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Unknown neurodegenerative disease in neonate

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Abstract. Aim. To present a rare case of unknown severe neurodegenerative disease in the newborn. Results. The case based in the analysis of results a detailed examination and diagnostic, the following observation and consequence in newborn baby. The differential diagnosis of the disease has been discussed between Hallevorden-Spatz syndrome, chorea-acanthocytosis and other diseases form the group of neurodegenerative diseases, but the final diagnosis has not been established. Conclusions. Clinical assessment, neuroimaging and molecular genetic diagnosis playing a major role in the diagnostic assessment of the group of neurodegenerative diseases.

Keywords: Newborn, neurological disorders, convulsions, neurodegenerative disease, Hallervorden -Shpatz syndrome, chorea-akantotsytozis.

1. Introduction

Baby girl T., was born at a gestational age of 36-37 weeks. Second pregnancy and second normal delivery, no stimulation. The amniotic sac was perforated; the fluids are transparent and clean; about 6 litres. Birth weight - 2490 grams, height 48 cm, blood group II (A) Rh+. There was no scream, primary resuscitation was carried out, after there were attempts to scream and independent breathing appeared. The Apgar score was 6/7 points. The baby was born in a "convulsion": a "forced" flexor posture was observed, with high tone in the limbs.

1.1. Information about parents

Mother was 34 years old (I (0), Rh-). She has a child from the first marriage, a girl - 12 years old, healthy. By other maternal anamnesis: autoimmune thyroiditis, from the of 14 old ages. Before the pregnancy mother start taking Eutirox, during pregnancy the dose was adjusted. During the entire pregnancy, the level of the thyrotropin hormone was in the normal range. The mother was diagnosed with instability of 3-5 vertebrae, which caused significant headaches. Before pregnancy, she underwent a medical course of treatment to improve the condition of the blood vessels the head, including acupuncture and reflexology. Headaches became more frequent during pregnancy in the first trimester. To reduce pain attacks, she took Magne B6 (up to 6 tablets per day), if it did not help, intramuscular injections of analgesic medicine were made (frequency, approximately once a week), only about 10 times per trimester. In the second trimester, the frequency and duration of headaches attacks were decreased. Also, mother suffer from allergic rhinitis since childhood: reaction to the b of blowing herbs. Father is 42 years old (II (A), Rh+). He has 19-year-old girl from first marriage. She is healthy.

1.2. Pregnancy

At 5-6 weeks mother has insignificant bleeding and moderate toxicosis in the first trimester, no vomiting. In the first trimester, severe and frequent headaches decreased, in the second and almost did not occur in the third. At the 13th week of pregnancy, there was a threat of miscarriage (bleeding). The first movement at 18 weeks was appear. At 28-29 weeks - flu. Mother was the office worker until the GA 29 week. At the GA 31 week, she was admitted to the hospital with complaints of moderate ascites, on CTG - 6 points by Fisher. At 34 weeks, false contractions appeared (staying in the hospital), polyhydramnios was diagnosed. Anti-Rhesus antibodies were not detected during pregnancy, at the GA 31 week a blood test for hemolysins was performed (the result was negative), at the GA 34 week a slight increase in the titer was recorded. Examination of the placenta (pathology examination): no pathology was found, some dyscirculatory disorder. A baby is desirable.

1.3. The baby at birth

Occurred very severe, a weak moan appeared despite of tactile stimulation, breathing by oxygen (free flow). Baby's pose: flexor hypertonus of the upper limbs and extensor hypertonus of the lower limbs. She was transferred to the NICU. Was intubated, respiratory support was established, convulsions (tremors) every minute. Consciousness is problematic. Baby girl was on a respiratory support, there are no active movements, there is no reaction of the pupils. Coma status.

1.4. Next in dynamics

Tonic-clonic convulsions, pseudo-bulbar syndrome, muscle dystonia syndrome was noted. The skin is pale/pink. No special disorders were noted on the part of the respiratory and cardiovascular systems. The belly was soft, the food was taken, the stool was regular, the diuresis was sufficient.

1.5. Examination

The blood test was normal with gradual anaemia, other blood tests (glucose, electrolytes and etc.) no abnormalities, lumbar puncture was performed: cerebrospinal fluid - normal, perinatal TORCH tests - no pathology was detected, karyotype was normal, hereditary disorders of aminoacid and acylcarnitine metabolism were excluded.

Other examinations: X-ray of the chest and abdominal, cervical part of spine - no pathology, ultrasound brain examination - immaturity, inhomogeneity of the echo-structure of the brain with hyper echoic areas. Encephalitis is not excluded. In MRI images - violation of the differentiation of white and grey matter, diffuse posthypoxemic edema of the white matter of the large hemispheres. In the projection of pale spheres, deposition of metal-containing enzymes.

