National consensus on diagnosis, treatment and prevention of hereditary neuromuscular disorders

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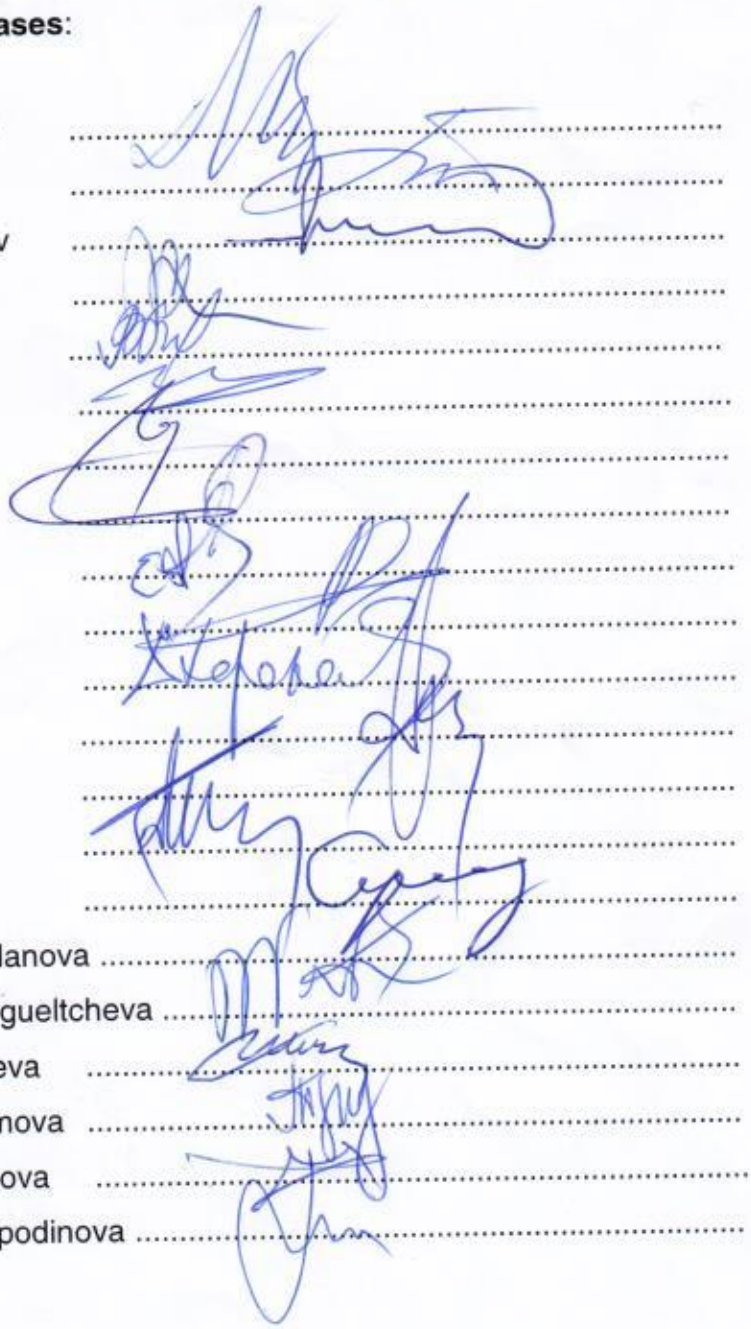
Bulgarian Society of Neuromuscular Diseases
Bulgarian Society of Neurology
Bulgarian Society of Child Neurology, Psychiatry and Developmental Psychology

National consensus on diagnosis, treatment and prevention of hereditary neuromuscular disorders

Today, 22 June 2021, we, the undersigned specialists, have reached a consensus on the diagnosis, treatment and prophylaxis of the hereditary neuromuscular diseases:



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Abbreviations used:

AD- autosomal-dominant

AR- autosomal-recessive

ALAT- Alanine aminotransferase

ASAT- Aspartate aminotransferase

ATF- Adenosine triphosphatase

CMD- Congenital muscular dystrophy

CM- Congenital myopathies

DAGC- Dystrophin-associated glycoprotein complex

ERT- Enzyme replacement therapy

ЕКГ- Electrocardiography

EMG- Electromyography

ENG- Electro neurography

EchoCG- Echocardiography

PDM- Potassium-dependent myotonia

CPK- Creatine phosphokinase

CS- Corticosteroids

MMT- Manual muscular testing

MRT- Magnetic resonance tomography

NMD- Neuromuscular diseases

NGT- Nasogastric tube

HSMP- Hereditary sensory and motor polyneuropathies

PMD- Progressive muscular dystrophies

GLMD- Girdle-limb muscular dystrophies

SMA- Spinal muscular atrophy

SC- speed of conduction

FVC- Forced vital capacity

FEV1- Forced expiratory volume of 1 s

FBT- Functional Breathing Testing

CNS- central nervous system

CMT- Charcot-Marie-Tooth

GAA- acidic alpha-glucosidase

MLPA - multiplex ligation-dependent probe amplification

Introduction: Hereditary neuromuscular diseases are rare, progressive and debilitating diseases with involvement of peripheral nerves and muscles. They are due to genetic defects (mutations) in genes, which encode the muscle proteins or enzymes, involved in energy metabolism, as well as inflammatory and autoimmune processes.

They persist with progressive weakness and atrophy of the muscles of the limbs, in some cases also of the paravertebral and respiratory muscles, rarely with hypertrophy. They are divided into muscular diseases (congenital muscular dystrophies and myopathies, progressive muscular dystrophies, myotonia, metabolic); neuropathies (hereditary); anterior horn diseases (spinal muscular atrophies); diseases with impaired neuromuscular transmission.

They are diagnosed based on a precise anamnesis of the onset of the disease, the localization of the weakness, the presence of other people with the disease in the family; clinical characteristic; neurological examination of loose paresis syndrome of different localization and degree of expression, hypotrophy, with or without fibrillation; EMG assay for the detection of myogenic, neurogenic, anterior horn or impaired neuromuscular transmission; biochemical investigations for the detection of elevated creatine kinase ASAT, ALAT, other enzyme deficiency; genealogical and molecular genetic studies to determine the genetic defect of the disease. The diagnostic process distinguishes muscular disease (congenital myopathy, muscular dystrophy, myotonic dystrophy, myopathy of exchange, inflammatory myopathy), neuropathy (hereditary), anterior horn damage (different types of spinal muscular atrophy).

Inherited neuromuscular diseases should be distinguished from acquired diseases - inflammatory and infectious myopathies, inflammatory, toxic and other polyneuropathies, acute or chronic diseases of peripheral motor neuron and autoimmune myasthenia.

General Practitioner Actions: history of onset, presence of inflammatory disease, congenital or slow-progressing muscle weakness, presence of family history; somatic status, FBC, CPK, ASAT, ALAT; ECG; referral to a neurologist; tracing of the somatic status of the patient - cardiological, respiratory problems.

Actions of the specialist neurologist in outpatient care: neurological status for loose paresis, analysis of laboratory tests for elevated values of CPK, ASAT, ALAT; EMG for the location of the disorder (myogenic, neurogenic, anterior horn, neuro-muscular transmission disorder). Direction to nervous diseases clinic to Specify type of disease, specialized genetic verification testing; tracking the course of the disease.

Neurologist's actions in hospital care: Clarification of the type of the disease (muscular, neurogenic, anterior corneal, impaired neuro-muscular transmission), clarification of the type of inheritance, referral of the patient for genetic testing and genetic counseling.

A. Muscle disorders: Congenital Muscular Dystrophies, Congenital Myopathies, Progressive Muscular Dystrophies, Metabolic Myopathies.

1. **Congenital muscular dystrophies (CMD)**

   They are genetically and clinically heterogeneous hereditary myopathies with predominant autosomal recessive inheritance pathways, characterized by nascent or early childhood muscular hypotension, retarded motor development, progressive muscle weakness, Joint contractures and dystrophic changes in histological muscle testing.

They are classified into four main groups, based on their molecular-genetic, clinical and biochemical features:

- CMD, due to a defect of laminin 2α, leading to primary basal membrane involvement (CMD with merosin deficiency MDC1A)
- CMD, caused by the abnormal glycosylation of α-dystroglycan (Walker-Warburg, Fukuyama, CMD Muscle-Eye-Brain)
- CMD, related with disorders, leading to severe contractures (CMD with rigid spine, CMD of Ullrich)
- CMD, due to primary or secondary deficiency of α-7-integrin

Another classification divides CMD into two groups, depending on the presence or absence of CNS involvement

- Pure forms of CMD that are divided into merosin-positive and merosin-negative
- CMD woth CNS involvement (Walker-Warburg, Fukuyama, CMD Muscle-Eye-Brain)

Epidemiology. The most common forms are CMD with merozine deficiency and CMD of Ullrich, although ethnic and regional differences in morbidity and disease are present. MDC1A accounts for about 30-40% of the cases with CMD in Europe and Brazil, and CMD of Ullrich - 9.4% of the CMD cases in Europe. In Japan, the CMD of Fukuyama has an incidence of 1 / 10,000 in newborn babies due to mutation with a

parental effect. In Finland, for similar reasons, the CMD type muscle-eye-brain disease is 1 / 50,000.

Etiology. In recent years, the presence of multiple genes and gene loci have been elucidated, whose mutations lead to the appearance of congenital muscular dystrophies (Table 1).

Table 1. CMD classification.

Type of CMD and mode of inheritance	Mutant gene / affected protein
CMD with merosin deficiency (AR)	LAMA2 (6q22-q23) Laminin 2-α chain of merosin
CMD with merosin deficit (AR)	? – (1q42)
CMD with impaired glycosylation of α-dystroglycan 1C (AR)	FKRP (19q13.33) fukutin linked protein
CMD with impaired glycosylation of α-dystroglycan 1D (AR)	LARGE(22q12.3–q13.1)
Fukuyama CMD – (AR)	FCMD (9q31–q33) fukutin
Walker-Warburg syndrom – (AR)	FCMD (9q31–q33) fukutin POMT1 (9q34.1) protein-O-mannosyltransferase 1 POMT2 (14q24.3) protein-O-mannosyltransferase FKRP (19q13.33) fukutin linked protein
CMD Muscle - eye-brain – (AR)	POMGNT1 (1p34.1) O-linked mannoso-beta,2-N-acetylglucosaminyl transferase FKRP (19q13.33) fukutin linked protein POMT2 (14q24.3) protein-O-mannosyltransferase 2
CMD with a rigid backbone - (AR)	SEPN1 (1p36.13) selenoprotein N1
Ullrich CMD – (AR)	COL6A1 (21q22.3) Alpha 1 type collagen VI COL6A2 (21q22.3) Alpha 2 type collagen VI COL6A3 (2q37) Alpha 3 type collagen VI
Bethlem myopathy – (AD)	COL6A1 (21q22.3) Alpha 1 type collagen VI

	COL6A3 (2q37) Alpha 3 type collagen VI COL6A2 (21q22.3) Alpha 2 type collagen VI
CMD with integrin deficit	ITGA7 (12q13) Integrin alpha 7 precursor

The majority of the genes, conditioning the CMD pathogenesis are associated with the function of the dystrophin-glycoprotein-associated sarcolemma complex, as a result of which abnormalities in extracellular matrix proteins (collagen and merosin) and glycosylation of α-dystroglycan are established. Merosin deficiency leads to easier damage to myofibers and dystrophic changes in muscles.

Clinical manifestations: The severity of affecting the muscles varies widely from a severe neonatal hypotonia (floppy baby), accompanied by respiratory and swallowing disorders with early lethality, to moderately severe motor delays and mild to moderate muscle weakness of the type of girdle limb, occurring in the early years of life. Patients often have multiple contractures (artrogriposis). The clinical course is slowly progressing or lacking progression.

CMD with a merosin deficiency is caused by mutations in the Lamin α-2 gene (LAMA), localized in 6q2.

The severe form, caused by the complete lack of merosin, is characterized by:

- Expressed muscular weakness and atrophies
- Joint contractures
- Inability to achieve an independent gait
- Dysmorphic features (big head, long and narrow faces, open mouth, high palate)
- Significantly elevated creatine phosphokinase in serum
- Specific extensive changes in the white matter MRI -assay

Slight clinical variations are due to a decreased amount of merosin. They go along with:

- Later onset and slow progression
- Patients achieve the ability to walk
- Muscle weakness in the type of girdle-limb
- MRI data confluent lesions in the white brain matter

Cognitive disturbances, epileptic seizures, and neuronal migration disorders are rarely reported in patients with CMD with a merozine deficiency.

Collagen VI - related disorders. A wide variety of mutations in one of the three collagen genes COL6A1, COL6A2, COL6A3, respectively encoding the α1, α2 and α3 chains of collagen 6, cause two types of CMD: *Bethlem type and Ullrich type.* With these diseases the synthesis, structure, secretion or function of collagen 6 are disrupted. These are diseases that are clinically characterized by varying degrees of severity of muscular weakness, hypotrophies, joint contractures, loose distal joints and respiratory failure.

Myopathy Bethlem type is an inherited disease with AD-type inheritance due to mutations of COL6A1, COL6A2 or COL6A3- genes. It is characterized by a benign course and slow progression:

• Clinical start in the neonatal period, child or adolescent age

• Slow progressing proximal and axial muscular weakness

• Early contractures in the area of interphalangeal joints of the elbow and the ankle joints

• Follicular hyperkeratosis and keloid formations

Ullrich type myopathy is caused by AD or AR inherited mutations in the genes, coding the collagen chains VI. With this myopathy, the clinical presentation is significantly heavier, more homogeneous than CMT type Bethlem, including:

• Muscular weakness from birth

• Facial weakness

• Torticollis

• Hip dislocation

• Contractures of proximal joints, loose distal joints

• Progressive scoliosis

• Breathing disorders occurring until the end of the first year

• Impossible independent gait

• Normal Intelligence

• Follicular hyperkeratosis, papillary rash, hyperhidrosis,

• Dysmorphic features (prominent ears, high palate)

• Wounds heal defectively, with keloid formation.

CMD, caused by to abnormal glycosylation of α-dystroglycan

Defects in the glycosylation of α-dygroglycan may be due to mutations in six genes encoding specific and putative glycosyltransferases: POMT1, POMT2, POMGnT, Fukutin, FKRP, LARGE, as mutations in the same gene may condition different CMD variants. These muscular dystrophies are AR inherited, showing genetic and clinical heterogeneity from isolated muscle involvement to engaging both CNS and eyes to varying degrees.

CMD type Fukuyama is the most common CMD in Japan due to a mutation with a parental effect. It is caused by mutations in the gene encoding fukutin, localized in 9q31-33. Fukutin is a glycosyltransferase whose function and association with other glycosylation enzymes is not well studied. The following is present:

- Reduced fetal movements and neonatal asphyxia
- Generalized muscle weakness and hypotension, with more pronounced involvement of proximal muscles from infancy
- Mental retardation and epileptic seizures (most commonly generalized tonic-clonic)
- Hypertrophy of the muscles of the tongue, lower legs and m. quadriceps,
- Dilatative cardiomyopathy, most commonly in the second decade of life
- Eye involvement includes dysplasia, melting, retinal detachment, sometimes accompanied by abnormal eye movements, strabismus, myopia and microphthalmia
- CNS abnormalities: cerebral and cerebrovascular polymicrogyria, dilated cerebral ventricles, brainstem hypoplasia, microglial proliferation of soft brain sheath, hydrocephalus, hypoplasia of the corticospinal pathways

Neuroimaging studies have found abnormalities in white brain matter that decrease with age, abnormalities in the occipital cortex, bridge hypoplasia and cerebellar vermis, cerebellar cysts.

CMD type „Muscle-eye-brain” is a disease with AD type of inheritance, in which besides the muscular involvement, more eye and cortical brain abnormalities are described. Implicated by mutations in the POMGnT1 gene located in Ip34-p32 encoding glycosyltransferase. These patients are identified with:

- Generalized muscle weakness and hypotension, with predominant proximal involvement
- Mental retardation, epileptic seizures

• Congenital ocular abnormalities: myopia, glaucoma, optic nerve and retinal hypoplasia

• CNS abnormalities: pachygyria, polymicrogyria, agyria, flat brainstem, cerebellar hypoplasia

• Other features are hydrocephalus, dysmorphic facies (narrow nose base, micrognatia, facial hypoplasia).

Walker-Warburg Syndrome is a genetically and clinically heterogeneous disorder with AR-type inheritance. It is due to mutations more often affecting POMT1, POMT2, POMGnT genes and, less frequently, fukutin, FKRP and LARGE.

- Polyhydramnios and decreased fetal movements during pregnancy
- Severe damage to muscles, brain and eyes with survival to 2-3 years
- Severe muscle hypotension and weakness
- Mental retardation
- CNS involvement - lissencephalia type 2, obstructive hydrocephalus, neuronal heterotopias, corpus callosum agenesis, non-separation of the cerebral hemispheres, leptomeningeal glio-mesodermal proliferations, pontocerebellar hypoplasia with IV cerebral ventricle dilation, rarely occipital encephaloceles and Dandy-Walker malformations, hypomyelinization
- Epileptic seizures
- Eye abnormalities - retinal detachment with subsequent blindness, microphthalmia, buphtalmus, optic nerve hypoplasia, coloboma, and other iris malformations, congenital glaucoma, cataracts, megalocornea
- Dysmorphic features such as cleft lip and palate, the prominent ears

These patients require palliatively the placement of a nasogastric tube, ventriculoperitoneal shunt, surgical repair of encephalocele.

Congenital muscular dystrophy type 1 C is a form of CMD caused by mutations in the FKRP gene, which can also cause girdle-limb muscular dystrophy. The severity of the clinical presentation correlates with the expression of the a-dystroglycan. These patients do not walk and have typical hypertrophy of the thigh and calf muscles. This form of the disease is progressive, affecting the respiratory muscles and the heart during the second decade of life. High CPK values are detected.

Congenital muscular dystrophy type 1 D is caused by mutations of the LARGE - gene and is clinically characterized by manifested muscular hypotension (floppy baby) and severe mental retardation due to defects in neuronal migration.

Congenital muscular dystrophy with a rigid backbone. Affected patients have homozygous or heterozygous mutations in the SEPN1 gene. The disease is clinically characterized by:

- Restriction of the spine flexion
- Progressive scoliosis, reducing vital capacity and leading to respiratory failure
- Weakness of the facial musculature, bulbar muscular weakness
- Joint contractures in the elbow and knees, scapulae alatae, pectus excavatus
- Limited weight gain

More commonly, the thigh adductors are affected, m. biceps femoris, m. Sartorius, while m. rectus femoris and m. gracilis remain relatively well preserved. Despite severe axillary muscle weakness and generalized muscular atrophy, patients with this disease have long maintained the ability to gait alone.

