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THE CASE OF MEROSINE-DEFICIENT CONGENITAL MUSCULAR DISTROPHY IN THE CHILD

Resume. Merosin-deficitnaya Congenital Muscular Dystrophy type 1A (CMD1A) – an autosomal recessive neuromuscular disease caused by a mutation of the gene LAMA2. CMD1A ranks first (50%) in the structure of all CMD in Western European countries. This disease is characterized by diffuse muscular hypotonia, weakness of the muscles of the trunk and proximal limbs, delayed motor development, contractures in the large joints, elevated CPK levels, and damage to the white matter of the brain without intellectual retardation. The article presents a clinical observation of a patient with a molecular-genetically confirmed diagnosis of "Congenital merosine-deficient dystrophy (CMD1A)". From birth, the boy was supervised by a pediatric neurologist about Verdnig-Hoffmann's spinal amyotrophy complicated by arthrogryposis. At the age of 3 years and 5 months, the child was examined by a geneticist: there was marked diffuse muscular hypotonia, weakness of the axial muscles, proximal muscles of the limbs, a symmetrical reduction in the tone of the muscles of the face. Kilevna deformity of the chest, contracture of the knee and ankle joints, quick fixation of the feet. Leukoencephalopathy with signs of hydrocephalic syndrome, cerebrospinal fluid dysfunction and atrophic changes in the brain, partial atrophy of the optic nerve discs OU. Considering the characteristic clinical picture and data of laboratory and instrumental studies (increased CPK, damage to the white matter of the brain with MRI, the primary muscular nature of the changes on ENMG), a diagnosis of muscular dystrophy was suspected. Molecular genetic analysis by the method of targeted sequencing, carried out abroad (San Francisco), revealed mutations with 2049_2050del (pArg683Serfs*21) and c.7732C>T(p.Arg2578*) in a compound-heterozygous state, which allowed the diagnosis of merosine-deficient state to establish a diagnosis of merosine-deficient CMD.

It is recommended for patients who from birth demonstrate the syndrome of a "sluggish child", have an increase in the level of CPK and damage to the white matter of the brain without intellectual disabilities to conduct molecular genetics research on CMD.

Key words: congenital muscular dystrophy, congenital merosin-deficitna dystrophy, CMD1A, merozin, LAMA2.

Congenital Muscular Dystrophies (CMD) were a diagnostic puzzle for doctors, «hiding» under the term «syndrome of a sick child». Clinically, they were divided into «pure» forms (suffering exclusively from the muscular system, secondary – bone and joint) and forms with structural damage of the central nervous system and other organs With the improvement of diagnostic methods (neuroimaging, molecular genetic), there was the possibility of early diagnosis and study of rare forms of CMD. So, in the 80's in Europe and America, data on CMD with the defeat of white matter of the brain appeared. In 1994, scientists found a deficiency of merosin protein in the muscles of such patients; then there was a mapped gene of merosin (LAMA2 – Laminin α2); in 1995 discovered LAMA2 mutations that lead to a shortage of merosin. Merosine-deficient Congenital Muscular Dystrophy of type 1A (CMD1A) (OMIM: 607855) is an autosomal recessive neuromuscular disease due to mutation of a gene encoding the α2-chain of laminin (merosin)-LAMA2 and characterized by diffuse muscular hypotonia, weakness of body muscles and proximal limb parts, motor development delay, contractions in large joints, increase in the level of creatine phosphokinase (CPK), and also the defeat of white matter of the brain without delaying intellectual development. CMD1A ranks first (50%) in the structure of all CMDs in the countries of the West. The awareness and guardianship of CMDs remains a problem. Often, the detection of signs of a defeat of a white matter of the brain according to the data of magnetic resonance imaging (MRI) in a "quill" child with an elevated level of CPK in blood plasma directs doctors to the wrong way to find leukodystrophy or perinatal pathology, while knowledge of key signs of CMD1A will allow suspect this pathology and facilitate molecular genetic diagnostics, as well as give the family a chance for prenatal diagnosis at the next childbirth [1-3].

The gene of merosin (LAMA2) is located on chromosome 6 (6q22-q23); 37 mutations are

described. The most common are deletions and mutations that result in the formation of a stop codon. The main function of merosin protein is the grip and orientation of myofibrils due to their interaction with collagen fibers of intercellular spaces and sarcolemia proteins. Signs of a defeat of white matter of the brain and polyneuropathy with CMD1A indicate the expression of LAMA2 in the structures of the central and peripheral nervous systems. There is a gene-phenotypic correlation. Clinical manifestations in CMD1A depend on complete or partial deficiency of merosin. The complete absence of merosin leads to early and severe clinical manifestations: pronounced hypotension with involvement of the facial muscles, disruption of sucking and swallowing, respiratory distress. Hypotonia and muscle weakness predominate in the axial muscles and muscles of the proximal limb parts. Over time, an outer ophthalmoplegia may develop. Characteristic contractions of large joints, dislocation of the thighs, violation of the formation of physiological bend of the spine. Restrictive breathing in the first decade of life can cause the death of the patient. The weakness of sucking and chewing, dysfunction of the motility of the gastrointestinal tract, respiratory failure, exacerbate amiotrophy, contribute to growth retardation and motor development of the child. The boundary of motor development of most patients is to achieve a stable sitting position. In mild forms of CMDA1A, the first signs appear in the second decade of life and vary widely, compared with cases of complete absence of merosin. In late forms, pseudo-hypertrophy of muscles may occur, not typical for classical forms of CMD1A. With moderate to moderate mild disorder, breathing and eating disorders are minimal, children can learn to practice walking, but contractions and dislocations are not rare. «Soft» forms of CMD1A with a partial deficit of merosin in the clinic resemble end-lumbar miodistrophy [4-6].