The baby was examined by a neurologist, genetics, and an ophthalmologist.

Clinical diagnosis: I. Severe damage to the central nervous system of unspecified genesis. Congenital degenerative brain disease? Hallervorden-Spatz disease? II. Convulsive syndrome of unknown ethology. Bulbar syndrome. III. RDS, DN II-III in the anamnesis. GA 35-36 weeks. High septic risk. The risk of haemolytic disease of the newborn according to the Rh factor. Multiple stigmas of dysembryogenesis.

Treatment: respiratory support (ventilation, then CPAP through nasal cannulas), anticonvulsant therapy (sibazone, thiopental, phenobarbital, kepra, depakin). Symptomatic treatment, infusion therapy, partial parenteral nutrition and maintenance of water and electrolyte balance. Hemodynamics was supported by dopamine.

On the 29th day of life, baby was transferred to the NICU in Children's hospital Okhmatdyt.

In the Children's hospital, at age 2 months after birth (Figure1). The baby was unsteadily severe: convulsions, which are manifested both on the encephalogram and clinically in the form of twitching and sobbing. Convulsions every 5 minutes, but there are breaks of up to an hour. When the child is conscious, he "fights" with a seizure attack (tenses up and turns red). He often reacts to the touch by stretching. Convulsions (pulling and sobbing) are observed both in sleep and when awake. In a "pulling" dream, she is woken up, her eyes may open without focusing, she may cry. Before the start of some "extractions", the eyes were open, tears were released, then the whole body tenses up and the attack begins. Can track objects. She sleeps most of the day. Sometimes crying continues, when crying - there are almost no convulsions. Wakefulness lasts about an hour or two a day. One or two episodes. Legs and arms are clamped. There are periods when they can be relaxed, but mostly they are clamped. When you try to change their position or bend/unbend, a convulsion begins. Reacts to light, squints from bright light. Can look for a long time without blinking. There are no chaotic movements like babies. There are no movements without seizures. Does not swallow. Expresses displeasure when sanctifying. There is no cough. Cheeks are sensitive. The lips do not close together. The tongue is mobile, it tries to interfere with the tongue when cleaning. Internal organs are normal. Some features are on the MRI, positive dynamics regarding increased myelination. Feeding through a tube, a formula. The volume expands gradually. During feeding, convulsions (pulling) become more frequent. Gained the weight.

With palliative care purpose, a tracheostomy was performed on the baby at 5 months old. She was transferred to the pediatric department for the purpose of rehabilitation. She was discharged home at the age 5,5 months old. Status at the discharge: weight 4600 grams, nutrition was Neocate (Nutricia) in amount appropriate to the age through a tube (does not swallow). Breathing through a tracheostomy. Periodically equivalent to seizures observed. Baby have been got the Depakin medicine; parents were trained in baby care methods.

Figure 1. In NICU, Children's Hospital (2 months old)

Other examinations: Diagnosis of hereditary metabolic disorders (NBO). Organic ACIDS.

1) The urine examination: increase the concentration of 4-hydroxyphenyl lactate, 4-hydroxyphenylpyruvate, adipic acid, suberic acid, sebacin hydroxyphenylpyruvate can be caused by liver diseases. A medicine product - paracetamol, with a concentration of 128.23 mM/M creatinine (normally absent) was also detected. It is recommended to carry out a study by the TMS method.

2) Karyotyping: Analysis: chromosome analysis of FHA-stimulated lymphocyte culture. Number of evaluated metaphases: 20. Number of compiled karyograms: 5 (according to ISCN 2013). Band separation: 400-550 bands in a haploid set. Method of differential staining of chromosomes (GTG). Conclusion of karyotyping: 46, XX. As a result of the cytogenetic study, a normal female karyotype without features was revealed (in 20 metaphase plates). This result does not exclude the possibility of a low level of mosaicism and a hidden chromosomal rearrangement, which cannot be detected using a standard cytogenetic method.

3) Description of presented native MRI of the brain. Tomograms were of poor quality, there is no sequence of DVI. On a series of MRI of the brain, the formations of the midline are not displaced. The ventricles of the brain have not changed in size. The white matter of the brain has an increased T2 and decreased T1 B1 MR signal, which is due to immature myelination and may correspond to the age norm. The cortex/white matter differentiation of the brain is not disturbed. The corpus callosum is thinned, the basal nuclei are insufficiently differentiated, the MR signal from them is moderately increased on T1 B1 symmetrically on both sides, which is also due to the age norm. Optic nerves, eye muscles, retrobulbar fiber, chiasm, pituitary gland, brain stem departments without features. Paranasal sinuses are not developed. It is not possible to differentiate posthypoxic changes in the brain (taking into account clinical data and history) against the background of immature myelination according to the results of this examination. It is advisable to repeat the MRI of the brain in dynamics.