The main feature of this form of the disease is the contrast between the relatively preserved muscle strength of the limbs and the severe muscular weakness of the axial neck and torso musculature. The prognosis depends on the severity of involvement of the respiratory muscles. In the majority of patients scoliosis progresses and becomes severe at the end of the first decade. Respiratory insufficiency necessitates the relatively early use of non-invasive ventilation beginning between 4 and 10 years of age.

CMD type 1B is characterized by generalized hypotension, delayed motor development, proximal muscle weakness, severe cervical muscular involvement and early development of respiratory failure. The neuropsychiatric development is within the norm.

CMD with α-7 integrin deficit. Clinically characterized by delayed motor development as with congenital myopathy, mental retardation without changes in MRI of the brain, congenital torticollis.

CMD, caused by LMNA- gene mutations. Lamins are proteins that are part of the nuclear membrane, which determine its shape and size. Mutations in the Lamin A / C - gene lead to various neuromuscular diseases, including muscular dystrophies such as the AD-form of Emery-Dreifuss type of muscular dystrophy, Girdle-limb type 1B muscular dystrophy, axonal motor and sensory polyneuropathy. Patients are

conventionally divided into two groups: the first are younger, with severe muscle weakness and very low motor development, and the second are older with a pronounced weakness of the cervical musculature under normal early motor development. All children have an early rapid progressive weakness of the axial muscles and the consequent lack of progression. Respiratory insufficiency occurs clinically earlier in the first group, but also in the second group it occurs before 8 years of age. Four of the patients have cardiac involvement - arrhythmias. The proximal upper limb muscles and the distal upper limbs are more severely involved. Rigid backbone with thoracic lordosis is developing early.

The diagnosis is based on the following studies:

- Clinical manifestations for neonatal onset in or onset in early childhood
- Presence to other eye anomalies, mental retardation, epileptic seizures
- Increased CPK values
- EMG data of myogenic damage
- Histological examination of muscles
- Cerebral MRT
- Genetic research

Treatment. Despite the large number of therapeutic strategies (mainly within gene therapy) that are being studied for CMD therapy, palliative care has been established at this stage depending on the age and condition of the patients. For this purpose, a multidisciplinary team, including neurologists (treatment of epileptic seizures), orthopedics (surgical treatment of joint contractures and scoliosis), physiotherapists, anesthesiologist-reanimator (respiratory resuscitation - non-invasive and invasive, nasogastric tube) is needed.

2. Congenital myopathies. A group of hereditary muscular diseases that are diagnosed based on structural changes in muscle fibers, visible after staining of the muscular biopsy material by histochemical methods. Table 2 lists the genes, the mutations in which the development of various forms of congenital myopathies is determined. They are classified into the following types:

2.1. Myotubular / centronuclear myopathy

Extremely rare form, including usually a severe X-linked recessive form with a pre- or neonatal onset, an autosomal-recessive form with an early onset or a later

childhood onset, and a relatively mild autosomal dominant form with a late onset. Typical histological picture.

Diagnostic criteria for the X-linked form:

- Male gender
- Perinatal start
- Severe generalized muscle weakness and hypotension with respiratory failure and often fatal outcome.
- There may be: polyhydramnios, swallowing disorders, thin ribs, hip and knee joint contractures, ophthalmoplasia, large head, elongated face, thin fingers.
- CPK normal or slightly increased

Diagnostic criteria for the AR form:

- Onset in early childhood, later childhood, or in adults under 30 years of age.
- Ophthalmoplegia may occur at early onset
- The proximal weakness is heavier than the distal
- Facial weakness
- Survival after the early childhood

Diagnostic criteria for the AD form:

- Late childhood onset or onset at mature age
- The proximal weakness is heavier than the distal
- Cramps in lower legs
- CPK normal or slightly increased
- In some families - ophthalmoparesis, ptosis, facial weakness, distal muscular weakness, contractures, rigid spine

2.2. Nemaline myopathy

Neuro-muscular disease characterized by muscle weakness in the presence of nemaline bodies (sticks) in the muscle fibers, in the absence of other known conditions, sometimes associated with sticks. There are AD, AR and sporadic forms.

Diagnostic criteria

- The onset is usually in early childhood, but may also be in later childhood or adulthood.
- Muscular weakness is the most severe in the face, neck flexion and proximal limb muscles, sometimes there may be distal involvement. Often there are respiratory disorders, and in small children – swallowing disorders.
- For congenital forms - arthrogryposis

• CPK is normal or slightly elevated

• EMG shows myopathic changes, but in some older adults in distal muscles - neuropathic. ENG is within the norm.

2.3. "Central core" congenital myopathy

Congenital myopathy with AD or AR inheritance. Mutations in the rianodine receptor on 19q13.1 are detected. Some of the mutations lead to "Central core" congenital myopathy and a tendency to malignant hyperthermia and others to malignant hyperthermia only. A characteristic histological picture.

Diagnostic criteria:

• Age of onset - early childhood and less often at later age

• Hypotension and delayed motor development

• Generalized muscle weakness, more proximal and more in the lower limbs

• Weakness of facial muscles, sternocleidomastoideus and trapezius and skeletal abnormalities may be observed

• Non-progressive or slow progressive development

• CPK is normal or slightly elevated

• EMG is myopathic or normal

• Risk of malignant hyperthermia with the use of some inhaled anesthetics and depolarizing muscle relaxants such as succinylcholine

Treatment: Regular rehabilitation and application of orthoses when necessary are essential.

2.4 Congenital myopathy with fiber disproportion is a form with a significant difference in the size of the muscle fibers between Type 1 and Type 2.

Diagnostic criteria:

• Onset in the first 1 year of life

• Delay in motor development and muscle hypotension

• Facial and weakness, expressed in the shoulder and pelvic girdle

• Non-progressive or slow progressive development

• Restrictive respiratory distress

• Bulbar weakness

• Joint contractures

• CPK is normal or slightly elevated

• EMG is myopathic or normal

Treatment: Regular rehabilitation and application of orthoses when necessary are essential.

2.4. Myopathy with accumulation of myosin is a form caused by mutations in the MYH7 gene

Diagnostic criteria:

• Onset in childhood

• Delay in the motor development

• Distal weakness in upper and lower limbs and pseudohypertrophy of lower legs

• Cardiomyopathy

• Slowly progressing

• Joint contractures

• CPK is normal or slightly elevated

• EMG is myopathic or normal

Treatment: Regular rehabilitation and application of orthoses when necessary are essential.

Table 2. Genes, the mutations of which is involved in the development of various forms of congenital myopathies.

	ACTA1	NEB	MTM1	MYH7	DNM2	RYR1	TPM2	TPM3	TNNT1	CFL2	SEPN1	BIN1	TTN
Nemaline myopathy	X	X				X	X	X	X	X			
Central core myopathy				X		X					X		
Centronuclear myopathy			X		X	X						X	X
Myotubular myopathy			X										
Congenital myopathy with fiber disproportion	X			X		X	X	X			X		
Myopathy with accumulation of myosin				X									

3. Progressive muscular dystrophy type Duchenne/Becker

They are hereditary diseases caused by mutations, affecting the dystrophin gene, located in the X chromosome, which are clinically manifested with progressive muscle weakness to severe disability, cardiomyopathy and, in some cases, mental retardation and nanism. They differ from each other in terms of onset, the severity of clinical symptoms and the rate of progression of the disease.

Epidemiology: PMD Duchenne type occurs at a frequency of 1 per 3500 live births. In 30% of them the mutation occurs de novo. Becker type PMD appears at a frequency of 1 per 30,000 live births. 50% of the mutations are de novo.

Etiology: The dystrophin gene is located on the X-chromosome in the locus Xp21 and is one of the largest genes in the human genome. Various mutations are responsible for the ΠMD Duchenne type. Most often they are:

- Deletions - about 60%
- Duplications - about 10%. They are mainly concentrated in the proximal part of the gene, around intron 7.
- Point mutations: one nucleotide replacements, insertions, small deletions and duplications - about 30%. Point mutations can be in the splice site or in the exon (meaningless).

In patients with Becker type PMD, 80% of the mutations responsible for the disease are deletions in the dystrophin gene.

Pathogenesis: Dystrophin is a protein with a molecular mass of 427 kDa. Its is found in its various isoforms it in the muscles, retina, neurons of the CNS. Dystrophin is a cytoskeletal protein located on the inner surface of the sarcolemma as a major element of the dystrophin-associated glycoprotein complex (DAGC). DAGC is a complex supramolecular organization - a bridge between the cytoskeleton, sarcolemma, and basal membrane that stabilizes the sarcolemma in muscle contraction and protects myofibriles from necrosis.

Clinical presentation of PMD type Duchenne is described with:

- Onset before the age of 5 years, some patients with delays in walking and clumsy gait before the onset of the disease or global delay in neuropsychology development
- Progressive muscular weakness, primarily engaging the proximal musculature, first of the lower limbs and subsequently of the upper limbs

• Difficult climbing of ladders, frequent falling, difficulty in standing up from a squat position or other movements that engage the muscles of the pelvis (m. Iliopsoas and gluteal muscles) and the proximal limb muscles (m. Quadriceps)
• Gowers phenomenon (when standing up from squat, the patient is leaning against his thighs, typical climbing up straightening with the help of his hands)
• Joggling gait, then patients begin to walk on fingers due to atrophy of the pre-tibial muscles
• Pseudohypertrophy of m. triceps surae
• Girdled hyperlordosis with stomach projection
• Scapulae alatae
• Joint contractures, with initial involvement of ankle joints and Achilles tendon (pes equinovarus) and subsequently knee, elbow, shoulder, hip and intervertebral joints. They develop kyphoscoliosis
• Loss of independent gait before the age of 13 years

- Breathing disorders are very typical in boys with PMD type Duchenne and are established shortly after the loss of the independent gait. Kyphoscoliosis, weakness of the intercostal muscles and the diaphragm impair the external breathing. A restrictive type of breathing disorder develops, and for 73% of patients the immediate cause of fatal outcome is the respiratory failure. Initial clinical symptoms due to hypoxemia and hypercapnia may be very mild, such as body mass reduction, tiredness, poor school success and sleep disturbances. Lung infections then become more common and more difficult to treat. If the developing hypercapnia is not treated, headache, general malaise and the risk of death due to acute respiratory failure, induced by intercurrent infections, increase significantly. Patients have decreased vital capacity, frequent pneumonia, and develop respiratory failure, which requires respiratory support at the advanced stages of the disease.

- Cardiac involvement (dilated cardiomyopathy) occurs in 50% to 80% of patients during the course of the disease, with heart failure, persistent tachycardia, rhythmic and conductive disorders and acute myocardial infarctions.
- Symptoms of involuntary muscle dysfunction result from muscle fiber necrosis, cell nucleus degeneration and fat infiltration. Gastric hypomotility is manifested by heaviness, abdominal pain and vomiting. In a minority of patients malabsorption syndrome with diarrhea, megacolon or motility disorders of the

esophagus is established. Constipation is the result not only of the involvement of smooth bowel muscles but also of the weakness of the striated abdominal musculature, resulting in a reduction in intra-abdominal pressure at defecation.

- In most patients with Duchenne type PMD, cognitive impairment of non-progressive nature is established.

The clinical presentation of PMD type Becker It is similar, but less severe than in Duchenne PMD type. The presence of dystrophin in reduced quantities, or structurally abnormal dystrophin, determines the later onset and lighter clinical picture in patients with PMD type Becker.

• The onset of the disease is after 7 years of age

• Gradually developing progressive muscle weakness such as the proximal muscles are more severely affected than the distal, and lower limbs are affected earlier than the upper ones

• Pseudohypertrophy of the lower legs

• Weakness in m. quadriceps femoris may for a long time be the only manifestation of the disease.

• Painful cramps during physical exercise, whether or not accompanied by myoglobinuria in some patients

• Loss of independent gait after 16 years of age. Some patients retain their ability to stand alone up to 30-35 years of age. In these patients, cardiomyopathies and mental retardation are less frequent and lighter.

• Cardiac involvement can develop regardless of the muscle weakness

The diagnosis is based on the characteristic clinical and paraclinical studies.

- There are different scales for assessing and monitoring the progression of muscle weakness in patients with dystrophinopathies and the effect of therapy:
  - Medical Research Council (MRC) manual muscle testing scale
  - The North Star Ambulatory Assessment
  - 6-minute walk test
  - 10-meter walk test

• Biochemical studies showed data on elevated CPK, ASAT, ALAT, and LDH values. Patients with PMD Duchenne type have CPK increased at least 10 times than the normal value (usually between 25 and 200 times), and in PMD type Becker - at least 5 times.

• Electromyography (EMG)

• Muscle biopsy - with variable dimensions of the muscle fibers (atrophic and hypertrophic), necrotic and regenerative fibers, endo- and perimyseal fibrosis, as well as hyalinated muscle fibers. Immunohistochemistry and Western blot showed no dystrophin in PMD Duchenne type and reduced dystrophin in Becker type.

• It is recommended ECG and echocardiography to be performed once a year

• A functional breathing test is conducted once a year

• Genetic study of the patients and their mothers and sisters

• MLPA (multiplex ligation-dependent probe amplification) to detect deletions and duplications

• Sequencing of the dystrophin gene to detect small deletions, insertions, point and splice mutations, accounting for about 35% of mutations in the PMD Duchenne type

Treatment and care of patients with dystrophinopathies. The main objectives of the complex therapy, carried out by a multidisciplinary team of specialists, are to extend the period of independent gait, deferral of complications such as Joint contractures, scoliosis, respiratory and heart failure, impaired gastrointestinal motility.

At present, the therapy with corticosteroids, ACE inhibitors, in-blockers, orthopedic surgery, respiratory rehabilitation and physiotherapy is mainly applied to improve the quality and extend the life of patients.

Ataluren is a small molecule, a medicine for oral use, approved by the European Medicines Agency for the treatment of patients with nonsense mutations at the age of 2 years or older, able to walk independently. It acts at the level of ribosomes to ensure the ignoring of the stop codon and the synthesis of full-length protein.

The recommended dose is 10 mg / kg bodyweight in the morning, 10 mg / kg bodyweight at noon and 20 mg / kg bodyweight in the evening (for a total daily dose of 40 mg / kg body weight).

The effect of treatment is evaluated through manual muscular testing (MRC scale), respiratory function assessment. It was found that continuing treatment, even after the loss of walking ability leads to a slowing of the progression of the respiratory muscle weakness. Patients with nmDMD who were ambulant or non-ambulant demonstrated a similar safety profile.

There were no apparent differences in either steady-state relative bioavailability or apparent clearance due to loss of ambulation. No dosing adjustment is needed for patients who are becoming non-ambulatory.

During treatment, ABP, renal and hepatic function as well as lipid profile are monitored.

Corticosteroids (CS). Prednisolone and Deflazacort are a golden standard in the treatment of muscular weakness in dystrophinopathies. Prednisolone / Prednisone is dosed at 0.75 mg / kg / day with a maximum dose of 30 mg / day, and Deflazacort - at 0.9 mg / kg / day, with a maximum dose of 36 mg / day. Their daily use or the use of alternative regimens, temporarily improves or slows the progression of the muscular dystrophy (6 months to 2 years), stabilizes the muscle strength and function, reduces complications such as scoliosis, improves respiratory function and reduces the incidence of heart complications. The mechanisms of action of the CS at the cellular level that lead to a delay in the disease progression, which remains unclear. There are various theories explored on experimental mouse models. Corticosteroid therapy begins at a plateau of motor functions between 4 and 8 years when neither progress nor regression of motor skills.

Daily intake has a proven better effect than the alternating intake. Continuation of treatment at doses of 0.3-0.6 mg / kg / day after loss of autonomous gait is recommended in order to maintain the muscle strength of the upper limbs, delay the development of scoliosis, respiratory and cardiac insufficiency. After initiation of therapy, the patient is monitored every 3-6 months order to take into account the effect of the treatment, as well as to report any adverse drug reactions (ADRs), which allows dose adjustment. Prolonged corticosteroid therapy has many ADRs, such as weight gain, arterial hypertension, congestive heart failure, ulcerative disease, hepatic steatosis, pancreatitis, iatrogenic hypercorticism with centripetal obesity, facies lunata, acne, hirsutism, steroidal diabetes, dyslipidemia, hypopotassemia, metabolic alkalosis, osteoporosis with compression fractures, convulsions, benign intracranial hypertension, emotional lability and psychosis, cataracts, and immunosuppression with recurrent infections. It is recommended to assess muscle function every 3 months, to track body weight, arterial pressure, respiratory capacity of the patients who are taking corticosteroid therapy. When ADR occurs, the dose may be reduced or alternatives to 15 days of intake, 15 days rest.

Patients with PMD Duchenne type have a lower bone density, even before they lose the ability to walk independently. Chronic corticosteroid therapy further reduces the bone density, requiring calcium (1000 mg / day) and vitamin D (400 E / day) intake. Bisphosphonates are recommended for children with fractures. Prior to starting corticosteroid therapy, it is important for the child to be vaccinated, according to the immunization calendar of the country and to have immunity against varicella and tuberculosis.

In patients with Becker type PMD, the effect of corticosteroid therapy has not been studied due to slower progression and the later disability onset.

Medication therapy of cardiac events. Dilated cardiomyopathy is a common complication in patients with dystrophinopathies. Its later appearance as compared to affecting the skeletal muscles, is caused by the reduced physical activity in patients due to loss of ability to walk alone. Cardiac involvement is the immediate cause of death in about 10% of these patients.

Recommended medications that delay the heart failure and improve the prognosis: ACE inhibitors (angiotensin converting enzyme) or angiotensin receptor blockers, β-blockers and spironolactone. This effect is achieved by preventing left ventricular remodeling and dilation, and the development of fibrosis, which reduces the risk of developing heart failure, ventricular arrhythmias and sudden cardiac death, and increases life expectancy in patients with dystrophinopathies. They are recommended as a first-line medication in patients with reduced ejection fraction, without clinical manifestations. In the event of heart failure, symptomatic treatment with loop diuretics and spironolactone is recommended.

Physiotherapy is an important element of the complex treatment of dystrophinopathies. It is applied at any time during the progression of the disease, both in ambulatory and non-ambulatory patients. Its main goals are to slow the decrease of the muscle strength and mass, to maintain the breathing volume, to prevent the development of joint contractures and to improve the quality of life of the patients. Physiotherapy should be started immediately after the diagnosis. The primary priority is to prevent the occurrence of asymmetric contractures of the Achilles tendons, knee and hip joints, thus reducing the risk of subsequent scoliosis. Passive stretching and the use of ankle orthoses are a major point of treatment at the stage when patients are still ambulatory. Ankle orthoses are placed at night because they impede walking during the day. The application of the above-described stretching methods should be

done 4-5 days a week. Boys should be encouraged to practice appropriate exercise and hydrotherapy. The use of knee-ankle orthoses may prolong the ability for self-walking and standing just in time. Often their use is preceded by tendon elongations of the Achilles tendons.

