occurs between the ages of 9 and 13.

3. Late infantile NCL - there is a manifestation of symptoms (developmental delay, ataxia and convulsions) at the age of 2 to 4 years. The clinic progresses rapidly to the loss of motor, cognitive and speech functions.

4. Juvenile NCL is the most common type of Batten’s disease. Symptoms begin between the ages of 5 and 10 and are usually manifested by loss of vision and seizures. Later, learning difficulties, movement disorders, including extrapyramidal and pyramidal (rigidity, bradykinesia, slow steps with flexion at the hips and knees, and shuffling gait) appear. These symptoms appear during puberty and gradually lead to the loss of independent movement. Patients usually die in the third decade of life.

5. The adult type of NCL progresses more slowly. The clinical picture of this type is characterized by generalized tonic seizures, myoclonus, severe dementia. Associated features include speech problems, cerebellar dysfunction, and parkinsonism [6].

NCL is one of the most common neurodegenerative pathologies in children with a worldwide prevalence of 1:1,000,000 to 1:14,000. Most NCLs are inherited in an autosomal recessive manner and are clinically characterized by epileptic seizures, psychomotor disturbances, visual impairment, and early mortality. An autosomal dominant inheritance variant caused by mutations in the DNAJC5/CLN4 gene has been reported [5].

Among all clinical forms, the most common in the world is neuronal ceroid lipofuscinosis type II (NCL2), or Jansky-Bilshovsky disease. This pathology is a

progressive disease inherited in an autosomal recessive manner. There is a decrease in the activity of lysosomal tripeptidyl peptidase-1, encoded by the NCL2 gene. Due to enzyme deficiency, pathological autofluorescent lipopigment accumulates in the CNS, consisting of the proteins saposin-A, saposin-B, and the subunit of ATP synthetase. Due to the "overflow" of the cell lysosomes with this lipopigment, there is a violation of the processes of hydrolysis and metabolism within the neuron itself [7].

In the classical late infantile form of NCL2 disease, this leads to a rapidly progressive neurodegenerative disorder with a highly uniform course of the disease. As a rule, the manifestation of the clinic is noted at the age of 2 to 4 years with unprovoked convulsive seizures. Speech delay often precedes the onset of seizures. Subsequently, patients experience a rapid decline in cognitive, speech, motor and visual functions with a complete loss of motor and speech functions by 6-7 years of age and subsequent blindness. Death occurs between the ages of 8 and 13 [8].

In the United States of America, the prevalence ranges from 1.6-2.4/100,000 births; in the Scandinavian countries, this pathology is recorded more often: from 2.5/100,000 in Denmark and 2.2/100,000 in Sweden to 3.9/100,000 in Norway, 4.8/100,000 in Finland and 7/100,000 in Iceland [9]. According to Kozina A.A. et al. (2020), the incidence of NCL2 in Russia is 0.24 per 100,000 people [5].

Previously, only maintenance therapy was available for patients with HCL2 disease. In 2017, intracerebroventricular enzyme replacement therapy with cerliponase-alfa, a recombinant human TPP1 enzyme, was first approved [4].

Here is a clinical case of NCL2 in a child. Patient N. was born 06.23.2015. The child from the 4th pregnancy (1st pregnancy - healthy boy; 2nd - medical abortion; 3rd - healthy girl,), proceeded with the threat of termination of pregnancy from the 2nd trimester. A child from 3rd spontaneous births at 39 weeks of gestational age. Body weight at birth - 3150 g, body length - 49 cm, Apgar score - 8/9 points.

The development of the child corresponded to age in the first months of life: she holds her head from 3 months, turns from back to stomach and back from 4 months, sits from 6 months, walks independently from 10 months, gurgles from 6 months, at 1 year she pronounces syllables, simple sentences - from 2 years of age.

At the age of 2 years 11 months against the background of complete health, the child was noted to have a single vomiting, adversion of gaze upwards, clonic twitching of the limbs and loss of consciousness.

At the age of 3 years 4 months of old, the child developed a paroxysm - a blue nasolabial triangle, loss of consciousness, twitching of the limbs. Diagnosed with epilepsy. An electroencephalogram (EEG) was performed for 20 minutes no pathologies, an EEG for 2 hours revealed theta activity in the frontal parts of the hemispheres.

The magnetic resonance imaging (MRI) of the brain, carried out at 3 years and 5 months of old of revealed a picture of areas of structural changes in the deep white matter of the parietal lobes (differentiate between delayed myelination and hypomyelination), moderately expressed compensated biventricular hydrocephalus, expansion of the subarachnoid convexital space.

Against the background of taking the drug Valproic Acid ("Depakine-chronosphere") 100 mg/day, the child had seizures in the form of "knocking" the legs, moving the eyes up, fading up to 5-6 times a day. Due to the lack of response to therapy, the dose of the drug was increased to 150 mg/day.

At the age of 3 years and 6 months of old the patient's general condition did not improve, epileptic seizures persisted. The EEG showed pronounced changes in the

bioelectrical activity of the brain, irritation of the diencephalic structures of the brain, the threshold for convulsive activity was reduced. The dose of Valproic Acid ("Depakin Chronosphere") was increased to 400 mg/day. At 3 years 7 months of old Topiramate 200 mg/day was added.