The presence of a patient with CMD1A can be suspected of clinical signs, expressed by an increase in blood CPK (more than 4 norms), persistent changes in the signal from the brain according to MRI/CT. When ENMG reveals typical signs of primary-muscle damage, with stimulation – signs of damage to myelin central and peripheral nervous system. The determining factor for the diagnosis of CMD1A is the molecular study of the LAMA2 gene, which allows to detect up to 96% of all mutations with full LAMA2 sycamens. Treatment is aimed at correcting secondary orthopedic complications, respiratory disorders and nutrition. When verified mutation LAMA2, an effective prenatal DNA diagnosis is possible on the 10-12th week of gestation. Life expectancy at CMD1A varies from several years in severe forms to 30 years or more. Only a small part of patients can go alone, with an incomplete lack of merosin [7–9].

We present the actual clinical observation of a patient with a genetically confirmed diagnosis of VMD1A. A child, 3 years 5 months, a physician geneticist inspected for the first time. Mother's heredity: diabetes mellitus; along the line of the father: cardiovascular pathology. In the pedigree of cases of neuromuscular diseases was not revealed. Her mother at the time of medico-genetic counseling is the second pregnancy. From anamnesis: a boy from a healthy mother 25 years old, the first desirable and planned pregnancy, which went through without any particulars. During pregnancy, the mother felt satisfactory fetal movements. Prenatal screening did not reveal a pathology. Childbirths are independent, urgent, in the pelvic presentation. Weight at birth 3350 g, length 52 cm, score APGAR 7/8 points. From birth to artificial feeding due to the weakness of sucking. After birth, the child was observed diffuse meteoric hypotension with involvement of the facial muscles, weak cry, reduction of reflexes, prolonged closure of the large basaltic. At the age of 1 – the delay in motor development, formed flexor contracture of large joints. Intellectual development did not suffer. For the first time he entered the neurological department of the Regional Children's Clinical Hospital (RCCH) at the age of 5 months. According to the mother, the child did not turn over, with verticalization he did not lean on his legs. Conducted general clinical trials of blood and urine, ultrasound examination of the abdominal cavity, ECG, EEG, CT (conclusion: hypoxic-ischemic lesion of the brain in the form of periventricular leukomalacia, vesicular discirculation, mixed hydrocephalus). From conducting further examinations the parents refused. The child is diagnosed with «Spinal amiotrophy of Vernig-Hoffman, complicated by arthrogrypus». The second time the child was examined and treated in the same department at the age of 3 years. Blood CPK: 1891 U/L (norm – up to 171 U/L). ENMG: moderate decrease in motor response amplitude. MRI of the head: a picture of leukoencephalopathy with signs of hydrocephalus syndrome, liver dysfunction and atrophic changes in the brain. Eyewitness review: Signs of intracranial hypertension. Partial atrophy of the optic nerves OU. Review by orthopedist: Equivalent stop setting. Written with the same diagnosis, recommended for medical genetic counseling. When examined by the physician-geneticist, the body structure is normostenic, expressed diffuse mythical hypotension, weakness of the axial muscles, proximal muscles of the extremities, and the face. Deformation of the chest, contractions of the knee

and lower leg joints. Facial hypomytic, symmetrical reduction of face muscle tone. Taking into account the characteristic clinical picture and data of researches (increase of CPK, defeat of white matter of a brain on MRI, primary-muscular character of changes on ENMG), suspected diagnosis of muscular dystrophy. Molecular genetic analysis by the method of target sequencing conducted abroad revealed mutations from 2049_2050del(pArg683 Serfs*21) and c.7732C>T(p.Arg2578*) in a compound heterozygous state, which allowed the diagnosis of a merosidentificient CMD. Taking into account the absence of pathogenetic therapy of CMD1A today, the child receives symptomatic treatment.

Consequently, a patient with a syndrome of skeletal child who demonstrates diffuse muscular hypotension and weakness of muscles (especially axial and proximal muscles) at birth or during the first 6 months of life, the presence of congenital contractures, respiratory and swallowing disorders, and in the subsequent examination – a significant increase in the level of CPK, motor development delay in combination or without violations of psychoemotional development, should be considered from the point of view of the possible presence of CMD. The basis of genetic prophylaxis of CMD1A in burdened families is a timely diagnosis of patients.