Orthopedic surgery. About 90% of the boys with dystrophinopathy develop clinically significant scoliosis. The appropriate prophylaxis against spinal disturbances in these patients should begin before they have lost their ambulation and it includes physiotherapeutic procedures and a proper posture, in order to avoid pelvic asymmetry. Once occurred, scoliosis can be corrected surgically. The best effect would come if those interventions are performed at the stage when the spine is still mobile and the Cobb angle is $20\text{-}40^0$. At these earlier stages of the disease, the respiratory and cardiac functions of these patients are well-preserved for their body to undergo surgical intervention. Patients contraindicated for surgery use appropriate stabilizing girdles and corsets. The tendon elongations of the Achilles tendons also have a significance for the prolongation in time of the ability of these patients to walk independently.

Maintenance of respiratory functions. Frequent respiratory infections and progressive respiratory failure in more advanced stages of the Duchenne type PMD require periodic monitoring of the respiratory function by spirometry and blood gas measurement, as well as appropriate therapy. Distressing symptoms, requiring therapy, are: signs of night hypoventilation (sleep disturbances, daily fatigue, impaired concentration), decreased appetite, SO2 <92%, AVC <60% of the expected, common respiratory infections. In the earlier stages, respiratory gymnastics and postural drainage show good effect.

Common respiratory infections require the use of a pneumococcal vaccine and an annual influenza vaccine, as well as adequate antibiotic therapy for treatment. Ventilation with positive pressure most often begins to be applied at around 17 years of age. A key indication of non-invasive night ventilation (NNV) is the detection of clinically manifested nocturnal hypoventilation. In the advanced stages of the disease, with established daily hypercapnia, non-invasive ventilation is also applied during the day. Administration of NNV leads to improvement of the quality of sleep, reduction of daily drowsiness, slowing down the progression of the respiratory weakness and improving the quality of life. It is empirically proven that the night ventilation (non-invasive or invasive by tracheostomy) results in long-term respiratory stabilization,

reduction of respiratory infections, and increased life expectancy. As the disease progresses, artificial ventilation periods are prolonged.

Oxygen therapy should be used with extreme caution because, despite the apparent improvement in hypoxemia, it can mask the underlying cause, such as atelectasis or hypoventilation, and increase the hypercapnia. In hypoxemia due to hypoventilation, it is advisable to restore and improve the airway patency manually or mechanically. Methods to improve coughing are also recommended - manually, via Ambu or cough assist.

Figure 1. Respiratory Tracking Algorithm in Patients with Duchenne type PMD.

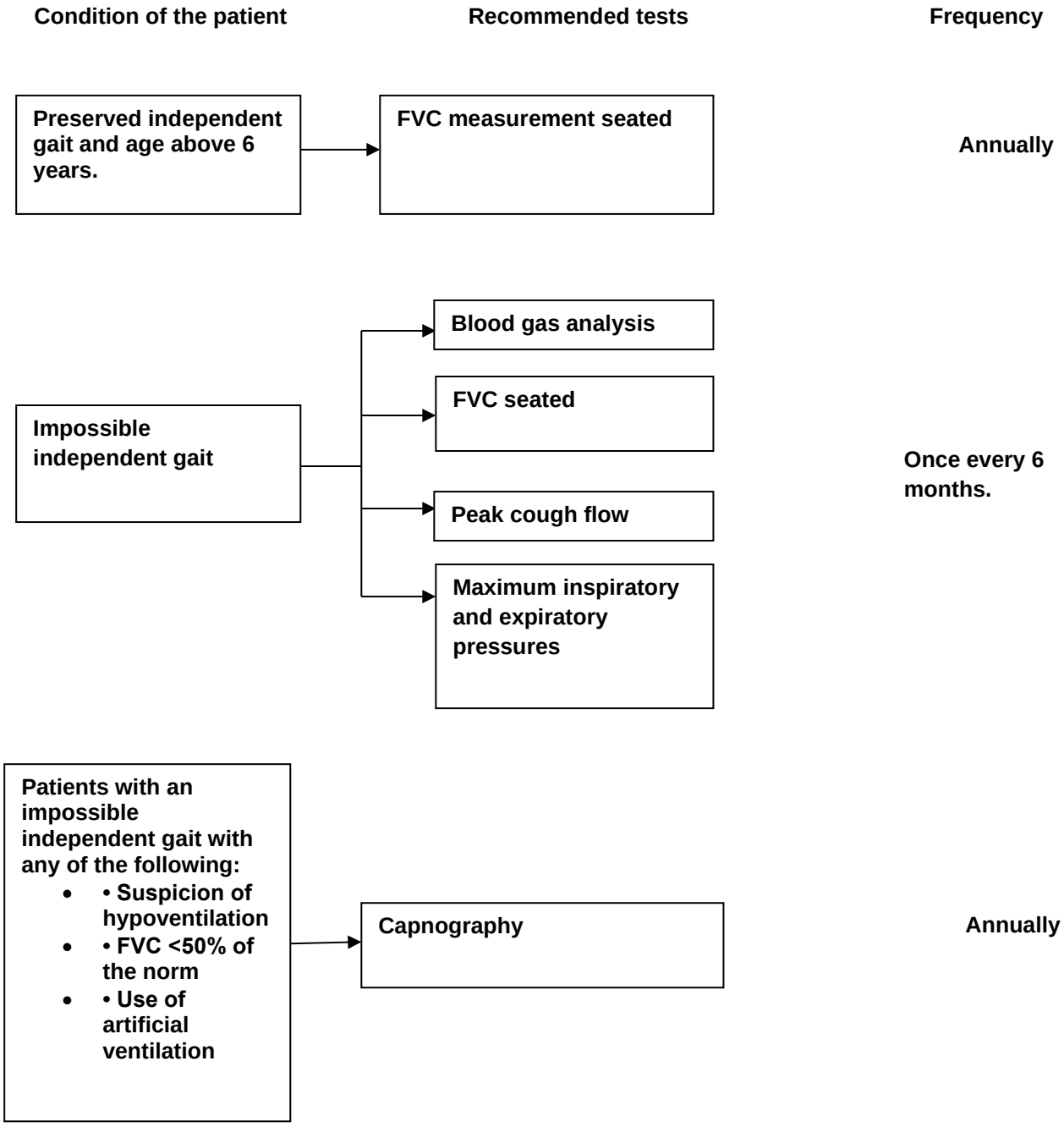


Figure 2. Respiratory interventions in patients with PMD Duchenne type

Step 1:
For PVD <40% use of manual techniques or mechanical insufflator / exsufflator

Step 2: manual and mechanical coughing techniques
Required in case of:
• Respiratory infections and peak cough flow <270 L/min*
• Basis peak cough flow <160 L/min or maximum expiratory pressure <40 cmH2O
• Basis FVC <40% or <1·25 L in adults

Step 3: nocturnal hypoventilation
• Manifestations of hypoventilation (patients with FVC <30%)
• Basis SpO2 <95% and / or CO2> 45 mm Hg in wakefulness
• Apnea / hypopnea index> 10 per hour from polysomnography or 4 or more episodes of dropping of SpO2 <92% or a decrease of SpO2 by 4% per hour during sleep
Techniques for improving the lung volume and restoring the airway passage should precede non-invasive ventilation.

Step 4: Daytime ventilation
In patients with night ventilation, the daytime ventilation shall be included under the following conditions:
• Independent extension of night ventilation and wake-up periods
• Impaired swallowing, dyspnoea, which is relieved by ventilation
• Difficult speech, dyspnoea
• Hypoventilation symptoms with basis SpO2 <95% and / or CO2> 45 mm Hg in wakefulness
Prolonged application of non-invasive ventilation by coughing support can facilitate endotracheal extubation in patients intubated in the course of infection or operative intervention.

Step 5: Tracheostomy
• The effect of the non-invasive ventilation is not optimal
• Three unsuccessful attempts for extubation, despite the use of optimal non-invasive ventilation and cough assistance
• Inability for non-invasive ventilation and coughing assistance methods to prevent aspiration and saturation fall below 95%, which requires aspiration

Nutrition. Patients with PMD Duchenne type are at increased risk of malnutrition and obesitas, which requires optimal nutrient control, so that the BMI maintains between 10 and 85 percentiles. The nutritional regime should be evaluated for energy, protein, liquid, calcium, and vitamin E. Swallowing evaluation should be done in case of weight loss of more than 10%, extension of meal times of more than 30 minutes, choking, aspiration pneumonia. Constipation and gastroesophageal reflux are some of the most common gastrointestinal complications in patients with PMD Duchenne type.

In these cases, laxatives - lactulose, polyethylene glycol or mechanical cleaning methods are recommended. For gastroesophageal reflux, H 2 blockers, proton pump inhibitors, prokinetics.

Anesthesia: In case necessity of general anesthesia, the increased risk of malignant hyperthermia in patients with dystrophinopathy and the use of halothane inhalation anesthetics and succinylcholine myorelaxants should be considered. Common venous anesthesia is strongly recommended. Absolutely contraindicated are depolarizing myorelaxants, such as succinylcholine. Patients are at risk of potentially fatal rhabdomyolysis and hyperpotassemia when administered with inhaled anesthetics. Before and after surgical procedures, consulting a cardiologist and a pulmologist is required, and the anesthesiologist must be prepared for possible cardiac and respiratory decompensation during and after surgery.

4. Progressive muscular dystrophies type girdle-limb (Girdle-limb muscular dystrophies GLMD)

GLMD are a group of genetically heterogeneous muscular dystrophies that are inherited by autosomal-dominant (AD) or autosomal-recessive (AP) mode, having a variable age of onset, from child to adult, and characterized by initial, predominant and progressive muscle weakness of the pelvic and shoulder girdles. All patients have acquired independent gait at some stage in their lives, and in order to be considered as a new form of GLMD, mutations in the corresponding new gene must be established in at least two unrelated families. The changes established by the histological examination of muscles and imaging techniques are dystrophic. The degenerative changes in MRI of muscle are defined as replacement of muscle tissue with fat or connective tissue of the T1 sequences, and dystrophic histological changes include necrosis with regeneration and fibrosis. Serum CPK must be increased.

The prevalence of GLMD is estimated at 1.63 per 100,000 population with a variation of 0.56-5.75 / 100,000 in different populations.

Classification: Based on the old classification of 1995, the GLMD forms were divided into AD type 1 and AP type 2, followed by the corresponding letter, in the order of the genes identified throughout the years (Table 3). Based on the progress of the molecular genetic studies, the number of forms increased strongly, which led to the depletion of the letters for the AP forms. In addition, it turned out that some of the forms could be classified in other disease groups - congenital myopathies, metabolic

myopathies, etc., which necessitated the proposal for a new classification before 2018. According to it, AD forms will be marked with D, and with R - AP, followed by the corresponding figure. X will denote the X-linked forms, if such are identified. Table 3 presents the forms according to the two classifications and the reasons for the elimination of some of them in the 2018 classification.

Etiology: The different forms of GLMD are caused by mutations in different genes, encoding proteins that have a structural function or are involved in the metabolism or in the signal transduction of muscle cells (Table 3).

Table 3. Genetic classification of GLMD(1995 and 2018)

Disease under the classification from 1995	Gene / locus / protein	Subgroup	Disease under the classification from 2018	Reason for exclusion from the GLMD group
GLMD1A	*MYOT/Myotilin*	Z-disk proteinopathies	Myofibrillar myopathies	Presence of distal weakness
GLMD1B	*LMNA/ Lamin A/C*	Nuclear membrane diseases	Emery-Dreifuss muscular dystrophy (EDMD)	Cardiac arrhythmias related to EDMD
GLMD1C	*CAV3/ Caveolin-3*	Caveola-associated muscular dystrophies	Rippling muscle disease	Rippling muscle disease, myalgias
GLMD1D	***DNAJB6/ DNAJ/Hsp40 homolog, subfamily B, member 6***	**Z-диск proteinopathies**	**GLMD D1 DNAJB6-related**	
GLMD1E	*DES*/Desmin	_	Myofibrillar myopathies	Cardiomyopathy, distal weakness
GLMD1F	***TNPO3/ Transportin-3***	Nuclear membrane diseases	**GLMD D2 TNP03- linked**	
GLMD1G	***HNRNPDL/*** **Heterogeneous ribonucleoprotein D-like protein**	**—**	**GLMD D3 HNRNPDL-linked**	

GLMD1H	3p23-p25.1/ Unknown	—	Not confirmed	Wrong linkage
GLMD1I	**CAPN3/ Calpain-3**	**Calpainopathy**	**GLMD D4 calpain3- linked**	
GLMD2A	***CAPN3*/ Calpain-3**	**Calpainopathy**	**GLMD R1 calpain3- linked**	
GLMD2B	***DYSF/ Dysferlin***	**Muscular dystrophies with impaired recovery of the cell membrane**	**GLMD R2 dysferlin- linked**	
GLMD2C	***SGCG/ ɣ-sarcoglycan***	**Sarcoglycanopathies**	**GLMD R5 ɣ - sarcoglycan-linked**	
GLMD2D	***SGCA/ a-sarcoglycan***	Sarcoglycanopathies	**GLMD R3 a – sarcoglycan-linked**	
GLMD2E	***SGCB/ b-sarcoglycan***	Sarcoglycanopathies	**GLMD R4 b-sarcoglycan-linked**	
LGMD2F	***SGCD/ d-sarcoglycan***	Sarcoglycanopathies	**GLMD R6 d – sarcoglycan-linked**	
GLMD2G	***TCAP/ Telethonin***	**Z-disc proteinopathies**	**GLMD R7 telethonin-linked**	
GLMD2H	***TRIM32/ Tripartite motif containing-32***	**—**	**GLMD R8 TRIM 32-linked**	
GLMD2I	***FKRP*/ Fukutin-related protein**	**α-dystroglycanopathies**	**GLMD R9 FKRP-linked**	
GLMD2J	***TTN*/ Titin**	**Z- disc proteinopathies**	**GLMD R10 Titin-linked**	
GLMD2K	**POMT1/ Protein-O-mannosyl transferase-1**	**α-dystroglycanopathies**	**GLMD R11 POMT1- linked**	
GLMD2L	**ANO5/ Anoctamin-5**	**Muscular dystrophies with impaired recovery of the cell membrane**	**GLMD R12 anoctamin5-linked**	

GLMD2M	**FKTN/ Fukutin**	**α-dystroglycanopathies**	**GLMD R13 Fukutin- linked**	
GLMD2N	**POMT2/ Protein-O-mannosyl transferase-2**	**α-dystroglycanopathies**	**GLMD R14 POMT2- linked**	
GLMD2O	**POMGNT1/ Protein-O-mannose b-1,2-N-acetylglucosaminyltransferase**	**α-dystroglycanopathies**	**GLMD R15 POMGnT1-linked**	
GLMD2P	**DAG1/ Dystrophin-associated glycoprotein-1 (a-dystroglycan)**	**α-dystroglycanopathies**	**GLMD R16 a-dystroglycan-linked**	
GLMD2Q	**PLEC1/ Plectin**	**Z-discproteinopathies**	**GLMD R17 plectin- linked**	
GLMD2R	DES/ Desmin	Z- **disc proteinopathies**	Myofibrillar myopathy	Distal weakness
GLMD 2S	**TRAPPC11/ Transport protein particle complex 11**	**α-dystroglycanopathies**	**GLMD R18 TRAPPC11-linked**	
GLMD 2T	**GMPPB/ GDP-mannose pyrophosphorylase B**	**α-dystroglycanopathies**	**GLMD R19 GMPPB-linked**	
GLMD 2U	**ISPD/ Isoprenoid synthase domain–containing protein**	**α-dystroglycanopathies**	**GLMD R20 ISPD-linked**	
GLMD 2V	GAA/ a-1,4-glucosidase	—	Pompe Disease	Metabolic myopathy
GLMD2W	LIMS2/ LIM и senescent cell antigenlike domains 2	—	PINCH-2 linked myopathy	In 1 family
GLMD2X	POPDC1/ Popeye domain–containing protein 1 Nuclear envelopathies	Nuclear membrane diseases	BVES- linked myopathy	In 1 family

GLMD2Y	TOR1AIP1/ Torsin-A interacting protein 1 or lamin-associated protein 1	Nuclear membrane diseases	TOR1AIP1- linked myopathy	In 1 family
GLMD2Z	**POGLUT1/ Protein O-glucosyltransferase 1**	**α-dystroglycanopathies**	**GLMD R21 POGLUT1-linked**	
Bethlem myopathy- AP	**COL6A1, COL6A2, COL6A3**		**GLMD R22 collagen 6-linked**	
Bethlem миопатия- АД	**COL6A1, COL6A2, COL6A3**		**GLMD D5 collagen 6-linked**	
Laminin α2-linked muscular dystrophy	**LAMA2**		**GLMD R23 laminin α2-linked**	
POMGNT2-Linked muscular dystrophy	**POMGNT 2**		**GLMD R24 POMGNT2-Linked**	

Pathogenesis: Based on the pathogenetic mechanisms that lead to muscle damage, the following subgroups of GLMD are differentiated:

α-dystroglycanopathies: α-dystroglycan is a glycosylated sarcolemma glycoprotein with a fundamental role in maintaining the sarcolemma integrity by providing a link between the dystrophin-associated glycoprotein complex and the extracellular structures. In this subgroup GLMD, there is an abnormal glycosylation of the α-dystroglycan, with reduced immunoreactivity in the muscle biopsies. α-dystroglycanopathies are a result of mutations in the gene, encoding the protein itself, or mutations in genes, encoding proteins, involved in its glycosylation (Table 2). α-dystroglycanopathies include 10 forms of GLMD. They have a broad clinical spectrum with affecting the muscles, eyes and brain, ranging from the severe muscle-eye-brain syndrome or Walker-Warburg syndrome, through the moderately severe congenital muscular dystrophy with a defect in neuronal migration, to the mild GLMD, with or without intellectual deficit and discrete brain anomalies.

Calpainopathy: Calpainopathy CAPN3 encodes a muscle-specific calcium-activated neutral protease, named calpain-3, which binds with titin and dysferlin and plays a major role in sarcomer remodeling. Although calpainopathies have a recessive inheritance, in recent years, dominant forms are also reported.

Caveolinopathies: Caveolae are small invaginations in the cell membrane of various cell types, including muscle cells, that play a major role in maintaining sarcolemic integrity, regulation of vesicle transport and signal transduction. Caveolae are made up of two major types of proteins - caveolins and cavins, the disturbed function of which leads to degeneration of the muscle fibers. They are separated from the GLMD group in the new 2018 classification.

Muscular dystrophies with impaired cell membrane recovery: This group refers to dysferlinopathy and anoctaminopathy-5. Dysferlin is important for the vesicle fusion in the cell membrane recovery, a similar function, though not fully understood, is supposed to have anocatamin-5.

