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# Analysis of Risk Factors in the Etiopatogenesis of Congenital Myopathy Syndrome

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**Abstract:** The article substantiates the relevance and outlines the basic principles of differential diagnosis of congenital myopathies. In the last decade, interest in the study of hereditary neuromuscular diseases has increased. This is due to the progress in molecular diagnostics, the emergence of new methods of genetic therapy, which has shown its effectiveness mainly in experimental studies, but already has practical application in the clinic.

**Keywords:** congenital myopathies, megaconial myopathy, Duchenne disease, histochemistry.

However, the pathogenetic mechanisms of the development of these diseases, as well as the body's compensatory capabilities in preventing or mitigating their course, remain poorly studied. Since the discovery of mitochondrial diseases [1], it has become obvious that mitochondrial dysfunctions play an important role in the development of pathological changes in many organs and, in particular, skeletal muscles. Since the number of mitochondrial diseases now significantly exceeds the number of the first classical mitochondrial syndromes (MERRF, MELAS, Kearns-Sayre, etc.), it becomes increasingly important to determine the common features of the clinical course of these myopathies. At the same time, the expanded use of methods for assessing mitochondrial dysfunction in myological practice has led to the understanding that many other neuromuscular diseases can be accompanied by “secondary” changes in mitochondria.

Thus, more than forty years ago, paracrystalline changes in mitochondria were described in congenital megaconial myopathy [2]. In the article by A. Afifi et al. [3], devoted to the possibility of determining the carriage of the mutant Duchenne gene by means of electron microscopy, the authors describe mitochondrial disorders detected in the study of muscle biopsy materials from mothers of sick boys. Evidence of the universality of the role of mitochondria in the pathogenesis of various muscle diseases is a study conducted by J. Muller-Hocker et al. [four]. During the histochemical study of muscle biopsies, the authors found that the violation of oxidative phosphorylation in mitochondria in various myopathies is associated with the proliferation of mitochondria.

In the domestic literature, attention is also paid to the study of mitochondrial disorders accompanying both mitochondrial myopathies and congenital structural myopathies and congenital muscular dystrophies [5, 6]. A feature of the work of Russian researchers was the task of comparing morphological and biochemical laboratory data with indicators of the clinical picture of diseases.

The rapidly growing volume of foreign literature data on the potential success of developments in the field of molecularly targeted treatment emphasizes the need to draw attention to the complex and currently “ungrateful” section of medicine devoted to congenital diseases. Without cardinal changes in the organization of medical diagnostic and rehabilitation measures in this area, in particular, in relation to congenital myopathies, domestic medicine will not be ready for the challenges of modern

science, which is on the verge of discovering fundamentally new forms of treatment. Thus, the emergence of new molecular therapies for certain nosological forms in this area will undoubtedly require at least adequate diagnostic capabilities, as well as appropriate changes in the organizational infrastructure, which would make it possible to quickly and efficiently identify appropriate patients for the provision of highly specialized care. .

With the expansion of our understanding of genetic heterogeneity, we increasingly understand that "congenital myopathies" is a rather broad and generalized concept [1–3]. Sometimes such a breadth on the verge of uncertainty casts doubt on the legitimacy of the very existence of this term. However, generalization is necessary to understand the nature of heterogeneous phenomena, and therefore we will first try to determine what should be understood by the term "congenital myopathies." It is hardly justified to be limited in this case only to such a characteristic as innateness. Apparently, it is most appropriate to include in this group congenital diseases, the primary etiopathogenetic defect in which is associated with damage directly to the striated musculoskeletal tissue. Thus, all ambiguities are immediately removed as to whether it is necessary to consider neurogenic diseases, such as Werdnig-Hoffmann spinal muscular atrophy, which also manifests itself from birth. Yes, and innateness itself, as shown, for example, by our experience, based on albeit infrequent, but still occurring cases of clinically obvious debut of some forms of the disease in adults, can be relative in these diseases. So, continuing our attempts to give a more or less definite description of the concept of "congenital myopathies", we formulate the following definition. Congenital myopathies are a genetically heterogeneous group of hereditary diseases of the musculoskeletal tissue, the common manifestations of which are, as a rule, an early (from birth or from the first months of life) onset, generalized muscle hypotension, symmetrical muscle weakness of predominantly the muscles of the shoulder and pelvic girdle, decreased or the absence of tendon reflexes, normal or moderately elevated blood levels of creatine phosphokinase, and short duration low-amplitude polyphasic polymorphic potentials on electromyography.

