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Myopathy in glycogen storage disease type IV: case report of a family

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ABSTRACT

Aim. To study the clinical presentation and differential diagnosis of a rare hereditary disease glycogen storage disease type IV with progressive skeletal myopathy in a case report of a family.

Materials and methods. Two patients were followed up in the specialized neurology unit of the regional clinical hospital and in the outpatient setting.

Results. Long-term follow-up and examination in two clinically similar cases of myopathy in siblings allowed us to diagnose a hereditary metabolic disease. The congenital muscular form of glycogen storage disease type IV was manifested by myopathy and peripheral tetraparesis with the development of bone deformities. Difficulty in the diagnosis was due to isolated myopathy progression with no signs of liver involvement. The diagnosis was established with account of clinical manifestations, the progressive course of the disease, electromyography findings, and the results of molecular genetic testing for pathogenic mutations associated with hereditary neuromuscular diseases.

Conclusion. Glycogen storage disease type IV can clinically manifest itself by progressive myopathy without liver involvement and changes in blood biochemistry. The presented clinical cases in siblings are identical. Myopathy does not have clinical features that are significant for the differential diagnosis with other hereditary neuromuscular diseases. Genetic testing identified a mutation in the *GBE1* gene and is considered as the main diagnostic criterion of the disease.

Keywords: glycogen storage disease type IV, myopathy, neuromuscular diseases

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Миопатический синдром при болезни накопления гликогена IV типа на примере семейного случая

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РЕЗЮМЕ

Цель. Исследование клинической картины и дифференциальная диагностика редкого наследственного заболевания – болезни накопления гликогена IV типа с поражением скелетной мускулатуры на примере семейного случая.

Материалы и методы. Наблюдение двух пациентов в условиях специализированного неврологического отделения областной клинической больницы и амбулаторно.

Результаты. Длительное наблюдение и обследование в двух клинически схожих случаев миопатии у сибсов позволило установить диагноз наследственной болезни обмена веществ. Врожденная мышечная форма болезни накопления гликогена IV типа проявлялась синдромом миопатии, периферическим тетрапарезом с развитием костных деформаций. Сложность диагностики обусловлена прогрессированием изолированного миопатического синдрома при отсутствии симптомов поражения печени. Диагноз установлен с учетом клинических проявлений, прогрессирующего течения заболевания, данных электромиографии, результатов молекулярно-генетического исследования патогенных мутаций, ассоциированных с нервно-мышечными болезнями.

Заключение. Болезнь накопления гликогена IV типа может клинически манифестировать в виде прогрессирующей миопатии без патологии печени и изменений биохимических показателей крови. Представленные клинические случаи у сибсов идентичны. Миопатический синдром не имеет клинических особенностей, значимых для дифференциальной диагностики с другими наследственными нервно-мышечными болезнями. Генетическое исследование выявило мутацию в гене *GBE1* и рассматривается как основной диагностический критерий заболевания.

Ключевые слова: болезнь накопления гликогена IV типа, миопатия, нервно-мышечные болезни

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INTRODUCTION

Advances in the field of genetics in recent years have expanded the understanding of the diversity of storage diseases and the prospects for their early diagnosis, which determines the relevance of research and systematization of clinical aspects of this pathology. Glycogen storage diseases are a group of hereditary enzymopathies that occur due to genetically determined defects in enzymes involved in glycogen metabolism. Metabolic disorders lead to changes in the structure of glycogen and its accumulation in organs and tissues, which underlies the formation of clinical manifestations. Glycogen storage diseases are characterized by a wide range of clinical phenotypes [1, 2].

Currently, more than 20 types of glycogen storage diseases, including subtypes, are known.

Nine types have been studied the most, differing in the characteristics of enzyme deficiency, clinical manifestation, and prognosis variability – from a favorable course to severe progressive forms with a fatal outcome in childhood. As the study of various aspects of this pathology proceeds, their classification is improved [1–3].

Glycogen storage diseases are attributed to the group of orphan diseases, their prevalence in the population is 1 : 20,000–1 : 43,000 [1, 3]. Low prevalence of hereditary storage diseases in the population, clinical polymorphism, and a large number of phenocopies determine the difficulty in diagnosing them [4–7]. Glycogen storage disease type IV is an autosomal recessive disorder manifested by amylo-1,4:1,6-glucan transferase deficiency caused by a mutation in the *GBE1* gene encoding this enzyme, which leads to the accumulation of glycogen with an amylopectin-like structure in various organs and tissues including liver and muscles [1, 2].