Diseases of the nuclear membrane are caused by mutations in genes, encoding proteins that construct this membrane. We refer the forms with impaired function of transportin 3 (*TNPO3*, GLMD 1F, GLMD D1) to this GLMD group.

Sarcoglycanopathies: The Sarcoglycan subcomplex is an element of the dystrophin-associated glycoprotein complex consisting of four elements (α-, β-, ɣ-, and ɗ-sarcoglycan), which are involved in sarcolemic integrity.

Z-disc proteinopathies: The Z-disk is a structure for connecting the thin filaments, which defines the limits of the sarcomere. Mutations in the genes, encoding proteins from the Z-disk, lead to so-called myofibrillary myopathies, characterized by sarcoplasmic aggregates of myofibrillar degradation products.

Clinical characteristics: GLMD patients have muscular weakness, primarily affecting pelvic and shoulder girdle muscles and the proximal limb muscles, with difficulty climbing stairways, straightening from squat position, and change of the gait into “jiggling”. In the different forms, specific features are observed regarding the age of onset, the rate of progression, the age of loss of autonomous gait, the presence of rhabdomyolysis, associated signs such as cardiac and respiratory affection.

α- dystroglycanopathies: Muscle pseudohypertrophy, cardiac involvement, and various cognitive impairments are typical for patients with GLMD2 α-dystroglycanopathies. Rhabdomyolysis can be detected in patients with mutations in the FKRP gene (GLMD2I) and the GMPPB gene (GLMD2T), whereas mutations in

TRAPPC11 trigger additional manifestations of hyperkinetic motor disorders and hepatosteatosis.

Calpainopathy: AR calpainopathy is characterized by early involvement of the adductors and the extensors of the hip joints and the flexors of the knee joint. Winged blades, possibly mild facial weakness and early joint contractures are present. In some cases, rhabdomyolysis is described in physical exercise. Cardiac involvement is not typical but restrictive type of respiratory disorder occurs in about 20% of patients, but in rare cases requires non-invasive ventilation.

Caveolinopathies: Mutations in the gene, coding caveolin-3 determine the development of GLMD1C, rippling muscle disease, asymptomatic elevated CPK, distal myopathy and cardiomyopathy. These patients have painful muscle cramps, "wave-like" movements of the muscles that can be provoked by percussion. These phenomena are not associated with EMG activity. According to the new classification (2018), they are separated from the GLMD Group.

Muscular dystrophies with impaired cell membrane recovery: Typically with GLMD2B, (GLMD R2) and GLMD 2L, (GLMD R12) there is presence of asymmetric atrophy of m. quadriceps femoris and m. biceps brachii. In both forms, impaired tolerance during physical activities and rhabdomyolysis are forthcoming the muscle weakness. Women have a milder clinical phenotype. Cardio-pulmonary involvement is not typical.

Diseases of the nuclear membrane: In all these forms, with the exception of GLMD1F, the muscular weakness is associated with cardiomyopathy and rhythmical and conduction disorders, requiring the insertion of a permanent electrocardiostimulator.

Sarcoglycanopathies: Most patients with sarcoglycanopathies have a Duchenne-like phenotype or a lighter PMD, Becker type. There is a disturbed tolerance to physical stresses and episodes of rhabdomyolysis. Cardiac and respiratory disorders are typical.

Z- disc proteinopathies: In these forms, there is a pronounced clinical variation with regard to muscle weakness, such as girdle-limb, distal, scapular-peroneal or axial. Peripheral neuropathy and cardiomyopathy are present in about 20% of the patients. Respiratory insufficiency in the early stages is typical for mutations in the TTN gene. GLMD2G typically affects the proximal and distal lower leg muscles and the cardiac

involvement. In GLMD2Q (GLMD R17), muscle weakness is associated with epidermolysis bullosa.

Table 4. Comparative presentation of the main features of AD and AR forms of GLMD.

Features	GLMD1/D	GLMD2/R
Way of inheritance	AD	AR
Subtypes	1A–1H	2A–2Z
Typical age of onset	Adolescent to late adulthood GLMD1D/D1 may have onset in childhood	Adolescent to adulthood
Limbs weakness	Light	Moderate to severe
CPK in serum	Normal to slightly increased, excl. GLMD 1C, where CPK is heavily elevated	From mild to severely elevated
Decreased tolerance to physical exercise / rhabdomyolysis	1C	2A (R1), 2B–2E (R2-R4), 2I (R9), 2L (R12) and 2T (R19)

Diagnosis: The main stages of diagnosis include:

• Determination of the characteristics of muscular involvement - girdle-limb, humeroperoneal, distal weakness

• Determining the type of inheritance

• Clarification of belonging to ethnic or religious minorities

• Screening of serum CPK

• EMG

• Assessment of cardiac status - ECG, echocardiography

• Evaluation of ventilation performance

• MRI of the muscles

• Muscle biopsy

• Molecular genetic testing - for mutations in a particular gene, sequencing of the exom or genome.

MRI of the muscles:

In GLMD2A/R1 the paravertebral muscles are affected in the early stages of the disease. In the hip area, the earliest atrophic changes are found in the adductors and

m. semimembranosus. Typical feature is the early engagement of m. gastrocnemius medialis and m. soleus.

In GLMD2B/R2 m. gluteus minimus is affected early. One of the first observed changes is myoedema in the area of the hip adductor muscles and m. gastrocnemius med.

In GLMD2I/R9 mm. glutei are one of the first to be affected during the course of the disease. In the thighs, the rear muscles are most involved, mostly - m. biceps femoris, m. semitendinosus and m. semimembranosus. In the area of lower legs, early atrophic changes are found in m. gastrocnemius and m. soleus.

In GLMD2J/R10 early and severe involvement of the m. tibialis ant. is established.

In GLMD2L/R12 early involvement of the posterior femoral muscles is established. Of m. semitendinosus, with relative preservation of m. sartorius, m. gracilis and m. rectus femoris. In the area of the lower legs m. soleus, m. gastrocnemius medialis are affected early.

In sarcolycanopathies, the adductors of the thighs, the gluteal muscles are the earliest and most severely affected with relatively preserved distal muscles of the lower legs and distal parts of m. quadriceps femoris.

In GLMD 2Z/R21 in the femoral musculature there is degeneration from the inside out.

Features of the muscle biopsy:

The muscular biopsy shows data of dystrophic changes. In some forms, other specific features may also be identified. In the case of calpainopathy, there may be eosinophilic infiltrates in the muscular biopsy without eosinophilia in the blood. Lobulated muscle fibers are found in the more advanced stages of the disease. In GLMD2B and GLMD2L interstitial and vascular amyloid deposits in skeletal muscles are found without systemic ones. Rimmed vacuoles are typical for transportinopathy-3.

Sarcoglycanopathies, along with dystrophic changes, also exhibit eosinophilic infiltrates.

An immunohistochemistry test reveals reduced to missing expression of a particular protein due to mutations in the corresponding gene.

Treatment and care

Cardiological treatment: Patients with GLMD with known cardiac involvement and those lacking genetic verification, are referred for cardiac assessment - ECG, echocardiography. For those with a history of syncope, arrhythmias, it is recommended to have an ECG Holter. Depending on the outcome, a cardiologist considers the need of a permanent cardiostimulator and the use of ACE inhibitors, beta-blockers and diuretics.

Dysphagia: With dysphagia, weight loss, the patient shall be referred to a gastroenterologist to assess the risk of aspiration, for training in swallowing techniques, and assessing the need for gastro- or yunostomy.

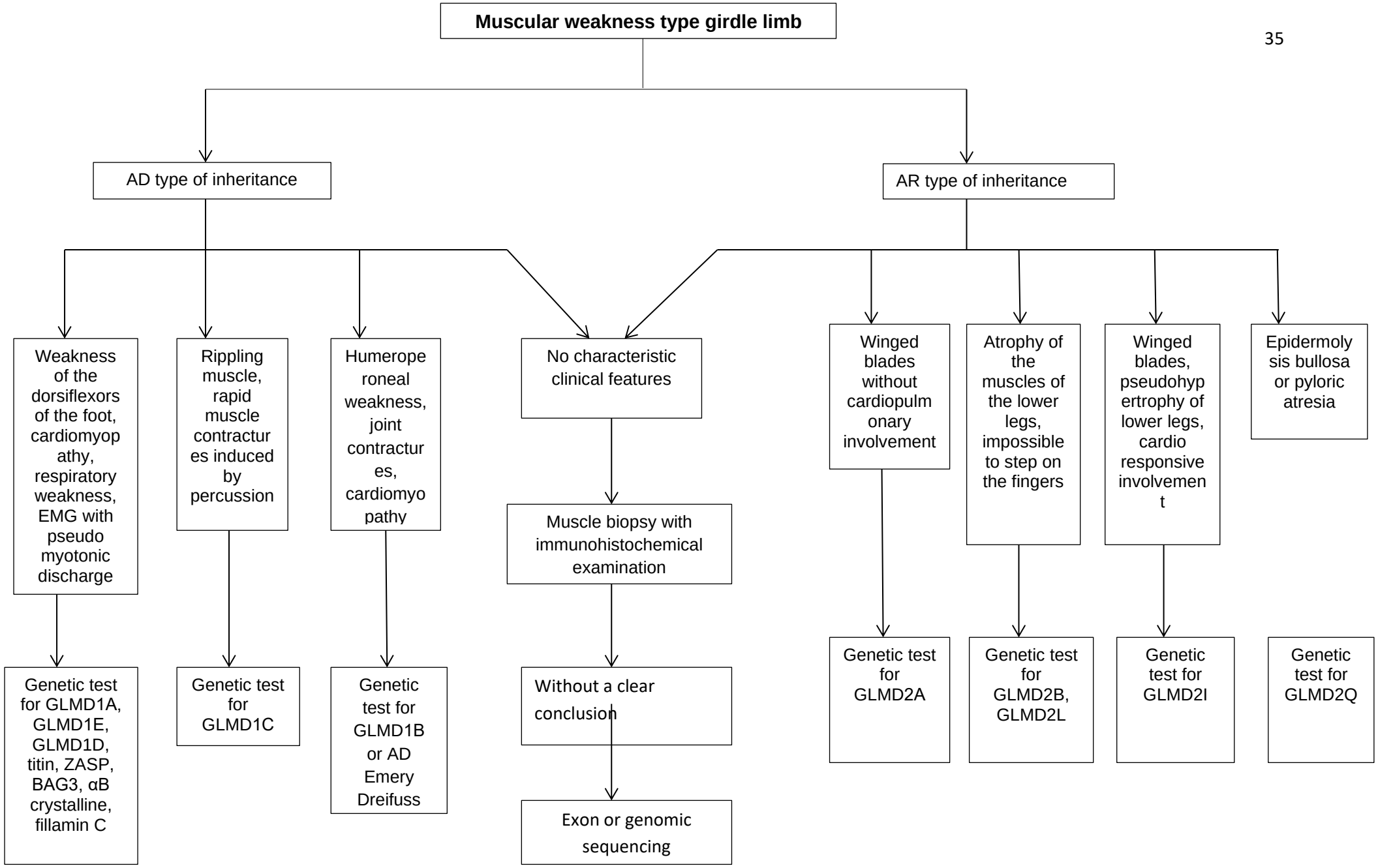
Pulmonary complications: Given that NMD patients may not have typical symptoms of respiratory failure, such as dyspnea, an annual assessment of the ventilator performance by the means of standing and lying spirometry is recommended for all of the patients. Pulmologist / anesthetist assesses the need of respiratory support by invasive or non-invasive ventilation.

Scoliosis- annual scoliosis monitoring is required by performing x-rays. If necessary, patients are directed to performing of orthopedic surgeries to maintain posture, mobility, maintain the cardiopulmonary function, and for improvement of the quality of life.

Rehabilitation - is systematically conducted by a rehabilitator with experience in NMD

To date, the most commonly diagnosed forms in Bulgaria are GLMD2A/R1 - calpainopathy, with mutations in exons 4 and 7 of the gene. Among the Roma population, a type 2C/R5 mutation with a C283Y parental mutation effect, with a phenotype similar to that of the PMD type Duchenne, was established. Among the Bulgarian Mohammedans the most common form is 2G/R7, due to homozygous mutation p.Trp25X in TCAP.

Figure 3. Diagnostic algorithm in patients with girtle-limb muscular dystrophies


Muscular weakness type girdle limb
AD type of inheritance
AR type of inheritance
Weakness of the dorsiflexors of the foot, cardiomyopathy, respiratory weakness, EMG with pseudo myotonic discharge
Rippling muscle, rapid muscle contractures induced by percussion
Humeroperoneal weakness, joint contractures, cardiomyopathy
No characteristic clinical features
Winged blades without cardiopulmonary involvement
Atrophy of the muscles of the lower legs, impossible to step on the fingers
Winged blades, pseudohypertrophy of lower legs, cardio responsive involvement
Epidermolysis bullosa or pyloric atresia
Genetic test for GLMD1A, GLMD1E, GLMD1D, titin, ZASP, BAG3, αB crystalline, fillamin C
Genetic test for GLMD1C
Genetic test for GLMD1B or AD Emery Dreifuss
Muscle biopsy with immunohistochemical examination
Genetic test for GLMD2A
Genetic test for GLMD2B, GLMD2L
Genetic test for GLMD2I
Genetic test for GLMD2Q
Without a clear conclusion
Exon or genomic sequencing

5. Facioscapulohumeral dystrophy (PCHD)

This is the third most common myopathy after Duchenne PMD type and the Steinert myotonic dystrophy. It is an autosomal dominant disease.

Etiology and pathogenesis. The disease is mapped on the long arm of the 4th chromosome - 4q35, where the *DUX4* - gene is located in the D4Z4 macro satellite repeats. They are typically between 11 and 100. Patients have fragments less than 35 kb, and the number of repeats is from 1 to 10. The reduced length of D4Z4 results in chromatin relaxation and suppression of DUX4 activity in 95% of patients. About 5%, so-called PCHD 2, are without a reduced fragment and a mutation in *SMCHD1* is established which results in a chromatin relaxation of D4Z4. Patients with the largest known deletions developed congenital PCHD. When the size of the remaining DNA fragment is 10-13 kb, the onset is between 1 and 16 years of age. At moderate deletions (16 kb size of the remaining fragment) - between 8 and 22 years. With small deletions and size of the remaining fragment of 35 kb, the onset is between 15-23 years. Some individuals, carrying the genetic defect, have asymptomatic or subclinical lesions.

Clinical picture. PCHD occurs in six stages:

I - affecting facial muscles

The initial muscular weakness affects the facial muscles, especially mm. orbicularis oculi, zygomatici and orbicularis oris. Typical for the disease is the preservation of: mm. masseter, temporalis and the external eye muscles. In the later stages, the eyelids do not touch, as part of the sclera remains visible. When smiling, the oral corners move across. Impact on the facial muscles is often asymmetric and leads to unusual patient vision. As the disease progresses, the face loses its normal folds and gains expressionless appearance.

II - affecting the muscles of the shoulder girdle

In the onset of the disease, typically there is weakness of the muscles that fix the blade. They engage in m. latissimus dorsi, pars ascendens of m. trapezius, mm. rhomboidei and m. serratus ant. "Winged blades" can be observed, but they may be missing while in rest. In case of abduction and especially when the hands are stretched forward, their presence becomes more visible. Affecting m. pectoralis major, especially its sternocostal head, leads to a prominent forward and upward movement of the axillary folds and a flat view if the front chest wall.

III – affecting the extensors of the foot. M. tibialis anterior is particularly severely affected by the development of a stepping gait

IV - affecting the pelvic girdle

V - impaired ability to climb stairs

VI - Loss of independent gait.

In PCHD can also be monitored:

• Mild rhythm-conduction disorders in 5% of patients (atrial tachyarrhythmias)
• Neurosensory reduction to full hearing loss
• Vascular changes in the retina
• Epilepsy
• Mental retardation
• Psychotic manifestations

Diagnosis. The diagnostic criteria include:

• Initial affecting the muscles of the face and shoulder girdle, with preserved external eye muscles, pharyngeal muscles and muscles of the tongue;
• Facial weakness is found in more than 50% of the affected family members;
• AD type of inheritance in the family cases;
• Data on myogenic EMG damage and muscle biopsy.
• CPKs are slightly elevated - up to 5 times normal.
• Molecular analysis with mutation data for the DUX4-gene or SMCHD1 gene

Treatment and prophylaxis. Treatment is symptomatic by physiotherapy, cardioprotective medications.

6. Emery-Dreifuss muscular dystrophy

It is a hereditary myopathy with a specific phenotype and two types of inheritance: X-recessive and autosomal dominant.

Etiology. It is caused by mutations in three different genes: an emerin *EMD* gene located on the Xq28 chromosome, *FHL1* on Xq26.3, and a laminin *LMNA* gene located on the 1q21 chromosome. The mutations in EMD and FHL1 are inherited in the X-recessive manner, and the mutations in the lamine gene are autosomal-dominant.

Pathogenesis. Genetic defects in the emerin gene lead to absence of the nuclear protein emerin and the defects in the laminin gene - to the absence of another

A / C nuclear protein lamin. The two nuclear proteins are in a common complex, and regardless of which of the two proteins is deficient, the clinical phenotype is the same. FHL1 in its three isoforms is expressed in the nucleus and the cytoplasm.

Clinical picture.

• Childhood onset

• Early contractures of the ankle, the elbow joints and the spine

• Progressive muscular weakness with predominant involvement of the armpit muscles and peroneal muscles approximately symmetrical

• Later weakness in the shoulder, pelvis and femoral muscles.

• Cardiac conduction disorders and / or cardiomyopathy data prior to 30 years of age

The diagnosis is based on the clinical triad: early contractures, slow progressing humeroperoneal muscular weakness, and development of cardiomyopathy. For verification and defining the type of the disease, it is important to conduct muscle biopsy and molecular-genetic testing. The biochemical study detects moderately elevated or normal CPK. EMG shows myogenic changes. The performance of ECG and echocardiography is important in order to assess the cardiac status of the patients. Immunohistochemistry testing reveals deficiency of muscle proteins called emerin or lamine A / C. Genetic analysis shows X-recessive or autosomal dominant type of inheritance. Molecular genetic analysis detects mutations in one of three genes.

Treatment and prophylaxis. Treatment is symptomatic, for some of the patients it is required to have permanent electrical cardiac stimulation.

7. Metabolic myopathies

This group of disorders is characterized by disturbances in the biochemical processes associated with ATP involvement and is manifested by muscle fatigue, weakness, increased muscle tone at exercise, and pain.

Classification. They are divided into three main groups:

• Carbohydrate metabolism disorders

• Lipid metabolism disorders

• Mitochondrial myopathies

7.1. *Carbohydrate metabolism disorders - muscle glycogenoses*

Generally, muscle glycogenoses are divided into two main types: A / causing disturbed exercise tolerance and B / causing constant muscle weakness.