**Clinical diagnostics**

1. Beginning in 1900, in a series of articles, the eminent German neurologist Hermann Oppenheim [4] described conditions observed in young children, the main symptom of which was muscular hypotension. Since then, many diseases have been described that debut with a decrease in muscle tone, and in 1958 Greenfield [5] proposed the term "sluggish child" (floppybaby). In early childhood, various causes often lead to the development of the same type of clinical syndromes, which is due to a small differentiation of the structures and functions of the nervous system. In this regard, methods of additional laboratory tests play a particularly important role in establishing a diagnosis at this stage.
2. It so happened historically that in domestic neurology, many pathological conditions of early childhood were explained for a long time by perinatal encephalopathy, hypertensive-hydrocephalic syndrome, and traumatic lesions of the cervical spinal cord. The overdiagnosis of these conditions is explained by the low availability in Russia of fine molecular genetic, biochemical, morphological methods of research until now.
3. Clinical manifestations of the "sluggish child" symptom complex
4. The term "sluggish child" is used in relation to young children, when muscular hypotonia develops during the formation of basic motor skills. Regardless of the cause, the "sluggish child" symptom complex is represented by the same type of clinical picture. Often already in the maternity hospital, it can be suspected on the basis of:
5. unusual "spread out" posture;
6. reduction of resistance in the joints during passive movements;
7. increasing the range of motion in the joints.
8. During a neurological examination, it is necessary to conduct 3 simple tests:
9. traction by the handles from a prone position - this most sensitive test of the study of postural

tone can be performed in newborns directly in the incubator. The child is pulled by the arms to a sitting position. In healthy children, the head comes off the surface at the same time as the body. During traction, the examiner feels the child's pull against traction and observes flexion in the elbow, knee, and ankle joints. There may be a slight tilting of the head with a well-marked flexion in the elbow joints. The response to traction is informative in a newborn with a gestational age of at least 33 weeks. The presence of a pronounced lag of the head of a newborn and its significant tilting, weak resistance to traction, insufficient flexion of the limbs and the absence of flexion in the elbow joints are pathological and indicate muscle hypotension;

10. horizontal suspension - the child, who is in a horizontal position, face down, is held by the torso. A healthy child does not lower his head, keeps his back straight, bending his arms at the elbow joints, legs at the hips, knees. Children with hypotension limply hang on the hands of the researcher;
11. vertical suspension - to perform this test, the researcher places his hands under the armpits of the child, not tightly clasping the chest, and lifts him up. Normally, the child's shoulders tense up, allowing them to hang vertically without falling through. The head is held straight and the legs are bent at the knees, hips and ankles. In a child with hypotension, with vertical suspension, the head hangs forward, the legs hang freely; the child may slip through the hands of the researcher due to weakness of the muscles of the shoulder girdle.

In the case of severe violations in all 3 tests, the doctor can conclude that there is a “sluggish child” symptom complex.

Later, a delay in motor development is detected.

When detecting muscle hypotension, it is necessary to exclude diseases such as:

- ✓ sepsis, infectious diseases (meningitis, encephalitis);
- ✓ congenital heart defects;
- ✓ diseases of the endocrine system (hypothyroidism);
- ✓ malnutrition (malabsorption, malnutrition);
- ✓ transient metabolic disorders (hypercalcemia, hypermagnesemia);
- ✓ drug intoxication of the mother (neuroleptics, benzodiazepines, hypnotics, magnesium sulphate);
- ✓ other curable conditions.