Later in 3 years 9 months of old due to an increase in the frequency of epileptic seizures, a change in therapy was carried out (Levetiracetam, "Keppra" 500 mg/day was taken at home).

At 4 years 1 month the girl was hospitalized in the Russian Children's Clinical Hospital (Moscow) due to persistent convulsive syndrome, loss of skills. Against the background of taking pulse therapy with Kortef (14.6 mg/kg/day), an improvement in the condition was noted, a decrease in the number of epileptic seizures. The girl began to move independently with support. A genetic blood test revealed a mutation in the ATPP1 gene.

At 4 years 4 months the patient received treatment at the Department of Medical Genetics of the Russian Children's Clinical Hospital (Moscow), where antiepileptic therapy was adjusted (Valproic acid 540 mg/day; Levetiracetam 900 mg/day), Cerliponase alpha was prescribed - 300 mg intraventricularly, once every 2 weeks, for a long time, continuously for life (Fig. 1). Cerliponase alfa is an enzyme replacement treatment for Batten disease, a neurodegenerative lysosomal storage disease. Specifically, Cerliponase alfa is meant to stop loss of motor function in symptomatic children over three years old with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2).

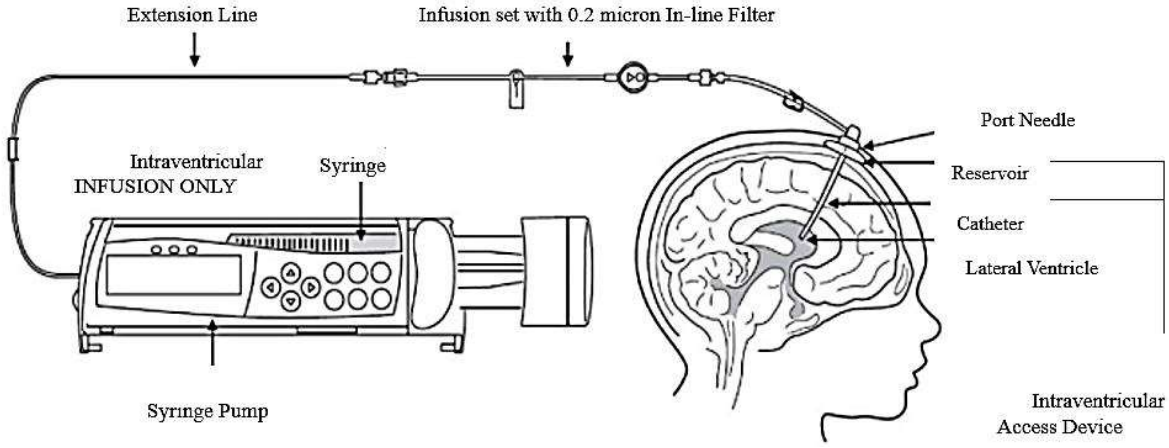

Figura 1. Intraventricular administration of Cerliponase alpha.

Later the patient constantly received therapy, against which the number of epileptic paroxysms was significantly decreased (Fig. 2). The child retains movement disorders, severe impairment of visual function, the lost written and oral speech has not recovered.

Figura 2. An intraventricular reservoir was installed in patient N.

Discussion. Many neurodegenerative diseases of childhood have similar symptoms, so delayed diagnosis of Batten's disease is not uncommon. Definitive diagnosis can be challenging in children, which require a thorough neurological and ophthalmic evaluation by a qualified and knowledgeable specialist [10].

Batten's disease appears after a period of seemingly normal development, despite the absence of a protein that is important for brain function. However, there is a small therapeutic window when specific treatment is able to stop and / or prevent the progression of the disease. Therefore, early diagnosis is critical for optimal therapeutic outcomes [11]. In this regard, the clinician must be familiar with the clinical features of the disease and suspect the diagnosis in order to conduct a genetic examination [4].

To date, many therapies have been proposed for this pathology, including gene therapy, stem cell therapy, anti-inflammatory drugs and small molecules, but most of them are currently in the early stages of clinical development. However, cerliponase-alpha, recombinant human TPP1, is the first and most recently approved treatment in the United States, European countries, Brazil, Australia, Mexico, Canada, Colombia, and Japan for the treatment of classic HCL2 disease. Cerliponase alpha is synthesized the Chinese hamster ovary. Chinese hamster ovary cells are an epithelial cell line derived from Chinese hamster ovary. It is often used in biological and medical research. Studies have shown that regular intraventricular delivery of this enzyme can slow down the decline in motor and speech function in patients with NCL2 [12].

In addition, several other gene replacement products are currently under development and early testing. One means is to use adeno-associated viruses (AAV9) as a neurotropic gene vector. Specific vectors, gene products, doses, routes of administration and target populations are likely to vary between studies. The ultimate goal of gene therapy for NCL is predicted to be the introduction of a functional gene into a sufficiently large number of neurons to prevent neurodegeneration [13].

Conclusion: The difficulty in diagnosing this pathology was due to the delayed molecular genetic examination on the epilepsy panel. Therefore, this examination should be included in the examination plan for the early onset of seizures in children without pronounced structural changes in the cerebral cortex and the presence of epileptic activity. This will allow to explain the nature of epilepsy and select a rational therapy for this disease.

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