Conclusion. The final diagnosis of the baby has not been established. Confirmation of the diagnosis Hallervorden-Spatz disease not established. The opinions of the doctors who treated the child and observed the child were constantly leaning towards an unknown (rare) neurodegenerative disease or metabolic syndrome, the genesis of which cannot be established by available methods.

At the age 4 months after birth, the baby was discharged home in a stable condition.

The vital functions were compensated: general clinical tests correspond to the age norm; the baby is breathing independently through a tracheostomy. Parents were trained in child care methods. She gained weight well, but her neurological status remained without positive dynamics: she constantly received supportive anticonvulsant therapy. At the age of one year, the child did not turn over well, did not sit, but maintained visual contact, followed the toys. Psychomotor development is far behind the physiological norm. Physical development corresponded to the norm for this age. According to the mother, she has periodic convulsions, especially due to SARS. She continued to receive anticonvulsant therapy, breathed through a tracheostomy. She was fed through a tube: Neocate mixture, adjusted according to age.

Parents attended the neurology clinic in Germany twice for the diagnosis purpose (no positive result). There is baby has been got palliative support (appropriate treatment and rehabilitation for improving the quality of life). The baby has been lived 2 years and 3 months. She was died from cardiovascular and respiratory insufficient. The parents refused of the autopsy.

2. Literary review and differential diagnosis

Hallervorden-Spatz disease now known as pantothenate kinase-associated neurodegeneration (PKAN) is a rare autosomal recessive neurodegenerative disorder associated with iron accumulation in the brain nuclei and characterized by progressive extrapyramidal dysfunction and dementia [14]. The disease was first described by J. Hallevorden and H. Spatz in 1922 on the example of a large family in which 5 sisters were sick out of 12 children. The frequency of the disease is on average 1-3 people per 1 million. The disease makes its debut in children aged 6 months to 12 years. The main contingent of patients (88%) are children under 6 years old. Code in MKH10-G23.0 [1, 2, 4]. In the literature, the term "Gallevorden-Spatz disease" has been replaced by "Neurodegeneration of the brain with iron accumulation (NBIA)", which clearly reflects the pathogenesis and pathomorphology of this group of brain degenerations and refers to progressive extrapyramidal diseases [3, 4, 6]. Before the onset of the disease, children may be clumsy, dyspraxic. Changes in mental functions often occur already at an early stage of the disease and in some cases are the first symptom of the disease. Before the onset of movement disorders, some children were diagnosed with attention deficit hyperactivity disorder and other various cognitive and behavioral disorders [6, 8, 12]. The most important diagnostic feature of the disease is progressive dementia. Typical aggressiveness, irritability, antisocial behavior, deterioration in school performance, apathy, and a decrease in the range of interests. Further, the disease is manifested by deterioration of gait, postural instability, then extrapyramidal symptoms appear: a typical sign of the disease is the development of severe oromandibular dystonia in 80% of the disease. Classically, the disease presents between ages 7 and 15 years. However, the disease onset has been reported in all age groups including infancy and adulthood. As PKAN has an autosomal mode of inheritance, each sibling of an individual has a 25% chance of being affected and a 50% chance of being an asymptomatic carrie [10,11, 14]. This activity reviews the evaluation and management of pantothenate kinase-associated neurodegeneration and highlights the role of the interprofessional team in the care of affected patients and their families. Neurodegenerative diseases with a debut in early childhood include a large heterogeneous group of diseases, the basis of which are specific genetic or biochemical disorders, chronic viral infections, as well as a

significant group of conditions of unknown etiology. Hereditary neurodegenerative diseases include sphingolipidoses, neuronal ceroidlipofuscinosis and sialidosis. Sphingolipidoses are characterized by the intracellular accumulation of normal lipid components of the cell membrane as a result of a violation of their catabolism [10,11]. Sphingolipidoses are divided into six categories: Niemann-Pick disease, Gaucher disease, GM1 gangliosidosis, GM2 gangliosidosis, Krabbe disease, and metachromatic leukodystrophy. Spinocerebellar degenerations (Friedreich's ataxia, ataxia-telangiectasia, olivopontocerebellar atrophy, abetalipoproteinemia) and degenerative diseases with damage to the basal ganglia (Huntington's disease, muscular dystonia, Wilson's disease, and Hallervorden-Spatz disease). In this case, due to the fact that the MRI of the brain revealed the deposition of metal-containing enzymes in the projection of the pale balls and the child had characteristic clinical manifestations, the most probable suspicion was Hallervorden-Spatz disease (Figure 2) [5, 7, 9]. In our case, we did not find such dispositions and this disease was not confirmed on subsequent brain MRI studies, but this disease can develop at an older age (accumulation disease).