With the exclusion of the above violations, they proceed to the next stage of differential diagnosis - the determination of the central or peripheral origin of muscular hypotension. More often, hypotension in newborns is caused by damage to the central nervous system (CNS) (about 80% of cases), 20% of cases are associated with damage to the motor unit, including all its elements - from the motor neuron to the muscle fiber.

Clinical differences between central and peripheral hypotension are as follows.

Hypotension in case of damage to the central nervous system usually in the future (usually up to 6 months) is replaced by spasticity, while hypotension in case of damage to the motor unit persists throughout the disease.

Muscle strength, determined primarily by range of motion, may not decrease or decrease slightly with central hypotension, while it is significantly reduced with peripheral hypotension.

The severity of tendon reflexes also differs significantly: with a central lesion, they are increased, with a peripheral lesion, they are reduced. It should be remembered that sometimes with severe hypoxic damage to the brain, reflexes can be suppressed for a long time. It is important to note that in congenital myopathies, reflexes are often normal or even elevated. Often you have to focus on the delay in the reduction of reflexes in newborns. If such a delay occurs, then we are talking about CNS damage. With a birth injury to the spinal cord, the severity of tendon reflex disorders depends on the

level of the lesion.

Muscle atrophy is noted only with hypotension of peripheral origin, but in infants it may be absent.

For the differential diagnosis, the presence of mental retardation, seizures, which are often found in central lesions, is important, although in some congenital neuromuscular diseases (for example, in congenital muscular dystrophies), defects in the central nervous system may also be noted.

Assessment of movement disorders in older children and adults

In a clinical examination of children with suspected congenital myopathy, a comprehensive assessment of motor disorders is of key importance.

Assessment of motor activity is carried out by such methods as: gait study, Gowers test, the possibility of climbing stairs, assessment on special scales, etc.

Widely known, simple and informative is the Gowers test. The patient should get up from a sitting position on the floor with legs extended. Normally, the test is performed up to 5 s. The presence of myopathic techniques is taken into account (kneeling, climbing with a ladder).

Effective methods for assessing the dynamics of the state, in which the time spent on the execution of the test is fixed, are:

- ✓ test with 8 steps up the stairs;
- ✓ a test of walking on a plane at a distance of 9 m.

Assessment of movement disorders on scales

The MRS scale (Medical Research Council Paralysis Scale 1976) is designed to assess the muscle strength of the arms and legs [6]; the parameters of muscle strength of the limbs are evaluated, presented in table. one.

**Table 1. Assessment of muscle strength of the limbs according to the MRS scale**

| | |
|---|---|
| 0 points | no movement |
| 1 point | minimal movement |
| 2 points | active movements, but the inability to overcome gravity |
| 3 points | the ability to overcome the force of gravity when performing a certain movement |
| 4 points | the ability, when performing a certain movement, to overcome not only gravity, but also sufficient resistance of the researcher |
| 5 points | complete preservation of motor function |

The Scott scale (Muscular Dystrophy Score, MDS) [6, 7] is used to assess the overall index of physical activity. For each patient, the sum of points is calculated according to the following scheme: 2 points - for each independently completed movement, 1 point - if assistance was provided and / or the movement required great effort, 0 points - if the movement was impossible to perform . The types of movements assessed on the Scott scale are presented in Table. 2. The maximum possible score on this scale is 40 and the minimum is 0.

Vinyosa scale [6, 8, 9]. The assessment on this scale is carried out according to 10 functional classes presented in Table. 3.

Functional diagnostics

Electroneuromyography (ENMG) is a modern and highly informative method for diagnosing neuromuscular diseases, based on recording spontaneous fluctuations in electrical potentials of muscle and nerve fibers. When ENMG is performed in patients with congenital myopathies, “primary muscle” changes are detected in the form of a type 1 interference curve [10], a decrease in amplitude, a decrease in the duration of muscle potential, and an increase in the number of polyphasic potentials. Motor fiber conduction velocities are usually normal. The severity of electromyographic changes depends on the form and severity of the clinical manifestations of the

myopathic symptom complex [11].