- *Muscle glycogenosis causing disturbed physical exercise tolerance*

Clinical picture. They usually arise after intense physical exercise. The most common signs are muscle aches, rapid tiredness, muscle stiffness, cramps and myoglobinuria. They are due to various specific muscle enzyme defects:

- Phosphorylase B kinase

X-linked: Xq12

Recessive: 16q12

- Phosphorylase / Disease of McArdle/ - 11q13
- Phosphofructokinase / Disease of Tarui/: 1cen-q32
- Phosphoglycerate Kinase - Xq13
- Phosphoglycerate Mutase – 7p12
- B-enolase – 17pter
- Lactate dehydrogenase – 11p15

- *Muscle glycogenosis causing constant muscle weakness:*

Clinical picture. Hypotension and persistent muscle weakness are established. Tendon reflexes are weakened. Often, they are accompanied by heart disorders: cardiomegaly, congestive heart failure, arrhythmia or respiratory disorders. Generally, they are due to generalized enzyme defects. The degree of enzyme activity correlates with the age of onset and the severity of the disease.

- Alpha glucosidase / glycogenose type 2 defficiency; Pompe disease/: 17q23
- Aldolase A: 16q22
- Amyl-1,6 glucosidase / glycogenose type 3/: 1p21
- Lamp 2: Xq24

Pompe disease

Also named type II glycogenosis or acid maltase deficiency. Rare metabolic, multisystem, lysosomal disease with autosomal recessive inheritance.

Epidemiology. The incidence of the disease varies from 1 in 40,000 to 1 in 300,000 in the different populations. In South China and Taiwan its incidence reaches 0.5-1% of the total population, so a massive neonatal screening is also performed. In Bulgaria, up to now, 8 late-stage patients have been diagnosed.

Etiology and pathogenesis. The disease results from mutations in a gene located on 17q25, encoding the enzyme acidic alpha-glucosidase (GAA), which metabolizes the lysosomal glycogen to glucose. The reduced or absent activity of this enzyme results in the accumulation of glycogen in the lysosomes of the skeletal muscles, the heart and the smooth muscles, and to a lesser extent in other tissues and organs, with subsequent structural disorganization and cellular dysfunction in various tissues.

Clinical picture. Clinical variability is established with respect to the onset age, the rate of progression and the severity of organ involvement affecting the deficiency of the acid alpha-glucosidase enzyme. The following forms are described: classical and non-classical infantile, with early childhood onset, juvenile and beginning in adulthood.

The classic infantile form of Pompe disease is the most severe. It is characterized by:

- Generalized muscle hypotension - " floppy baby syndrome” "
- Delayed motor development and rapid progressive muscle weakness.
- Cardiac involvement within hypertrophic cardiomyopathy, cardiomegaly with possible left ventricular outflow obstruction and heart failure
- Frequent respiratory infections, respiratory insufficiency and disturbed breathing during sleep
- Difficulty eating
- Other signs that can be detected are macroglossia and myopathic fatigue, tremor, muscle spasms, mental retardation, hearing disorder due to glycogen deposition in the sensor cells of the cochlea

These events develop most often in the second month, averaging 1.6 months. (0-6.8). Patients are usually diagnosed up to the 5th month. The lethal outcome occurs until the 7th month. Very few survive up to age of 1 year.

Patients with non-classical infantile form of Pompe disease have a lighter phenotype, with symptoms beginning at about 5 months of age, lighter cardiomyopathy and longer survival, averaging 19 months.

Forms of late-onset in childhood, adolescence or adulthood are heterogeneous in terms of age of onset and severity of progress with progressive engagement of

skeletal and respiratory muscles. Symptoms and signs at the onset of the disease can be classified as:

- Girdle-limb muscular weakness, axial muscular weakness
- Difficulty in running, climbing stairs, standing up
- Myopathic gait
- Myalgias and asymptomatic CPK elevations
- Breathing disorders - restrictive type
- Some patients develop pronounced stiffness of the spine, known as the "rigid spine" and resemble the clinical picture of congenital myopathy. Heart attack in the late form is much less common, with rhythm and conduction disturbances. In several patients basilar artery aneurysms are also described as a result of glycogen deposition in the smooth muscles of the blood vessels

Diagnosis is based on clinical, biochemical, histological and genetic tests.

Tests. EMG shows data of myogenic damage. Increased levels of creatine phosphokinase (CPK), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), lactate dehydrogenase (LDH) are observed. In the infantile form, X-rays show data of pronounced cardiomegaly, and EchoCG proves hypertrophic cardiomyopathy. Functional Breath Testing (FBT), oximetry and capnography, polysomnography for assessing the severity of respiratory disorders.

The disease is confirmed by the demonstration of alpha-glucosidase deficiency in a dry drop of blood on filter paper, in cultured fibroblasts and muscle biopsy, and is genetically verified for subsequent prenatal diagnosis in the affected families. Histological examination of muscle with immunohistochemistry and electron microscopy is a complementary method, especially in difficult cases with clinical manifestation of vague girdle-limb muscle dystrophy in adults. Histological examination of muscles establishes limited degeneration of myocytes with heavier involvement of type I muscle fibers, as well as glycogen accumulation in the form of PAS (Periodic Acid Schiff) - positive vacuoles. The electron microscopic examination detects glycogen in cytoplasm and artophagous vacuoles.

Treatment is complex: pathogenetic enzyme-replacement therapy, cardiac treatment, treatment of pulmonary inflammation and respiratory care (in obstructive sleep apnea - nasal C-PAP, at night hypoventilation Bi-PAP, O2 at night or

permanently in case of hypoxia); moderate rehabilitation; general social and psychological care, genetic counseling and prenatal diagnosis. Enzyme replacement therapy (ERT) with acidic alpha-glucosidase at a dose of 20 mg / kg applied intravenously every 2 weeks, is the pathogenetic treatment. Patients with childhood form of the disease have been shown to improve motor, respiratory and cardiac functions, by reducing left ventricular hypertrophy, resulting in prolonged survival. In late forms of the disease, ERT leads to stabilization of the muscle strength and the respiratory function, with marked variability of effect in individual patients

7.2. *Disorders of the lipid metabolism - lipid myopathies*

Lipid myopathies are caused by genetic defects, leading to lipid biochemical disorders in the muscles. Most of them are related to the carnitine metabolism. Carnitine is an important component of the fat metabolism - it carries long chain fatty acids through the mitochondrial membrane. It is taken with food, it is also synthesized in the liver and the kidneys, transported and involved in the muscle contraction (90% of the carnitine is found in the muscles).

Classification. In general, they are divided into two groups: lipid myopathies with impaired physical activity tolerance, cramps, myoglobinuria and lipid myopathies with permanent muscle weakness.

- *Lipid myopathies with impaired tolerance at physical exercise.*

They are lipid myopathies with a defective carnitine transport.

Etiology. Most often due to carnitine-palmitoyl transferase II deficiency, caused by mutations in the CPT2 gene, located on the 1p32 chromosome. Both autosomal-recessive and autosomal-dominant forms are described. This is the most common cause of recurrent myoglobinuria.

Clinical picture. The onset of the disease varies from adolescence to adulthood. Characteristic is the occurrence of rhabdomyolysis after an activity requiring fatty acid oxidation (prolonged exercise, cold exposure, dieting, low carbohydrate and high fat, infections, valproate treatment). Muscle weakness and myalgias appear.

Tests. Serum CPK is normal or slightly increased between the episodes and is high during rhabdomyolysis. The activity of the enzyme carnitine-palmitoyl transferase II is reduced to 80-90% of the norm.

The treatment is frequent meals, carbohydrate-rich and low-fat meals. It is necessary to avoid heavier physical loads.

- *Lipid myopathies with permanent muscle weakness*.

Represent lipid myopathies, lacking carnitine.

Etiology. They are most often due to deficiency of the enzyme acyl-coA dehydrogenase, caused by mutations in different genes.

Clinical picture. The onset is usually in childhood or in early adulthood. It is characterized by the development of symmetrical proximal weakness. There may also be facial weakness. There is no pain and rhabdomyolysis. Some patients develop cardiomyopathy and congestive heart failure. The progression is slow.

Tests. Serum CPK is moderately elevated. EMG shows myogenic changes. Muscle biopsy detects low levels of carnitine.

Treatment is a low-fat diet, L-carnitine, 2-4 g / day, Riboflavin, 5-20 mg / day.

7.3. *Mitochondrial myopathies*

The final metabolites of fat and carbohydrate metabolism are involved in the cycle of the tricarboxylic acid, and the end of the oxidation involves the breathing chains in the mitochondria. In mitochondrial defects, the mitochondrial oxidation is impaired. This results in involvement in the metabolism also of anaerobic mechanisms and increasing the serum lactic and pyruvate levels.

Classification. Different clinical phenotypes are distinguished: Kearns-Sayre syndrome, congenital muscular dystrophy with mitochondrial structural changes, progressive external ophthalmoplegia, encephalomyopathies, cardiomyopathies, etc.

Etiology. They are caused by various mutations in the mitochondrial genome.

Clinical picture. The onset is in childhood, with gradual intensification of the symptoms. In addition to the progressive muscle weakness, patients may also have a number of other signs: eyelid ptosis, heart disorders, deafness, endocrine disorders (hypoparathyroidism, dysmenorrhea), mental retardation, etc..

Diagnosis is based on the conduct of clinical, biochemical, histological and molecular-genetic studies.

Tests. Elevated serum values of lactate and pyruvate are detected. EMG shows myogenic changes. The muscular biopsy demonstrates the typical ragged red fibers. Cardiomyopathy, most often hypertrophic, may be detected in cardiac echocardiography, but dilated or restrictive cardiomyopathy may also be present.

Histochemical studies have identified various oxidative phosphorylation disorders. Molecular analysis detects various mutations in mitochondrial DNA.

Treatment – Creatine 2 x 10 g/per day, vitamins, rehabilitation

8. Distal myopathies

They are a clinically and genetically heterogeneous group of diseases in which the distal muscles of the arms and / or legs are initially and pre-treated.

Classification is based on clinical, histological, immunohistochemical and molecular-genetic criteria. Over 15 different forms of distal myopathies are differentiated (Table 4).

Table 5. Types of distal myopathies and clinical features

Type of distal myopathy	Type of inheritance	Gene / Locus	Early involvement	CPK values	Finds from Muscle Biopsy
Wellander type	Autosomal-dominant	TIA1/2p13	> 40 hand extenders	Normal or slightly elevated	Myopathic ± vacuoles
Tibial muscular atrophy, Udd, / Finnish /	Autosomal-dominant	TTN/ 2q31	40-50 the anterior distal muscles of the legs	Normal or slightly elevated	Myopathic, vacuoles
Gowers-Laying type	Autosomal-dominant	MYH7, 14q11	1.5 – 25 the anterior distal muscles of the legs	Elevated - up to 3 times the norm	Light myopathic, vacuoles
KLHL9-linked distal myopathy	Autosomal-dominant	KLHL9	8-16 the anterior distal muscles of the legs	1.5-14	Myopathic
Distal ABD-philaminopathy	Autosomal-dominant	7q32.1/ FLNC	the distal muscles of the arms	Normal or slightly elevated	Grouped atrophic fibers
Distal Dystrophy + rimmed vacuoles	Autosomal-dominant	19p13.3	10-50 distal muscles of the arms	Normal or slightly elevated	Myopathic, vacuoles

Oculopharyngeal distal	Autosomal-dominant	?	40 extraocular	3 times higher	Myopathic, vacuoles
Distal myopathy with voice and pharyngeal weakness	Autosomal-dominant	MATR3/5q31	35-57 distal muscle, vocal cords	Normal or elevated up to 8 times	Myopathic, vacuoles
Myopathy + Paget's disease and dementia	Autosomal-dominant	*VCP*/9p13	20-40 proximal and distal muscles of the legs	Normal or slightly elevated	Myopathic, vacuoles
Myopathy + Paget's disease	Autosomal-dominant	?	35-42 distal muscles of the legs; scapular	Normal or high	Myopathic
Myopathy with cytoplasmic bodies	Autosomal-dominant	?	40-50 hands	Normal or slightly elevated	Myofibrillar inclusions
Hereditary myopathy with inclusion bodies + early respiratory failure	Autosomal-dominant	6q27	32-75 distal muscles, respiratory muscles	Normal or slightly elevated	Myopathic, Eosinophilic inclusions, vacuoles
Distal myopathy with preservation of anterior distal muscles	Autosomal-dominant	?	0-30 distal muscles of the leg and arms	Normal or slightly elevated	Varying in size fibers, no vacuoles
Distal myopathy with pes cavus and areflexia	Autosomal-dominant	19p13	15-50 distal muscles of the lower limbs, dysphonia, dysphagia	2-6 times	Dystrophic, vacuoles
New Finnish distal myopathy (MPD3)	Autosomal-dominant	8p22-q11 and 12q13-q22	Over 30 years, hands and front muscles of the legs	1-4 times	Dystrophic, vacuoles, eosinophilic inclusions
Desmin	Autosomal-dominant or recessive	DES/2q35	20-40 the legs	Slightly elevated	Myopathic, increased desmin

αB-crystallinopathy	Autosomal-dominant	CRYAB/11q22	Adulthood, legs	Slightly elevated	Myopathic, increased desmin
Myofibrillar + cardiomyopathy	Autosomal-dominant	10q22.3	20-60 distal muscles	Normal or slightly elevated	Myopathic, myofibrillar
Skapuloperoperoneal	Autosomal-dominant	12q13.3	20-58 the legs	1.5 to 10 times higher	Myopathic, focal desmene inclusions
Type Marxbury-Grig	Autosomal-dominant	LDB3/10q22.3-q23.2	44-73	From normal to 6 times higher	Myopathic, desminic inclusions, small vacuoles
Miyoshi Type	Autosomal-recessive	DYSF, 2p13	20-50 the posterior distal muscles of the legs	Elevated - 10 to 50 times	Myopathic. There are no vacuoles
GNE myopathy / Nonaka type, AP hereditary myopathy with inclusion bodies /	Autosomal-recessive	GNE/9p12-p11	20-40 the front distal muscles of the legs	Elevated - up to 5 times the norm	Myopathic, vacuoles
NEB- related distal myopathy	Autosomal-recessive	NEB/ 3p22.1	Childhood, front tibial muscles, finger extensors	Normal or slightly elevated	Atrophic Fiber, nemaline rods
Distal anatoctinopathy	Autosomal-recessive	ANO5/ 11p14.3	Asymmetric engagement of lower legs	Over 10 times	Non-specific changes

In Bulgaria, in Roma patients, GNE myopathy has been diagnosed as a result of homozygous mutation with the effect of p.Ile587Thr in the kinase domain of the GNE gene. In Bulgarian patients, the disease starts in the third decade, but in rare cases - significantly earlier. The distal weakness in the lower limbs is a leading symptom in the majority of the affected, with only a small group initially finding distal weakness in the hands. M. quadriceps femoris and respiratory muscles remain mildly affected even in the advanced stages of the disease. When tracking GNE patients with myopathy, the independent gait is lost aaveragely 10.34 ± 4.31 years from the onset of the disease. Compared to other cohort patients with this disease, there is a high incidence of cardiac involvement in our group. Significant inter- and intra-family variation in the clinical

course and severity of the disease suggests the influence of gene modifiers and environmental factors

9. Myotonia and myotonic dystrophies

These are diseases, united in a common group, due to the presence of a myotonic phenomenon - difficult relaxation after strong muscle contraction. It is a symptom of dystrophic and non-dystrophic myotonic diseases.

Myotonic dystrophies type 1 (Steinert's disease) and type 2 (PROMM) are genetic multi-system diseases with autosomal dominant type of inheritance and incomplete penetrance, that are clinically characterized by myotonic phenomena (difficulty relaxation after strong muscle contraction), progressive muscle weakness and atrophy, cataracts, cardiomyopathy, gonadal atrophy, and cognitive disorders. In Steinert's disease (MD1), weakness of the distal muscles is more typical, whereas in PROMM (MD2), the clinical picture is lighter and predominantly affecting the proximal muscles. Regarding the age of onset and the severity of the clinical symptoms, inter- and intra-family variations are observed.

9.1. Myotonic Dystrophy (Steinert's Disease) is an autosomal dominant disease with incomplete penetrance.

Classification. There are four basic forms distinguished, according to the onset of the disease and the severity of symptoms: congenital myotonic dystrophy, myotonic dystrophy of the early childhood, classical myotonic dystrophy and mild form.

Epidemiology. Steinert's disease is the most common form of adult muscular dystrophy. Its frequency in the general population ranges from 1/100 000 in some areas in Japan, to 1/10 000 in Ireland, and due to the effect of the progenitor in Canada (Quebec), its incidence reaches 1/530.

Etiology. Caused by dynamic mutations - Amplification of trinucleotide (CTG) repeats in the DMPK gene, located on the 19q13.3 chromosome.

Pathogenesis. The onset and the severity of the disease depend on the number of amplified repeats. The bigger it is, the earlier it starts and the disease develops more severe. Sex-differentiated expression of the gene was also detected. The disease is more severe if it is inherited by the mother.

Clinical picture. The onset of the disease and the clinical manifestations have wide variability, depending on the form.

Congenital myotonic dystrophy is more frequent in newborn of mothers with myotonic dystrophy. It is characterized by generalized and severe muscle weakness from birth, hypotonia, difficulty in sucking and swallowing, respiratory failure. No clinical myotonia is manifested, but it can often be detected with EMG. Muscular hypotonia and motor weakness can improve over the years, but later the patients develop symptoms of the classical form. Up to 11 years old, a clinical myotonic phenomenon also appears. The mental retardation of non-progressive nature is very typical of the congenital form.

The myotonic dystrophy of early childhood usually starts between 5 and 10 years. A generalized weakness develops, particularly affecting the face and the distal parts of the limbs. Mental retardation is also established.

Classical myotonic dystrophy. There is a pronounced myotonic phenomenon as well as weakness of the following muscles: m. orbicularis oculi, pharyngeal muscles, distal limb muscles. Atrophy of the chewing muscles is typical. As the disease progresses, more generalized muscular involvement develops, but it is never severe for the proximal limb muscles and the torso musculature. Other signs of the disease are cataracts, cardiomyopathy, endocrine disorders, sterility, cognitive deficits with functional and lymphatic disorders, attention, visual perception and memory.

The mild form is clinically characterized by cataracts, frontal balding, minimal to absent muscle deficiency or diabetes mellitus.

Diagnosis is based on clinical, EMG and genetic research.

Tests. CPK is slightly elevated. EMG shows myotonic phenomena and myogenic changes in several muscles. The neuropsychological study can determine the degree of the cognitive impairment. Molecular genetic testing reveals amplification of trinucleotide repeats.