Glycogen storage disease type IV is located on 3p12.2 chromosome [1, 2, 6]. The prevalence of this type of glycogen storage disease is between 1 : 600,000 and 1 : 800,000 [7]. There are several known clinical types of glycogen storage disease type IV: classic hepatic, non-progressive hepatic, fatal perinatal neuromuscular, congenital neuromuscular, childhood neuromuscular, adult neuromuscular with isolated myopathy. Various and topically heterogeneous syndromes of diffuse damage to the nervous system are possible [2, 6, 7]. The accumulation of genotype and phenotype correlations in this rare disease is now important.

CLINICAL CASE 1

Patient M., 7 years old, was examined in the neurological department of the regional hospital with complaints of periodic pain in the back and lower extremities. The parents noted that the child had weakness in the muscles of the back and limbs, impaired gait and posture. The child has been ill since birth and has a disability. It is known from the medical history that this was the first pregnancy, at the time the mother had anemia and threatened miscarriage in the first trimester. The boy was born at 40 weeks, spontaneous vaginal delivery. Birth weight was 3,340 g, body length was 56 cm. The Apgar score was 9/9 points.

After birth, diffuse hypotonia and hyporeflexia were noted. At an early age, the child was followed up with the diagnosis of "Spinal cord ischemia at the lumbar level, movement disorder." Weakness in the limbs, hypotension, and delayed motor development were noted in the patient. The parents were healthy, the mother was 34 years old, and the father was 43 years old. The patient's five-year old brother had similar symptoms; his three-year old sister was healthy. The child was repeatedly examined and received courses of treatment in multidisciplinary hospitals. The general condition was not affected, and no somatic symptom pathology was detected. The child's condition was interpreted as a movement disorder with delayed motor development due to perinatal pathology of the nervous system and subsequently as a possible hereditary neuromuscular disease.

Taking into account the slowly progressing motor disorders and the ineffectiveness of the treatment (metabolic therapy combined with exercise therapy, massage and physical therapy), myopathy was considered in the differential diagnosis. The level of creatine phosphokinase (CPK) in the blood throughout the entire follow-up period was within the normal range. The results of electromyography (EMG) revealed vague signs of primary muscle damage. Repeated EMG revealed symptoms of an anterior horn lesion, and, therefore, spinal muscular atrophy type 1 was included in the differential diagnosis. Magnetic resonance imaging (MRI) of the brain and lumbar spine and spinal cord did not reveal any pathology.

Neurological status. The child was active, mental and speech development was age-appropriate. The functions of the cranial nerves were not impaired. Muscle tone in the extremities was reduced and symmetrical. Tendon reflexes were of medium intensity in the arms, while in the legs, they were low and symmetrical. Muscle strength in the extremities was 3–4 points; it was decreased in the distal parts. The patient had muscle hypotrophy in the limbs and back; pronounced lumbar hyperlordosis, thoracolumbar scoliosis, and flat valgus feet. The patient rose from sitting and lying positions supporting himself. The gait was waddling. Sensitivity, statics, and coordination were regular.

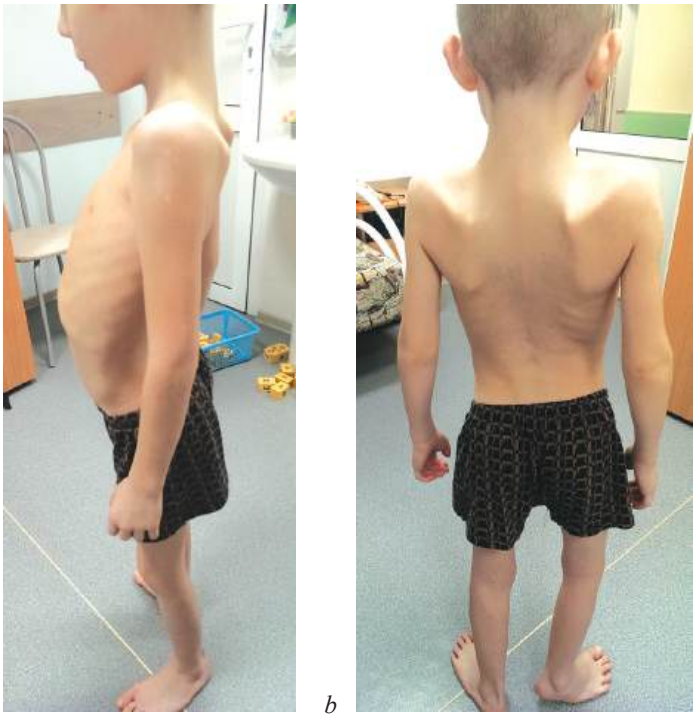
To clarify the type of myopathy, whole exome sequencing was performed. A search was conducted for pathogenic mutations associated with muscle dystrophies, as well as other hereditary diseases with similar phenotypic manifestations. A previously

described heterozygous mutation in intron 5 of the *GBE1* gene (chr3:81698005A>G, rs192044702) leading to disruption of the canonical splice site (c.691+2T>C, NM_000158.3) was identified.