**Table 2. Types of movements assessed on the Scott scale**

| |
|---|
| 1. Lifting the head |
| 2. Turn from back to stomach through the right side |
| 3. Turn from back to stomach through the left side |
| 4. Turn from stomach to back through the right side |
| 5. Turn from stomach to back through the left side |
| 6. Sits down (takes a sitting position) |
| 7. Sitting |
| 8. Gets up (takes a standing position) |
| 9. Worth it |
| 10. Stands on heels |
| 11. Stands on toes |
| 12. Stands on the right foot |
| 13. Stands on the left leg |
| 14. Jumps on the right foot |
| 15. Jumps on the left foot |
| 16. Gets up from a chair |
| 17. Ascending step with right foot (climbing stairs) |
| 18. Descending step with right foot (downstairs) |
| 19. Left foot ascending step (stair climbing) |
| 20. Descending step with the left foot (downstairs) |

***Ultrasound diagnostics and magnetic resonance imaging***

These non-invasive methods make it possible to assess the relative safety of muscle tissue and study its changes over time.

Ultrasound examination (ultrasound) of the muscles makes it possible with a high degree of probability to distinguish a healthy patient from a patient with a neuromuscular disease. In addition, it is possible to differentiate patients with neurogenic and primary muscle lesions [12, 13]. The effectiveness of this method is low in young children [14].

**Table 3. Functional classes of the Viños scale**

| |
|---|
| 1. Patient has obvious postural and gait disturbance but walks and climbs stairs without support |
| 2. The patient walks but climbs the stairs with the help of the railing |
| 3. Patient walks but climbs stairs 8 standard steps using railings in more than 25 seconds |
| 4. Patient walks but cannot climb stairs |
| 5. The patient walks without support, but cannot lift his mother's leg to step on steps or cannot get up from a chair. |
| The patient walks only in an orthopedic corset |
| 7. Patient in a wheelchair. Sits upright, can control the chair and perform all vital actions from the chair |
| 8. Patient in a wheelchair. Sitting upright but unable to perform all vital activities from chair |
| 9. Patient in a wheelchair. Sits upright only with support. Can perform a minimum of vital actions from a chair |
| 10. The patient is chained to the bed. Cannot perform life-saving activities without assistance |

Magnetic resonance imaging (MRI) allows you to determine the state of muscle tissue with a higher resolution, to identify the localization and extent of the lesion. Like muscle ultrasound, MRI can detect nonspecific changes, such as fatty infiltration [14, 15]. The possibilities of the method make it possible to solve some specific differential diagnostic problems, for example, to distinguish between acute and chronic muscle denervation [16–18].

**Conclusion**

Congenital myopathy is a concept that hides a huge group of diseases, the true dimensions of which we still do not really imagine. By the end of the 20th century, the remarkable advances in molecular and clinical genetics made the heterogeneity of these relatively indistinguishable diseases more than just obvious. The number of identified nosological forms from the last quarter of the last century and up to the present day has been growing and is growing catastrophically in the literal sense of the word. Before this wave of new names, definitions, genetic determinants and pathogenetic schemes, the possibilities of functional and laboratory diagnostics, the vast majority of not only neonatologists and pediatricians, but even neurologists are lost. At the same time, the etiopathogenetic and diagnostic boom in theoretical myology discouragingly does not correspond to the miserable possibilities of treatment. And this discrepancy psychologically substantiates the self-justification of a doctor who does not even try to understand more and more genetically heterogeneous, but clinically similar diseases, traditionally accompanied by unified and infinitely primitive treatment algorithms. And yet, the successes of science, primarily molecular medicine, which are more and more noticeable in neighboring areas, make us expect the same in the field of neuromuscular diseases with increasing trepidation, and, consequently, raise the question of the need for an active dissemination of knowledge about them and attracting the widest research circles to the dramatic problems of myology.

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