Treatment and prophylaxis. Treatment for myotonia with Procainamid 500-1000 mg / day, 3-4 times / day, Chinine 500-600 mg / 12 h, Phenytoin 300-400 mg / day, Mexiletine 200 mg / 8 h, Carbamazepine, 600 mg / day is performed. Monitoring of cardiac status and respiratory capacity as well as periodic physiotherapy are important. If necessary, cardioprotective medications are used, and in case of conduction disorders, a pacemaker can also be placed. In case of severely reduced vital capacities, invasive and non-invasive ventilation can be administered. In connection with the established anticipation with the disease (in each next generation,

it starts earlier and runs more severely), it is advisable to carry out prenatal diagnostics in the affected families.

9.2. PROMM – Proximal myotonic myopathy is an autosomal dominant disease.

It is caused by a transcribed but nontranslated expansion of CCTG nucleotide repeats in intron 1 of the ZnF9 (Zinc Finger protein 9) gene. There is no correlation between the size of the amplification and the age of onset of the disease and the severity of the clinical picture.

The clinical picture is similar to that of myotonic dystrophy, but is usually lighter. Proximal and distal muscle weakness, myotonia, cardiac involvement, cataracts are observed. No congenital form is described.

Differential diagnosis with classical myotonic dystrophy is not always easy. Proximal myotonic dystrophy is characterized by more pronounced muscular pain, proximal weakness of the femoral muscles, and mild cognitive impairment.

9.3 Non-dystrophic myotonies belong to the group of channelopathy**.**

Hereditary channel ion channels disorders (channelopathies) are a group of diseases caused by mutations in the genes, coding the ion channels. Myotonia is a symptom that may be present in both sodium and chloride channelopathies. Chloride channelopathies include the dominant Myotonia congenita (Thomsen) and recessive generalized myotonia (Becker).

- **Thomsen type congenital myopathy** is an autosomal dominant disease with 100% penetrance. It is caused by allelic mutations in the gene for the muscle chloride channels. The disease can begin from birth to early childhood. Clinical signs are tightness of the muscles, especially after resting. Muscle function improves with prolonged exercise. The disease does not progress. Although patients often report an increase in the cold myotonia, this is not evidenced by the objective measurement of muscle relaxation times.

Diagnosis is based on clinical results, EMG and results of molecular-genetic tests.

- **Becker type generalized myotonia** is an autosomal recessive disease. It is caused by mutations in the gene encoding chloride muscle channels. The disease usually begins in the first decade, significantly rarely - in the second or third decade.

Clinical signs are tightness of the muscles, especially after rest, but with prolonged exercise, the muscle function improves. In some patients, there is a significant, transient weakness after resting, which improves several minutes after making exercises. Weakness is more pronounced in the upper limbs, and myotonia - in the lower limbs. In many cases there is hypertrophy of thighs and lower legs. Complaints are usually progressing several years after appearance, and then there is no change.

Diagnosis is based on clinical, EMG and genetic data.

Treatment with membrane stabilizers such as Procainamid 500-1000 mg / day, 3-4 times / day, Chinine 500-600 mg / 12 h, Phenytoin 300-400 mg / day, Mexiletine 200 mg / 8 h, and others. It is recommended to avoid physical exertion, cold exposure, depolarizing muscle relaxants.

- **Congenital paramyotonia** is an autosomal dominant disease with 100% penetrance. It is caused by mutations in the gene coding the sodium channels. The onset of the disease is from birth. Clinical signs are myotonia, which is exacerbated by multiple contractions (paradoxical myotonia). In many families, paramyotony, which significantly deteriorates when performing exercises in cold environment, can be followed by a weakness. Recovery from weakness may take several hours. In some families there is myotonia, dependent on cold and exercise, but without weakness. They are often misdiagnosed like myotonia congenita. There are families with the classic symptoms of congenital paramyotonia, combined with episodes of hyperPP. No permanent weakness is observed.

Treatment is with antiarrhythmic drugs, such as mexiletine. Prior to the onset of anti-myotonic therapy with mexiletine, it is recommended to study the cardiac status and to examine its serum concentrations due to its narrow therapeutic spectrum. In paramyotonic hyperplasia, the combined use of mexiletine and hydrochlorothiazide may prevent spasms and weakness, induced by cold and spontaneous attacks of hypercalcemic periodic paralysis.

10. Periodic paralysis

These diseases refer to the group of channelopathies in which periods of transient muscle weakness are observed. Sodium channelopathies include hyperkalemic periodic paralysis (hyperPP), normokalemic periodic paralysis (normoPP), congenital paramyotonia (CP) and potassium-dependent myotonia (PDM). Hypokalemic periodic

paralysis, the only disease in this group that is not associated with myotonia, is calcium channelopathy.

10.1. Hyperkalemic periodic paralysis is an autosomal dominant disease with complete penetrance. It is caused by mutations in the gene coding the sodium channels. The onset of the disease is from early childhood to the second decade. Its severity is very variable. Clinical signs are episodes of weakness, usually in the morning, lasting for 10 minutes, up to about 1 hour, very rarely up to 1-2 days. In some patients the frequency of episodes is very rare and others have episodes of generalized weakness almost every day. During the episodes, the serum K level is at or above the upper limit. Challenging tests for the episodes of weakness are rest after exercise, starvation, or oral application of K. Some patients always have mild signs of myotonia before or at the beginning of episodes. Others show signs of paramyotonia, and in others, myotonic signs are absent. At the end of the paralytic episode, serum K levels may fall below normal. Patients examined at that time may be misdiagnosed as hypoPP.

The treatment of more severe episodes is by intravenous administration of 10% Glucosae, Insulin, Calcium gluconicum and Salbutamol inhalations. Prophylaxis includes to avoid starvation and intake of foods rich in potassium, salt consumption increase, acetazolamide and potassium-losing diuretics.

10.2. Normokalemic periodic paralysis. A small number of families are described. Episodes may last for several days without increasing the serum K concentration. In one of the affected families, a mutation in the gene coding for sodium channels has been demonstrated. Mutations in the same locus in other families cause hyperPP. This gives some authors the grounds to believe that normokalemic periodic paralysis is a variant of hyperPP.

Potassium-Dependent Myotonia (PDM) is an autosomal-dominant disease. It is caused by mutations in the gene, coding for sodium channels. Up to now, five different mutations have been described.

Clinical picture. It may occur as a fluctuating or permanent myotonia.

Fluctuating myotonia ranges in different days and is provoked by physical exercise. Potassium infusion enhances myotonia but does not cause weakness, as in hyperPP. Other depolarizing agents (eg suxamethonium) may also cause or enhance myotonia with severe respiratory disturbances during general anesthesia, if the patient and the anesthesiologist are unaware of the disease. Even in the absence of clinical

myotonia, the latent can be verified with an EMG. In the acetazolamide-dependent form, also described as atypical myotonia congenita, myotonia may also fluctuate, and to provoke muscle aches.

The permanent myotonia is manifested by persistent generalized myotonia and muscular hypertrophy, especially in the neck and shoulder area. Episodes of severe myotonia of the thoracic muscles may be life-threatening due to the impaired respiratory activity, especially in children. As myotonia is severe and is enhanced by depolarizing agents, potassium should never be used as a diagnostic agent.

10.3. Hypokalemic periodic paralysis is an autosomal dominant disease with reduced penetrance in women. The male / female ratio is 3-4: 1. Two mutations of the gene (CACLN 1 A3) encoding 1 subunit L-type calcium channel (DHP) cause the clinical picture in more than 50% of the families. The onset of the disease in the severe cases is in early childhood, and in 60% it is before the age of 16. Mild cases are with late onset (in the third decade). It occurs with episodes of weakness, usually in the second half of the night or in the early morning. Initially, they are rare, but after several months or years they become more frequent, sometimes daily. Weakness may vary in severity from mild temporary weakness of isolated muscle group to generalized paralysis. Normally, the strength gradually recovers during the day. Sometimes the weakness lasts two to three days. Provocative factors for night episodes are often increased physical activity or the intake of carbohydrate-rich food in the previous day. However, mild physical activity may sometimes prevent or postpone the light episodes. During severe episodes, serum potassium decreases and may cause sinus bradycardia and ECG signs of hypokalemia. There is a lack of both clinical and electrical myotonia. Regardless of the severity and the frequency of the paralytic episodes, 30% of patients develop progressive proximal myopathy with permanent residual weakness.

Treatment of mild attacks is by oral administration of Kalnormin 1 g, and in severe cases- i.v. Kalium chloride, 0.3 - 0.5% solution in 5% Glucose. ECG and serum potassium are monitored. Prophylaxis - Acetazolamide, 125-250 mg, 1-3 times a day, potassium-sparing diuretics, beta-blockers.

General anesthesia in patients with certain muscular disorders may result in complications, resembling malignant hyperthermia. In myotonia and periodic paralysis, succinylcholine and other depolarizing myorelaxants can cause strong myotonic reaction in separate muscles (eg m., Masseter, less frequently

respiratory and other skeletal muscles). Myotonia can also be exacerbated by potassium and anticholinesterase medications, as well as in pregnancy and hypothyroidism. For treatment, Mexiletine, 200 mg / 8 h, Lidocaine 50-100 ml 0.5% solution, and derivatives thereof are used. In a progressive crisis of malignant hyperthermia or a severe myotonic reaction, Dantrolene.

B. **Diseases of the peripheral motor neuron**

1. Spinal muscular atrophy (SMA)

They represent a large group of genetic diseases, characterized by degeneration of peripheral alpha motoneurons in the anterior horns of the spinal cord and motor nuclei of the cranial nerves, leading to progressive muscle weakness and atrophy. The most common form of SMA is AR disease, caused by mutations in the gene encoding the protein, the survival motor neuron 1 (SMN1), located on 5q11.2-q13.3. Approximately 96% of the patients had a deletion of exons 7 and 8 of the SMN1 gene, in rare cases only exon 7. In 3-4% of cases, another mutation was found in combination with the typical deletion. The SMN locus on the 5 chromosome also contains a SMN2 gene that is structurally close to SMN1. SMN2 is intact in all patients with SMA, the number of copies ranging from 1 to 4 and can determine the severity of the disease. SMN1 encodes the major amount of the full-length SMN protein, whereas 90% of the SMN2 mRNA does not include exon 7, thereby synthesizes rapidly degrading SMN protein.

Pathogenesis: SMN protein is of particular importance for the normal functioning of the alpha motoneurons.

It is classified in the following forms based on the achieved motor functions:

• Type 1 SMA, where children cannot sit without a support
• Type 2 SMA, where children can sit but cannot walk
• Type 3 SMA in which patients can walk
• Type 4 SMA with adult onset

Clinical characteristics. The main symptoms of the disease include muscle hypotension, progressive proximal muscle weakness, more pronounced in the lower limbs, bulbar weakness in the more advanced stages of the disease. There is a weakness of the intercostal respiratory muscles with relative saving of the diaphragm, resulting in a "bell-shaped" chest and paradoxical breathing. In the form of childhood

onset, there is muscle hypotension and weakness with less pronounced bulbar and respiratory involvement.

The diagnosis is based on:

• Clinical characteristics

• EMG study with data on anterior horn injury

• CPK ranges from normal to slightly increased

• The final diagnosis is made by molecular-genetic testing (Figure 4). A gold standard in genetic verification is the quantification of SMN1 and SMN2, by multiplex ligation dependent (MLPA) or quantitative polymerase chain reaction or by new generation sequencing (NGS) (Figure 4).

The number of SMN2 copies determines the severity of the disease in most cases, although there are exceptions. Patients with SMA type 1 have 2 SMN2 copies, those with SMA type 2 - 3, those with SMA type 3 - 4, and with those with SMA type 4 SMN2, the copies are from 4 to 6.

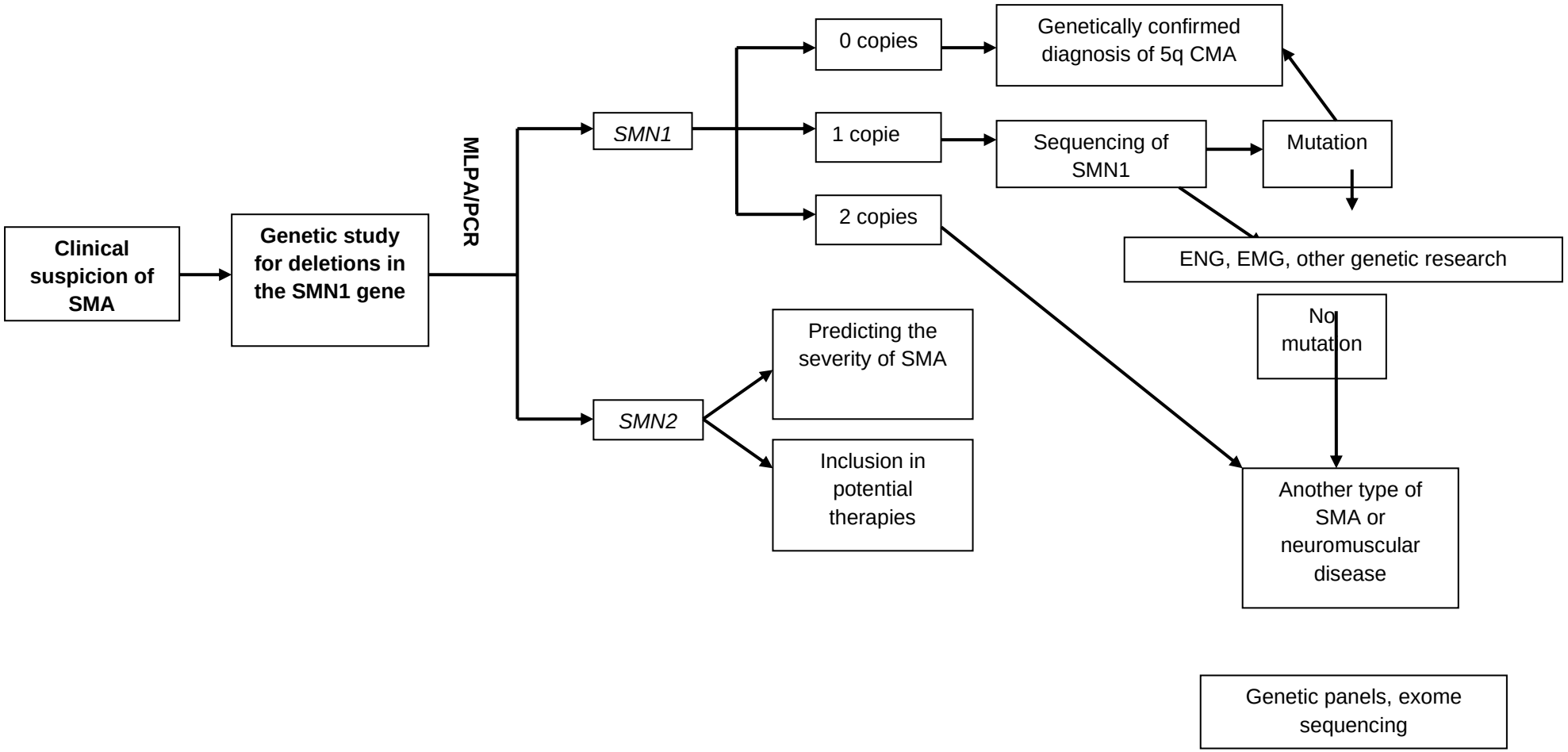

Clinical suspicion of SMA
Genetic study for deletions in the SMN1 gene
MLPA/PCR
SMN1
SMN2
0 copies
1 copie
2 copies
Genetically confirmed diagnosis of 5q CMA
Sequencing of SMN1
Mutation
ENG, EMG, other genetic research
No mutation
Predicting the severity of SMA
Inclusion in potential therapies
Another type of SMA or neuromuscular disease
Genetic panels, exome sequencing

Figure 4. Diagnostic algorithm for SMA patients.

Treatment and follow-up of patients with SMA requires a multidisciplinary approach.

SMA treatment will be performed at:

• For patients aged 0 to 3 years shall be performed at the Clinic for Child Neurology in Specialized Hospital for Active Treatment of Children's Diseases "Prof. Dr. Ivan Mitev" in Sofia and in the Clinic of Pediatrics and Genetic Diseases at the University Multiprofile Hospital for Active Treatment "St. Georgi" in Plovdiv

• For patients aged 3 to 18 years - at the Clinic of Nervous Diseases of University Multiprofile Hospital for Active Treatment "Alexandrovska", Clinic of Nervous Diseases for Children at University Multiprofile Hospital for Active Treatment in Neurology and Psychiatry "St. Naum" and at the Clinic of Pediatric Neurology in Specialized Hospital for Active Treatment of Children's Diseases "Prof. Dr. Ivan Mitev" in Sofia and the Clinic of Pediatrics and Genetic Diseases at the University Multiprofile Hospital for Active Treatment "St. Georgi" in Plovdiv

• For patients over 18 years of age - at the Clinic for Nervous Diseases of the University Multiprofile Hospital for Active Treatment “Alexandrovska”, at the University Multiprofile Hospital for Active Treatment in Neurology and Psychiatry “St. Naum” and the Clinic of Neurology at University Multiprofile Hospital for Active Treatment "St. Georgi" in Plovdiv

The neurologist assesses muscle strength, joint contractures every 6 months.

Zolgensma (onasemnogene abeparvovec) is the first gene therapy medicinal product for the treatment of 5q spinal muscular atrophy. It uses adeno-associated virus serotype 9 (AAV9) based vector for the incorporation of functional copy of *SMN1* gene in motor neurons. AAV9 crosses the blood-brain barrier. It was registered by FDA (Food and drug agency) on 24.05.2019 and by EMA (European Medicines Agency) on 18.05.2020. It is indicated for the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene.

Recommended dose of Zolgensma is 1.1×10^{14} vector genomes (vg)/kg.

Before the administration of Zolgensma, baseline laboratory testing is required, including:

- AAV9 (anti-adenoviruses antibodies)
- Complete blood count
- liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin
- Creatinine
- Troponin-I

The drug is administered once in a lifetime, as a single-dose, intravenous infusion for 60 minutes. An immune response to the viral capsid may occur and can lead to elevations in liver transaminases, elevations of troponin I, or decreased platelet counts. To dampen the immune response, immunomodulation with corticosteroids is required – on the day before the infusion, systemic administration of a dose equivalent to 1mg/kg/day of prednisolone is started, lasting for 1 month. On the 30th day of the administration, the liver function should be evaluated. In case of normal liver function corticosteroid dose is decreased gradually – 2 weeks at 0.5 mg/kg/day and then 2 weeks at 0.25 mg/kg/day and then is stopped. In case of elevated transaminases, the systemic application of corticosteroids should continue at a dose, according to levels of transaminases.

Thrombocyte count and liver function should be assessed weekly for 1 month and every two weeks for an additional 2 months post administration of Zolgensma.