The mutation has been described in compound heterozygous form along with other mutations in patients with glycogen storage disease type IV. Based on the data obtained, it should be regarded as pathogenic. In the same *GBE1* gene, a previously undescribed heterozygous mutation in exon 7 (chr3:81692139C>T, rs369574719) leading to an amino acid substitution in position 262 of the protein (p.Arg262His, NM_000158.3) was identified. Homozygous and compound heterozygous mutations in the *GBE1* gene have been described in patients with glycogen storage disease type IV (OMIM: 232500). Pathogenicity prediction algorithms evaluate this mutation as likely pathogenic (SIFT: 0.000, Polyphen2_HDIV: 1.000, Polyphen2_HVAR: 1.000, MutationTaster: 1.000, PROVEAN: -4.760, LRT: D). A mutation leading to amino acid replacement in the same position of the protein (p.Arg262Cys) was described in a compound heterozygous form together with another mutation in a patient with glycogen storage disease type IV (OMIM: 232500.0016). According to all the information obtained, the identified mutation should be regarded as likely pathogenic.

Upon further follow-up, progression of myopathy and secondary skeletal complications were noted (Fig. 1). Over time, the following symptoms progressed in the patient: the hypotrophy of the skeletal muscles of the limbs and back, thoracolumbar scoliosis to the left, lumbar hyperlordosis, flat back syndrome, flat valgus feet, retraction of the Achilles tendons, shortening of the right lower limb by 2 cm, secondary contracture of the right knee joint, first degree joint dysfunction, secondary extension contracture of the ankle joints, second degree joint dysfunction, weakness in the extremities, which was more pronounced in the proximal parts – up to 3 points, symmetrical tendon hyporeflexia.

The gait was waddling, involving extra muscles. The patient could not jump, run, or walk on his heels. Blood biochemistry test did not reveal any abnormalities. Clinically and following the results of additional examinations, no somatic symptom pathology was identified. Based on clinical manifestations, the progressive course of the disease, EMG data, and the results of molecular and genetic testing, a clinical diagnosis was established: “Congenital metabolic disease. Glycogen storage disease type IV, congenital muscular form, myopathy syndrome, peripheral tetraparesis, bone deformities”.



a *b*

Fig. 1. Patient M.: *a* – hypotrophy of the muscles of the extremities and back, lumbar hyperlordosis, flat back syndrome, flat valgus feet; *b* – curvature of the spine to the left in the lower thoracic and lumbar regions, shortening of the right lower limb

CLINICAL CASE 2

Patient G. is a 5-year-old brother of patient M. presented above (Fig. 2). The parents noted weakness in the muscles of the back and limbs, impaired gait and posture. The child has been ill since birth and has a disability. The child was born from the 2nd pregnancy, during which the mother was diagnosed with anemia and had threatened miscarriage in the first trimester. The child was born at 37–38 weeks of gestation by C-section due to breech presentation. Birth weight was 2,860 g, body length was 55 cm. Apgar score was 7/8 points. There was a delay in motor, mental and speech development.

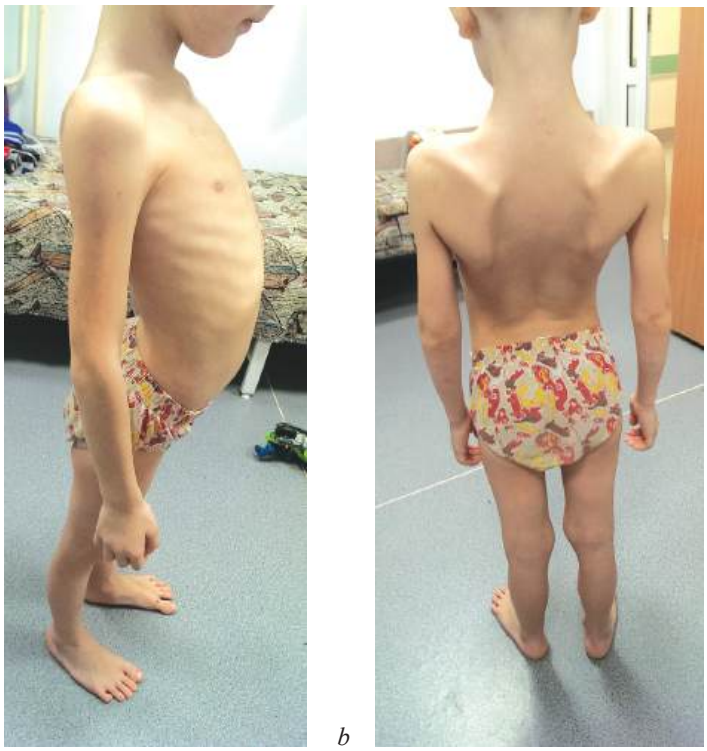


Fig. 2. Patient G.: *a* – hypotrophy of the muscles of the extremities and back, lumbar lordosis, flat back syndrome, flat valgus feet; *b* – curvature of the spine to the right in the lower thoracic and lumbar regions, pelvic asymmetry