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ВИПАДОК МЕРОЗИНДЕФІЦИТНОЇ ВРОДЖЕНОЇ М'ЯЗОВОЇ ДИСТРОФІЇ У ДИТИНИ

Резюме. Вроджена мерозиндефіцитна м'язова дистрофія 1А типу (ВМД1А) – аутосомно-рецесивне нервово-м'язове захворювання, обумовлене мутацією гена LAMA2.. ВМД1А посідає перше місце (50%) в структурі усіх ВМД в країнах Західної Європи. Ця хвороба характеризується дифузною м'язовою гіпотонією, слабкістю м'язів тулуба та проксимальних відділів кінцівок, затримкою моторного розвитку, контрактурами у великих суглобах, підвищенням рівня КФК, ураженням білої речовини головного мозку без затримки інтелектуального розвитку. У статті наведено власне клінічне спостереження пацієнта з молекулярно-генетично підтвердженим діагнозом:

«Вроджена мерозиндефіцитна дистрофія (ВМД1А)». Хлопчик з народження знаходився під спостереженням дитячого невролога з приводу спінальної аміотрофії Вердніга-Гоффмана, ускладненою артрогрипозом. При огляді лікарем-генетиком в віці 3 роки 5 місяців звертала увагу виражена дифузна м'язева гіпотонія, слабкість аксіальної мускулатури, проксимальних м'язів кінцівок, симетричне зниження тонусу м'язів обличчя. Килевидна деформація грудної клітини, контрактури колінних та гомілково-ступневих суглобів, еквінусна установка стоп. Лейкоенцефалопатія з ознаками гідроцефального синдрому, ліквoрної дисфункції та атрофічних змін головного мозку; часткова атрофія дисків зорових нервів OU. Враховуючи характерну клінічну картину та дані лабораторно-інструментальних досліджень (підвищення КФК, ураження білої речовини головного мозку за МРТ, первинно-м'язовий характер змін на ЕНМГ), запідозрений діагноз м'язової дистрофії. Молекулярно-генетичний аналіз методом таргентного секвенування, проведений за кордоном (Сан-Франциско), виявив мутації c.2049_2050del(pArg683Serfs*21) та c.7732C>T(p.Arg2578*) в компаунд-гетерозиготному стані, що дозволило встановити діагноз мерозиндефіцитної ВМД. Рекомендовано, пацієнтам, які від народження демонструють синдром «кволої дитини», мають підвищення рівня КФК та ураження білої речовини головного мозку без порушення інтелекту проводити молекулярно-генетичне дослідження на ВМД.

Ключові слова: вроджена м'язова дистрофія, вроджена мерозиндефіцітна дистрофія, ВМД1А, мерозин, LAMA2.

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СЛУЧАЙ МЕРОЗИНДЕФИЦИТНОЙ ВРОЖДЕННОЙ МЫШЕЧНОЙ ДИСТРОФИИ У РЕБЕНКА

Резюме. Врожденная мерозиндефицитная мышечная дистрофия 1А типа (ВМД1А) – аутосомно-рецессивное нервно-мышечное заболевание, обусловленное мутацией гена LAMA2. ВМД1А занимает первое место (50%) в структуре всех ВМД в странах Западной Европы. Эта болезнь характеризуется диффузной мышечной гипотонией, слабостью мышц туловища и проксимальных отделов конечностей, задержкой моторного развития, контрактурами в крупных суставах, повышением уровня КФК, поражением белого вещества головного мозга без задержки интеллектуального развития. В статье приведено клиническое наблюдение пациента с молекулярно-генетическим подтвержденным диагнозом «Врожденная мерозиндефицитная дистрофия (ВМД1А)». Мальчик с рождения находился под наблюдением детского невролога по поводу спинальной амиотрофии Верднига-Гоффмана, осложненной артрогрипозом. В возрасте 3 года 5 месяцев ребенок осмотрен врачом-генетиком: отмечалась выраженная диффузная мышечная гипотония, слабость аксиальной мускулатуры, проксимальных мышц конечностей, симметричное снижение тонуса мышц лица. Килевидная деформация грудной клетки, контрактуры коленных и голеностопных суставов, еквинусная установка стоп. Лейкоэнцефалопатия с признаками гидроцефального синдрома, ликворной дисфункции и атрофических изменений головного мозга частичная атрофия дисков зрительных нервов OU. Учитывая характерную клиническую картину и данные лабораторно-инструментальных исследований (повышение КФК, поражение белого вещества головного мозга с МРТ, первично-мышечный характер изменений на ЭНМГ), заподозрен диагноз мышечной дистрофии. Молекулярно-генетический анализ методом таргентного секвенирования, проведенный за рубежом (Сан-Франциско), выявил мутации c.2049_2050del(pArg683Serfs*21) и c.7732C>T(p.Arg2578*) в компаунд-гетерозиготном состоянии, что позволило установить диагноз мерозиндефицитной ВМД.

Рекомендуется пациентам, которые от рождения демонстрируют синдром «вялого ребенка», имеют повышение уровня КФК и поражения белого вещества головного мозга без нарушения интеллекта проводить молекулярно-генетическое исследование на ВМД.

Ключевые слова: врожденная мышечная дистрофия, врожденная мерозиндефицитна дистрофия, ВМД1А, мерозин, LAMA2.

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