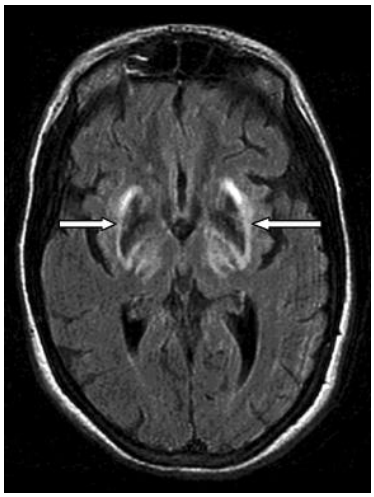

Figure 2. Bilateral hypointense globi pallidi due to iron deposition in a patient of Hallervorden-Spatz disease on T2W MRI. (Contributed by Jinnah Hospital; Lahore, Pakistan) [14]

2.1. Infantile PLAN (classic)

The disease begins in early childhood — from 6 months to 2 years. Sick children are often born from a pathological pregnancy and have a complicated perinatal history. The disease debuts with axial hypotonia and regression the psychomotor development. The onset of the disease is possible after a non-specific intercurrent disease. The disease progresses rapidly. Nystagmus, strabismus, optical pallor appears as a sign of optic nerve atrophy. Next, spastic tetraparesis with pyramidal signs develops (but hyperreflexia is diagnosed at the beginning, and then are flexia). Cerebellar symptoms are diagnosed. Joint contractures are formed. By the age of 5, bulbar dysphagia occurs, which makes it difficult to help the patient. Dystonia and other extrapyramidal symptoms, convulsions appear closer to the end of the first decade. Death occurs from secondary complications. Life expectancy up to 10 years [1, 4, 6, 13].

Neuroacanthocytosis (chorea-acanthocytosis, choreoacanthocytosis) is a rare hereditary neurodegenerative disease, characterized by multisystem neurological manifestations and the presence in the blood of special altered erythrocytes with a "star", silo-like surface - acanthocytes (Greek: Acanth - horn). In most cases, the type of inheritance is autosomal recessive; the gene of this form is mapped on chromosome 9q21 [10,11]. Families with autosomal dominant chorea-acanthocytosis syndrome have also been described. Morphological changes in neuroacanthocytosis consist in the death of neurons and atrophy of the striatum, the pallidum, the reticular part of the substantia nigra, and the death of neurons of the cortex of the large hemispheres and cells of the anterior horns of the spinal cord may be detected less often. The above changes are accompanied by reactive gliosis [1, 4, 6, 10, 11, 13].

2.2. Therapy

Causal (etiological) therapy for Hallervorden-Spatz and other neurodegenerative diseases are unknown. There were attempts to treat the enzyme defect. Chelates ("traps") of iron, such as Deferoxamine, do not give an effect, however, since 2007, attempts have been made to conduct treatment with the iron chelator Ferriprox (Deferipron®). In animal experiments, deep brain stimulation led to increased dystonias and hyperkinesias. Hypokinesia can be treated with levodopa, hyperkinesia with anticholinergics. However, the effect of levodopa in patients with PANK2 gene mutation is very questionable. Baclofen or benzodiazepines are often prescribed for muscle relaxation and pain relief [5, 7, 9]. The newest methods of therapy for Hallervorden-Spatz disease include the administration of pantothenic acid and magnetic stimulation of the brain. Hallervorden-Spatz disease is characterized by a steady progression of symptoms [2,14]. The most aggressive course is characteristic of the childhood form: 6-15 years after the appearance of the pathology, complete disability occurs. The late version of the disease has a more favourable prognosis, especially if it is accompanied by mild dementia [6, 8,12]. Thanks to therapy, the degree of symptoms can be reduced, and the patient's ability to self-care can be preserved. The average duration of an atypical form of the disease is 20 or more years [4, 13].

3. Summary

Clinical assessment, neuroimaging and molecular genetic diagnosis playing a major role in the diagnostic assessment of the group of neurodegenerative diseases. The identification of the underlying causative genes helps to clarify the phenotypes of the disorders collectively known as "metabolic neurodegenerations" and to provide clinicians with a differentiated approach to the diagnosis and treatment of these complicate diseases.

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