He was followed up by a neurologist from an early age due to perinatal pathology of the nervous system, myopathy syndrome, and delayed motor and speech development. Courses of outpatient and inpatient treatment were conducted 2–3 times a year, no effect was observed. The patient was examined in a regional hospital. The blood level of CPK and aminotransferases was within the normal range. MRI of the brain, lower thoracic and lumbar spine did not reveal any pathological changes. EMG confirmed myopathy without any signs of anterior horn lesion. Abdominal ultrasound revealed hepatomegaly.

Neurological status. The mental and speech development were age-appropriate. The functions of the cranial nerves were not impaired. Muscle hypotrophy of the limbs and shoulder girdle, diffuse hypotonia, pterygoid shoulder blades, and a decrease in muscle strength in the arms and legs to 3–4 points were noted. Tendon hyporeflexia was noted in the limbs, without asymmetry or pathological reflexes. The gait was waddling, involving extra muscles. The patient used myopathy-specific movements when standing up (Gower's sign). Sensitivity was not impaired. Thoracolumbar scoliosis to the right, lumbar hyperlordosis, flat back syndrome, and pelvic asymmetry were noted. The patient had flat valgus feet with flattening of the longitudinal arch. The clinical diagnosis was established: "Congenital metabolic disease. Glycogen storage disease type IV, muscular form (clinically), myopathy syndrome, peripheral tetraparesis, secondary bone deformities".

CONCLUSION

The presented clinical cases of glycogen storage disease type IV reflect the diversity of clinical forms of this pathology and demonstrate the complexity of differential diagnosis in cases of skeletal muscle damage without manifestations of hepatic pathology. Myopathy

dominates in the clinical presentation and does not have specific features that make it possible to distinguish this disease from other hereditary myopathies. The absence of an increase in the blood CPK level characteristic of a primary muscle lesion during the entire follow-up period increased the diagnostic value of EMG for making the diagnosis. The ambiguity of the interpretation of EMG results determines the relevance of the differential diagnosis of muscular dystrophy with spinal muscular atrophy. The similarity of clinical symptoms in siblings, the progressive course of the disease, symmetrical and systemic muscle tissue damage, and development of the secondary bone deformities served as the reason for a genetic test. Clarifying the diagnosis was possible only with the use of DNA diagnosis and identification of mutations in the *GBE1* gene. Thus, genetic testing is an effective method in the differential diagnosis of neuromuscular diseases, the results of which can be used as a reliable guideline for medical genetic counseling.

REFERENCES

1. Baranov A.A., Namazova-Baranova L.S., Surkov A.N., Gundobina O.S., Vishneva E.A., Margieva T.V., et al. Management of children with glycogen disease (nosological forms with liver damage). Current clinical guidelines. *Pediatric Pharmacology.* 2020;17(4):303–317 (in Russ.). DOI: 10.15690/pf.v17i4.2159.
2. Gümüş E, Özen H. Glycogen storage diseases: an update. *World J. Gastroenterol.* 2023;29(25):3932–3963. DOI: 10.3748/wjg.v29.i25.3932.
3. Kutsev S.I. Path of a patient with a rare diagnosis: regulatory documents and organization of the process of treatment and diagnosis of an orphan disease in the Russian Federation. *Neuromuscular Diseases.* 2017;7(4):61–63 (in Russ.). DOI: 10.17650/2222-8721-2017-7-4-61-63.
4. Poponnikova T.V., Fedoseeva I.F., Galieva G.Yu., Moshneguts S.V. Clinical case of a rare neurodegenerative disease with iron accumulation in the brain, type 4, in a 15-year-old child. *Russian Bulletin of Perinatology and Pediatrics.* 2019;64(5):109–113 (in Russ.). DOI: 10.21508/1027-4065-2019-64-5-109-113.
5. Fedoseeva I.F., Poponnikova T.V., Galieva G.Yu., Ilyasova O.V. Clinical observations of late infantile and juvenile forms of Niemann – Pick disease type C. *Bulletin of Siberian Medicine.* 2017;16(3):210-217. (in Russ.) DOI: 10.20538/1682-0363-2017-3-210-217.
6. Moses S.W., Parvari R. The variable presentations of glycogen storage disease type IV: a review of clinical, enzymatic and molecular studies. *Curr. Mol. Med.* 2002;2(2):177–188. DOI: 10.2174/1566524024605815.
7. Ellingwood S.S., Cheng A. Biochemical and clinical aspects of glycogen storage diseases. *J. Endocrinol.* 2018;238(3):131–R141. DOI: 10.1530/JOE-18-0120.

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