Zolgensma is contraindicated in case of hypersensitivity to the active substance or to any of the excipients.

Effect of treatment is evaluated through CHOP-INTEND in patients with SMA type 1 and Hammersmith Functional Motor Scale Expanded (HFMSE) in SMA type 2 patients.

Inclusion criteria for initiating Zolgensma therapy

- Genetically proven 5q SMA resulting from mutations in the *SMN1* gene
- Clinical diagnosis of SMA type 1 OR
- Patients with 5q SMA with a bi-allelic mutation in *SMN1* gene and up to 3 copies of the *SMN2* gene
- Patients up to 2 years of age OR
- Body weight up to 20 kg
- Patients, using SMA care standards

Exclusion criteria for initiating Zolgensma therapy

- Patients with hypersensitivity to the active substance or any of the excipients
- Presence of Anti-AAV9 antibodies titres above 1:50 at baseline. Re-testing should be performed if AAV9 antibody titres are reported as above 1:50 in two weeks. If Anti-AAV9 antibodies titres are back to normal, the patient can be treated.
- Patients with liver function impairment – transaminases more than 3 x ULN.
- Patients with thrombocytopenia

Nusinersen (SPINRAZA) is a modified antisense oligonucleotide that binds to the intron, following exon 7 in the pre-information RNA of SMN2. Thus, it modulates mRNA splicing to include exon 7 and to synthesize a larger amount of full-length SMN protein. This is the first drug, approved for the treatment of all forms of 5q SMA (December 2016 by the Food and Drug Agency of the FDA and May 2017 by EMA). The recommended dose of the drug is 12 mg (each vial is 5 ml / 12 mg) administered intrathecally. Therapy starts with four loading doses - three every 14 days and the fourth dose - 30 days after the third. The maintenance doses are then administered over four months. In pre-symptomatic treatment initiated in SMA type patients, a motor development similar to that of healthy children was observed. In other clinical trials, children on therapy achieve statistically significant improvement in motor function. There is a statistically significant increase in survival for patients with SMA type 1. The medicine is approved for all forms of the disease and for all ages, and efficacy and safety data are already available in patients over 18 years of age.

The most common side effects are infections of the upper and lower respiratory tract, constipation, pulmonary atelectasis, proteinuria, as well as headache, nausea and lumbar pain, associated with the procedure itself.

Inclusion criteria for initiating Nusinersen therapy

- Genetically proven 5q SMA resulting from mutations in the SMN1 gene
- Patients, using SMA care standards
- Individual forms of SMA are required in addition:

In patients with SMA type 1

- The patient was without symptoms for SMA at 1 week of age.

- The patient should have at least 2 copies of the SMN 2 gene.
- The patient should have SAO2> 95% without need for assisted breathing (including CPAP - constant positive air pressure) or supplemental oxygen

In patients with SMA type 2

- The patient has at least 2 copies of the SMN 2 gene.
- The patient is not dependent on assisted ventilation or oxygen - SAO2> 96%

In patients with SMA type 3

- The patient has at least 2 copies of the SMN 2 gene.
- The patient is not dependent on assisted ventilation or oxygen - SAO2> 96%

Exclusion criteria for initiating Nusinersen therapy

- A history of central or peripheral nervous system disease that would hinder intrathecal
- Severe scoliosis, which would hinder intrathecal drug administration
- A history of implanted shunt
- Participation in a SMA clinical study
- Disturbance in blood clotting, which would make the use of the medicine dangerous for the patient

Criteria for evaluation of treatment and continuation of treatment:

- 3 months after the sixth and before the seventh dose and then every 6 months, if the treatment continues.
- The patient should not be aggravated by any of the following parameters:

1. General motor function, measured under the motor function measurement scale of Hammersmith Functional Motor Scale Expanded (HFMSE).

In patients with SMA type 1 the evaluation of the motor functions is performed under the scales:

- Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
- Hammersmith Infant Neurological Examination (HINE)

In patients with SMA type 2 the evaluation of the motor functions is performed under the scales:

- Hammersmith Functional Motor Scale Expanded (HFMSE) score
- Revised Upper Limb (RULM)
- Manual muscular testing (MRC scale)

In patients with SMA type 3 the evaluation of the motor functions is performed under the scales:

- Hammersmith Functional Motor Scale Expanded (HFMSE) score
- Revised Upper Limb (RULM)
- Manual muscular testing (MRC scale)
- 6 Minutes walking test (6MWT) – if independent walking is possible

2. Respiratory function assessed by spirometry, evaluation of PAO2 and PACO2 over a period of time without additional oxygen supply.

A pre-training is required for the performing of these tests.

Necessary conditions for application of the medicine in a medical establishment:

• Application room

• Intrathecal application protocols

• Room for follow-up after the intrathecal administration

• Staff with experience in intrathecal manipulation, diagnosis and follow up of patients with SMA

• Conditions and personnel to apply anesthesia if necessary

• Conditions for resuscitation if necessary

Specialists, necessary for the preparation of the patient, performing the procedure and to follow up the patient:

• Neurologist

• Pulmonologist

• Cardiologist

• Anesthesiologist

• Physiotherapist

• Nurse

• If necessary - radiologist

Length of stay in a hospital - 48 hours

• The day before Nusinersen's application:

• Evaluation of the full blood count, coagulation, urea, creatinine

• Consult an anesthesiologist (if anesthesia is to be performed)

• Local hypersensitivity testing of local anesthetics if local anesthesia is envisaged)

• Evaluation of the motor function (before the first application, 3 months after the sixth dose and subsequently every 6 months)

- In the day of application of Nusinersen
    - Obtaining the medicine from the hospital pharmacy.
    - Filling in required documents (patient's medical record, Nusinersen therapy schedule and appointment).
    - Evaluation of anthropometric indicators - height and weight.
    - If necessary, the judgment of the treating physician can be applied:
        - Local anesthesia with:
            - Lidocain - creme
            - Lidocain solution for injection 20 mg / ml - 10 ml (local infiltration anesthesia after scarification).
        - General anesthesia after prior consultation by an anesthesiologist, pulmologist and cardiologist with Ketamine, Midazolam or Kalinox (50% / 50% compressed medical gas - N2O, oxygen O2)
    - Drug Administration:
        - 1st application (Day 0): the patient should not have taken food 2 hours before the injection and the coagulation profile should be within the norms (as assessed by a doctor).
        - Next applications: on an empty stomach 1 hour before injection.
        - The Nusinersen vial is removed from the refrigerator for at least 30 minutes before application.
        - After withdrawal of Nusinersen into the syringe, the medicine should be stored in the dark if the application is not immediately (up to 6 hours).
        - Preparing an operating trolley with the necessary lumbar puncture (LP) equipment

        - i.v. (intravenous injections) syringes, (3 pcs) of 10 ml, three-part syringes-
        - Two black needles for lumbar puncture (22 G 0.7 x 38 mm от 22 G 0.7 x 90 mm).
        - Sterile compresses x 8 sterile dressings (2 packs), Opsite, postoperative (6.5 x 5 cm)
        - Three 2 ml liquor tubes.
        - Sterile gloves, aprons, masks, surgical sheets without slots.
        - Disinfectant.
    - The vial must not be shaken.
    - The withdrawn volume of liquor via LP is identical to that of Nusinersen for one procedure (5 ml). The withdrawn volume of liquor is distributed in the three tubes, which should be immediately labeled and stored for storage at -80 ° C.
    - Nusinersen should be infused slowly for 2-3 minutes.
    - The patient should be in an antidecubital position for 1 hour after the manipulation.
    - Provision of cardio-respiratory monitoring equipment (if required).

• Observation of the patient after the procedure

    - Check the performance of: hour 0 / hour 1 / hour 2 (T ° / breath / pulse / saturation / RR) in the first procedure and in the next one only 1 hour.
    - Feeding is allowed after the first hour if the patient is well.
    - Post-puncture syndrome monitoring
    - Monitoring of the injection site for local reactions.
    - General condition: temperature, vomiting
    - The physician allows the patient to be discharged after an assessment of his condition. The patient can leave the clinic after the application, not earlier than 2 hours in the first procedure or 1 hour in the following procedures, if he has taken food, fluids, and feels well.
    - Preparing the patient's medical records

- Returning the empty vial and its pack to the hospital pharmacy. It is not thrown away.

Risdiplam is an orally taken drug. It is an SMN2 mRNA splicing modifier to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript, leading to an increased production of functional and stable SMN protein. Risdiplam crosses the blood-brain barrier and distributes both in CNS and in other tissues of the body.

It is indicated for the treatment of all types of 5q SMA in patients 2 months of age and older. The recommended dose of risdiplam is determined by age and body weight - 0,2 mg/kg/day in children 2 months to < 2 years of age, 0.25 mg/kg/day in patients ≥ 2 years of age and < 20 kg, and 5 mg/day in patients ≥ 2 years of age and ≥ 20 kg.

Most frequent adverse reactions are rash, mouth ulcerations, nausea, diarrhoea, pyrexia, arthralgia.

Inclusion criteria for initiating Risdiplam therapy

- Genetically proven 5q SMA resulting from mutations in *SMN1* - gene
- Patients, using SMA care standards
- Additional requirements in individual forms of SMA:

In patients with SMA type 1

- The patient should be at 2 months of age or older.
- The patient should have at least 2 copies of *SMN2* gene.
- The patient should have SAO_2> 95% without a need for assisted breathing (including CPAP – constant positive air pressure) or supplemental oxygen.

In patients with type 2 SMA

- The patient should have at least 2 copies of *SMN 2* gene.
- The patient is not dependent on assisted ventilation or oxygen - SAO2 > 96%

In patients with SMA type 3

- The patient should have at least 2 copies of *SMN 2* gene.
- The patient is not dependent on assisted ventilation or oxygen - SAO2 > 96%

Exclusion criteria for initiating Risdiplam therapy

- Hypersensitivity to the active substance or to any of the excipients
- Presence of severe gastrointestinal and liver diseases
- Patients with liver function impairment – transaminases more than 3 x ULN
- Participation in a SMA clinical study

Criteria for evaluation of the treatment and continuation of treatment, before treatment initiation and every 6 months afterwards:

In patients with SMA type 1 the evaluation of the motor functions is performed under the scales:

- Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
- Hammersmith Infant Neurological Examination (HINE)
- Bayley Scales of Infant and Toddler Development Third Edition (BSID-III)

In patients with SMA type 2 the evaluation of the motor functions is performed under the scales:

- Hammersmith Functional Motor Scale Expanded (HFMSE) score
- Revised Upper Limb (RULM)
- Manual muscular testing (MRC scale)

In patients with SMA type 3 the evaluation of the motor functions is performed under the scales:

- Hammersmith Functional Motor Scale Expanded (HFMSE) score
- Revised Upper Limb (RULM)
- Manual muscular testing (MRC scale)
- 6 Minutes Walking Test (6MWT) - if independent walking is possible

2. Respiratory function assessed by spirometry, evaluation of PAO2 and PACO2 over a period of time without additional oxygen supply.

Physiotherapy - The following exercises are of particular importance in the various forms: stretching (including using splints and orthoses), positioning, mobility

exercise, breathing gymnastics. They are consistent with the form and severity of SMA and are performed under the control of a physiotherapist with experience in NMD.

Orthopedic interventions. In patients with SMA type 1 and 2, scoliosis above 20° should be monitored every 6 months before reaching bone maturity and annually thereafter. The use of spinal splints is recommended for hypotonic children with scoliosis over 20° in which reaching bone maturity is taking longer periods. The patient is referred to orthopedic surgery, when a Cobb angle ≥50 ° or increases with ≥10° annually. Additional factors such as deterioration of respiratory function, pronounced kyphosis, impaired body balance are assessed. The evaluation of the ventilation capacities is essential before and after the operative intervention. Patients aged 8-10 years are implanted with stabilizers, allowing bone growth. In patients over 12 years of age spinal fusion is performed.

Unilateral or bilateral hip correction and joint contractures are performed in patients with significant pain.

Treatment of gastrointestinal and swallowing disorders. For all forms of SMA, it is important to assess the presence of gastroesophageal reflux, constipation, delayed gastric discharge or vomiting.

In patients with SMA type 1, bulbar weakness with dysphagia and masseter contractions are typical. Temporary nasogastric (NGT) or nasojeunal tubes are required until permanent gastrostomy is placed. Nutritionist considers the necessary amounts of nutrients, fluids and electrolytes that should be considered optimal growth.

In patients with SMA type 2, swallowing disorders are common and require the use of NGT to help provide the necessary amounts of nutrients. These patients, as well as patients with SMA type 3 who have lost their independent gait, are at increased risk of obesity given the limited movements. In these cases, they are referred to a nutritionist for optimal nutrition. It is important to fine-tune vitamin D intake for the prevention of osteopenia and osteoporosis.

Respiratory care. Respiratory disorders are typical for patients with SMA.

For SMA type 1, performing of oximetry and capnography every 3 months is of particular importance, and the assessment during sleep is more objective. If hypoventilation is detected, it is important to ensure optimum airway patency - manually and mechanically - Cough Assist® or VitalCough®. Initially, the pressure of insufflation and exsufflation should be slowly increased by 30-40 cm H_2O positive or negative pressure. Non-invasive positive-pressure ventilation should be used in all

symptomatic children with SMA prior to manifestation of symptoms of respiratory failure. The judgment of the ventilation mode is done by an anesthesiologist-resuscitator with experience in the field of NMD. Breathing aid in indicated non-invasive positive pressure ventilation should be used in all symptomatic infants and non-sitting subjects before developing respiratory failure signs. CPAP should not be used for the treatment of chronic respiratory insufficiency but can be used with caution to maintain functional residual respiratory capacity in smaller patients who cannot synchronize with the ventilator in NIV mode and who are not explicitly hypercapnic. This also applies to the weaker non-sitting. It is extremely important to select a suitable mask, at least two types, and to use nasal mask at first. Non-sitting patients are highly recommended to initiate NIV by clinical titration and to focus on correction of gas exchange and reduction of respiratory muscles efforts. Invasive ventilation is used with insufficient effect of non-invasive ventilation. Tracheotomy is an option in individual patients where non-invasive ventilation is insufficient or unsuccessful or if a suitable mask is not available. The decision should be individual, depending on the clinical status, prognosis and quality of life, and be based on discussion with the family.

Methods to improve coughing are also recommended - manually, via Ambu or cough assist devices.

Bronchodilators are used in case of suspicion of asthma. Mucolytics shall not be applied over a long period of time.

In patients with SMA types 2 and 3, spirometry is recommended every 6 months, and in case of suspicion of nocturnal hypoventilation, a polysomnography test is recommended.

In patients with ineffective cough, maintenance of airway patency by manual or apparatus methods analogous to those of SMA type 1 is of particular importance. When breathing failure is detected, bilevel non-invasive ventilation is recommended. Although patients with SMA type 2 and 3 are seldom required if signs of respiratory failure are present and no effect of non-invasive ventilation is invoked invasive.

Figure 5 shows a monitoring and respiratory care algorithm for patients with SMA.

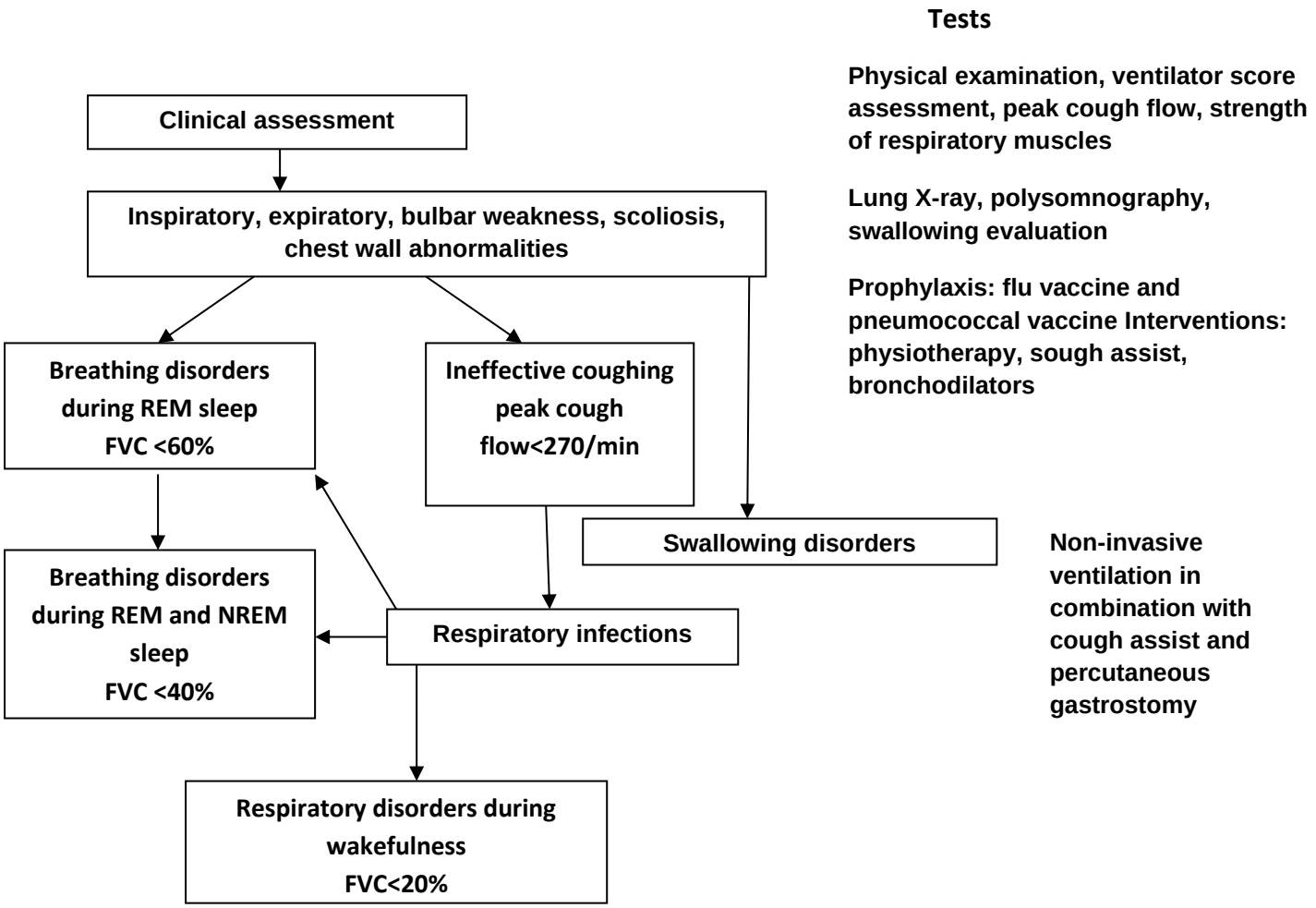


Figure 5. Clinical algorithm for diagnostics and respiratory care of patients with SMA.

Emergency conditions in patients with SMA

Recurrent infections can aggravate the condition of SMA patients and may require emergency hospitalization with subsequent recovery of the airway patency, non-invasive or invasive ventilation, and oxygen therapy. Oxygen supplementation should not be empirically administered without CO2 monitoring and should not be used as an alternative to positive pressure ventilation. Depending on the condition of the patient, antibiotics, parenteral nutrition, water-electrolyte balance restoration are applied.

Table 6 presents rare forms of proximal non5q SMA that are involved in the differential diagnosis of spinal muscular atrophy.

Table 6. Genetic causes and clinical features of non-5q spinal muscular atrophy.

(OMIM)	Gene	Locus	Phenotype	Clinical symptoms
Autosomal dominant				
Early onset				
(181405)	*TRPV4*	12q24.11	Scapuloperoneal SMA	Progressive scupuloperoneal muscular weakness and laryngeal paralysis
(158600)	*DYNC1H1*	14q32.31	SMA with involvement of lower limbs-1	Proximal muscle weakness in lower extremities
(615290)	*BICD2*	9q22.31	SMA with involvement of lower limbs-2	Proximal muscle weakness in lower extremities Congenital Joint contractures affecting the central motor neuron
Late onset				
(182980)	*VAPB*	20q13.32	SMA with late onset, type Finkel	Proximal muscle weakness, muscle cramps and fasciculations
(615048)	-	22q11.2-q13.2	SMA, type Jokela	Proximal muscle weakness, muscle cramps and fasciculations
(604484)	*TFG*	3q12.2	SMA, type Okinawa	Mild sensory disorders, painful muscle cramps, myotonia, dysphagia
(159001)	*LMNA*	1q22	SMA with cardiac involvement	Progressive muscular weakness and cardiomyopathy
(602433)	*SETX*	9q34	Late SMA with pyramidal signs	Proximal and distal muscular weakness, tremor of the hands, live tendon reflexes
АВТОЗОМНО-РЕЦЕСИВНИ				
Early onset				
(159950)	*ASAH1*	8p22	SMA with progressive myoclonic epilepsy	Refractory therapy Myoclonic epilepsy, dysphagia, respiratory weakness
(607596)	*VRK1*	14q32.2	Pontocerebellar hypoplasia with infantile SMA	Pseudocerebellar hypoplasia, microcephaly, mental retardation

(614678)	*EXOSC3*	9p13.2	Ponto cerebral hypoplasia with infantile onset SMA	Pseudocerebellar hypoplasia, microcephaly, mental retardation
(611890)	*GLE1*	9q34.11	Arthrogryposis with involvement of the peripheral motor neuron	
(614707)	*SLC52A3, SLC52A2*		Brown-Vialetto-Van Laere syndrome	Pontobulbar involvement and neurosensory deafness
Late onset				
XXXX	*HEXB*	5q13.3	SMA	Proximal muscle weakness in the lower extremities
X-LINKED				
Early onset				
(301830)	*UBA1*	Xp11.23	Lethal Infant SMA with Arthriptopase	Hypotension, arrhythmias, dysmorphic features, Joint contractures
Late onset				
(313200)	*AR*	Xq12	Bulbospinal SMA, Kennedy's disease	Proximal and bulbar muscle weakness, endocrine disorders

C. Diseases of the neuromuscular transmission

1. Congenital Myasthenic Syndromes are a group of hereditary congenital diseases, affecting the neuromuscular transmission.

To date 32 genes have been described, mutations in which lead to congenital myasthenic syndromes. Establishing the correct molecular defect is critical not only for genetic counseling, but also for the treatment of these patients.

They are classified as presynaptic, synaptic associated with basal lamina and postsynaptic, depending on the localization of the defective protein in the neuromuscular synapse.

Clinically, they exhibit abnormal muscle fatigue and load-induced muscle weakness, ptosis, ophthalmoparesis, bulbar and respiratory disturbances. The disease usually debuts at childbirth, infant age or early childhood, but it is also described later in some patients. The neuromuscular transmission abnormality is demonstrated by the pathological decrement in repetitive stimulation and the increased jitter in EMG of a single muscle fiber. No antibodies to the acetylcholine receptor as well as anti-MuSK antibodies are detected.

Immunosuppressive therapy has no effect. Acetylcholinesterase inhibitors have a variable effect in the various forms.

Table 7. Congenital myasthenic syndromes, genes, mutations in which lead to congenital myasthenic syndromes /CMS/:

CMS type	Gene	Onset	Initial events	Congenital contractures, dysmorphic facies	Ptosis / ophthalmoparesis	Facial and bulbar weakness	Weakness in limbs, axial weakness and scoliosis	Respiratory crises	Effect of the anti-acetylcholinesterase therapy
Presynaptic									
Choline O-Acetyltransferase	CHAT	years	Hypotonia, apnea	-	+/-	+	Generalized load-induced weakness	+	Significant
Unconventional myosin 9	MYO9A	0-1	Ptosis hypotension, respiratory and bulbar weakness	-	+/-	+	Muscular hypotonia	+	Significant
PREPL	PREPL	0-1	Hypotension and difficulty in swallowing	-	-	-	Progressive muscle weakness	No data	Significant
Vesicular ACh transporter (VAChT)	SLC18A3	0-1	Episodic apnea	+	-/-	-	Generalized load-induced weakness	No data	Significant
High-affinity choline	SLC5A7	0-5	Episodic apnea, ptosis and	-	+/+	-	Progressive muscle weakness	+	Significant

transporter 1 (ChT)			ophthalmoparesis						
Synaptosome Associated Protein 25	SNAP25B	0-1	Congenital contractures, respiratory disturbances	+	-/-	+	Progressive muscle weakness	+	Significant
Synaptotagmin 2	SYT2	Child age	Proximal and distal weakness in limbs, feet deformities	+	-/-	-	Progressive muscle weakness	-	Significant
MUNC13-1	UNC13-1	0	Severe hypotension and respiratory failure	-	-/-	-	Progressive muscle weakness	+	Absence of effect
Synaptobrevin 1	VAMP1	0-1	Hypotension, muscle weakness, swallowing disorders	+	-/-	+	Progressive muscle weakness	+	Significant
Synaptic									
Collagen Type XIII 1 Chain	COL13A1	0-1	Breathing and swallowing disorders	-	+/-	-	Progressive muscle weakness	Progressive respiratory	Significant

								weakness	
Endplate AChE deficiency	COLQ		Ptosis, hypotension, weak suction and crying, respiratory failure, delayed motor development	-	+/+	+	Generalized weakness, sometimes with girdle-limb distribution, myopathic gait, axial weakness, scoliosis.	+	No effect or deterioration
Laminin 5 deficiency 5	LAMA5	0-1	Respiratory disorders, ptosis, ophthalmoparesis, proximal muscle weakness	-	+/+	-	Proximal muscle weakness	-	Significant
Laminin 2 deficiency	LAMB2	0-1	Respiratory disorders, ptosis, ophthalmoparesis, proximal muscle weakness	-	+/+	-	Proximal muscle weakness	-	Significant
Postsynaptic									

Agrin (neuronal)	AGRN	Early infant	Ptosis, muscular weakness	-	+/-	-	Light proximal muscle weakness	-	No effect
Primary AChR deficiency	CHRNA, CHRNB, CHRND, CHRNE	Variable	Ptosis, ophthalmoparesis	-	+/+	-	Proximal muscle weakness in some	-	Partial
Slow channel syndrome	CHRNA, CHRNB, CHRND, CHRNE	0-20	Ptosis, muscular weakness	-	+/+	+	Pronounced weakness in early onset, mild weakness at late onset, axial weakness, scoliosis	Progressive respiratory weakness	No effect or deterioration
Fast channel syndrome	CHRNA, CHRNB, CHRND, CHRNE	0-1	Ptosis, ophthalmoparesis, respiratory crises	**-**	**+/+**	**-**	Generalized muscular weakness	**+**	There is an effect, which decreases with time
Slow conduct syndrome	CHRNE	1	Bilateral ptosis, difficulties sucking, weak crying	-	+/+	+	Generalized load-induced weakness	Rarely	Significant
DOK7	DOK7	2 , possible later onset	Difficulty in walking and running, myopathic gait	-	+/-	+	Weakness with limb-limb distribution, myopathic gait, axial weakness and scoliosis	Progressive respiratory	Lack of effect, deterioration

								weakness	
LRP4	LRP4	0-1	Breathing and swallowing disorders	-	+/-	+	Proximal and axial muscle weakness	+	Weak effect
MuSK	MuSK	1-3	Ptosis and easy muscle fatigue	-	+/-	+	Proximal muscle weakness	+	Weak effect
Plectin deficiency	PLEC1								
Rapsyn	RAPSN	0-1 possible later onset at later age	Hypotension, muscle weakness, aphtosis, respiratory crisis, congenital arthrogryposis At the late onset - a mild weakness	+	+/-	+	Generalized load-induced weakness	Yes, on the background of infections	Significant
Myasthenia on the sodium channel	SCN4A	0-1	Delayed motor development, respiratory weakness	+	-/-	+	Generalized load-induced weakness	+	No effect

In Bulgaria patients of Roma origin have been diagnosed with AR congenital myasthenic syndrome. A 1267dELG mutation in the ε -subunit of the acetylcholine receptor was detected.

The clinical phenotype consists of: immediate post-natal onset, ptosis and external ophthalmoplegia, pathological bulbar and proximal muscular fatigue with 24-hour dynamics and intensified by physical effort. Myasthenic symptomatology is most severely manifested in the first years after birth.

With ageing, stabilization occurs in the condition of the patient, and in later age some of the symptoms (bulbar and proximal muscle fatigue) fade and disappear. External ophthalmoplegia is the most persistent symptom of this disease.

Repetitive stimulation shows a decremental response at low frequencies.

Symptoms are partly influenced by anticholinesterase therapy.

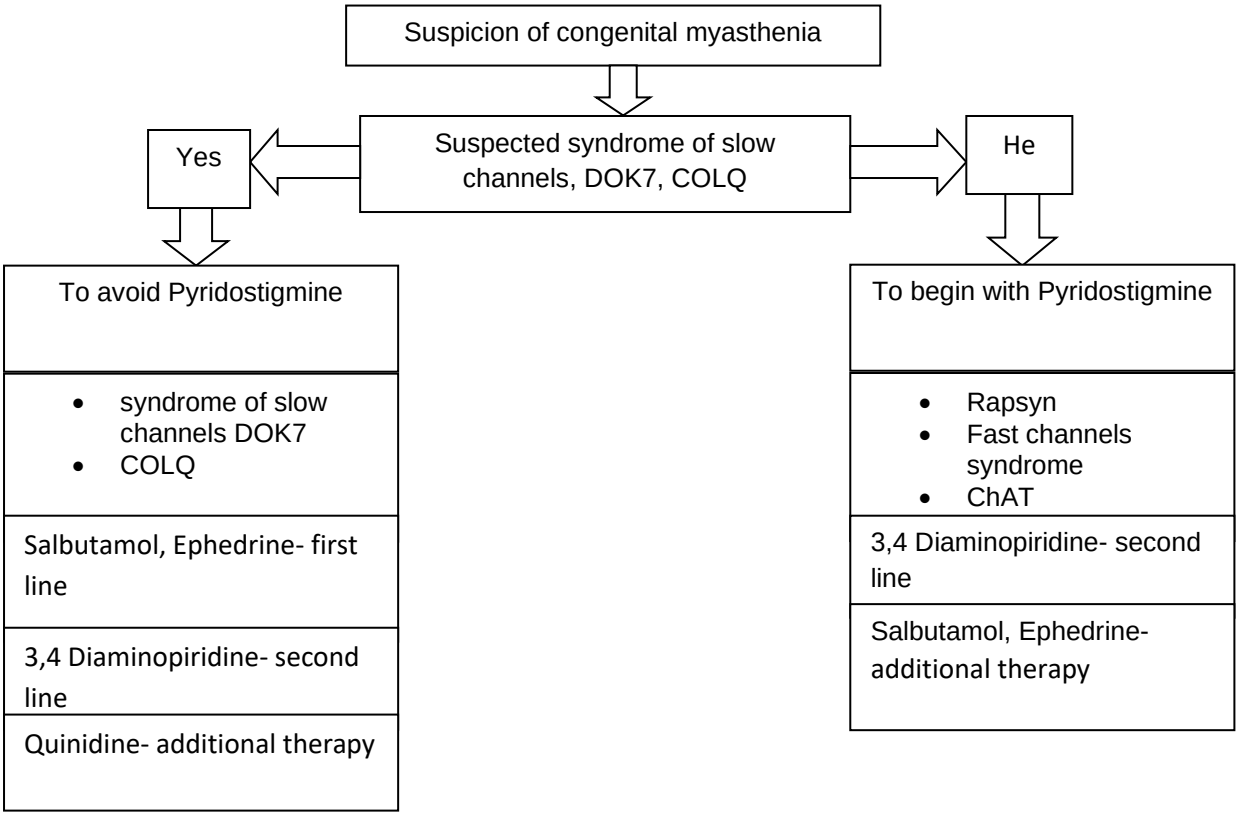


Figure 6. Algorithm for the treatment of the most common forms of congenital myasthenic syndromes

D. Diseases of the peripheral nerves

1. Hereditary sensory and motor polyneuropathies

They are subdivided into hereditary motor and sensory (HMCN), hereditary motor (HMN), hereditary sensory (HSN), and hereditary sensory and autonomic (HSAN) neuropathies. HMCN is characterized by progressive distal muscular weakness and atrophy, primarily affecting the legs and especially the peroneal muscles. In addition to muscle weakness, there may be less pronounced loss of sensation, and tendon reflexes are missing or weakened. Often, there is a high bow on the feet (pes cavus). The phenotype of HMCN consists of motor and sensory neuropathy in the absence of another systemic disorder and without established acquired reason.

The current classification (Table 7) of non-syndromic HMCN retains the primary subdivision according to the speed on transmission (ST) through the peripheral nerve of demyelinating (De) Charcot-Marie-Tooth (CMT 1) with low ST (≤ 38 m / s by n medianus) and axonal (Ac) CMT 2 with normal or close to normal ST (> 38 m / s by n. medianus). There is also a third large group of SMT with intermediate ST (Me). In view

of the mode of inheritance, autosomal-dominant, autosomal-recessive and X-linked forms are observed. Further subdivision of CMT 1, CMT 2 and CMT with intermediate ST is based on the established genetic defect. In the class of demyelinating type III, the X-linked dominant CMT-connexinopathy and hereditary neuropathy, prone to paralysis when pressing (HNPPP) are distinguished. Also, in this group are severe demyelinating neuropathies with early onset - Dejerine-Sottas syndrome and congenital hypomyelinization (CH).

The progress of molecular-genetic research calls for the creation of a new genetic defect classification presented in Table 8.

Table 8. Forms of HMCN

Type IMSN	**Gene**	**Chromosome**
CMT1A	PMP22	17p11
CMT1B	P0 or MPZ	1q22
CMT1C	LITAF/SIMPLE	16p13.1-12.3
CMT1D	EGR2	10q21
CMT1F	NF-L (NF-68)	8p21
HNPP	PMP22	17p11
NABP/HNA	?	17q25
CMTX1	Cx32	Xq13
CMTX2	?	Xp22.2
CMTX3	?	Xq26
DI-CMTA	?	10q24.1-q25.1
DI-CMTB	DNM2	19p13.2-p12
DI-CMTC	YARS	1p34-P35
DI-CMTD and others	PMP22, P0/MPZ, Cx32	
CMT2A1	KIF1Bb	1p36.2
CMT2A2	MFN2	1p36.2
CMT2B	RAB7	3q13-q22
CMT2B1	LMNA	1q21
CMT2B2	?	19q13.3
CMT2C	TRPV4 gene	12q24.13
CMT2D	GARS	7p15
CMT2E	NF-L (NF68)	8p21
CMT2F	HSPB1	7q11-q21
CMT2G	?	12q12.q13.3
CMT2H	?/ GDAP1	8q21.3

CMT2I	P0/MPZ	1q22
CMT2J	P0/MPZ	1q22
CMT2K	GDAP1	8q21
CMT2L	HSPB8	12q24
CMT2M	DNM2	19p13
CMT2N	AARS	16q22
CMT2O	DYNC1H1	14q32
CMT2P	LRSAM1	9q33
DSS/HMSN3/CMT3	PMP22, EGR2, P0/MPZ, PRX	
CHN	PMP22, EGR2, P0/MPZ	
CMT4A	GDAP1	8q13-21.1
CMT4B1	MTMR2	11q23
CMT4B2	SBF2	11p15
CMT4C	SH3/TPR domain protein with unknown function	5q32
CMT4D (Lom)	N-myc downstream-regulated gene 1 (NDRG1)	8q24.3
CMT4E	EGR2	10q21
CMT4F	PRX	19q13.1-q13.3
CMT4-Russe (4G)	HK1	10q22
CMT4H HMN VII	Frabin (FGD4) ?	12p11.21-q13.11 2q14
HSN IA	SPTLC1	9q22.1-q22.3
HSNII	HSN2	12p13
HSANIII	IKBKAP	9q31
HSAN IV/CIPA	NTRK1, TrkA	1q21-q22
HMSN-P	?	3q13.1
HMSN-R	?	10q23.2
Giant axonal neuropathy	Gigaxonin	16q21.4

Table 9. Genetic classification and clinical features of HMCN

Gene	**Type of inheritance**	**Type neuropathy**			**Other phenotype features**	**OMIM**	**Other names**
		Ак	**Де**	**Ме**			
Most common genes							

GDAP1	AR	●			Vocal cord paresis	GDAP1-linked hereditary motor and sensory neuropathy	CMT2K
	AR	●	●	●			CMT4A CMT2H CMT2K CMTRIA
	AD, AR	●				OMIM 607831	
GJB1	X-linked	●			Women are in some cases equally severely affected as men	CMT neuropathy X type 1	CMTX1
HINT1	AR	●			Neuromyotonia	OMIM 601314	
MFN2	AD, AR	●			Optical atrophy	CMT neuropathy type 2A	CMT2A2 CMT2I/2J
MPZ	AD	●	●	●		OMIM 118200	CMT1B CMT2I/J DI-CMTD
PMP22	AD		●			OMIM 601097	CMT1A CMT1E
SH3TC2	AR	●				CMT neuropathy type 4C	CMT4C
Other genes							
AARS	AD	●				OMIM 601065	CMT2N
ABHD12	AR		●		Deafness, cataracts, pigment retinitis	OMIM 613599	PHARC
AIFM1	X-linked	●			Deafness, cognitive deficit	OMIM 300169	CMTX4

ARHGEF10	AD		●			OMIM 608136	
ATP1A1	AD	●					
ATP7A	X-linked	●			Distal sections of lower limbs	ATP7A-linked disorders of the copper transport, OMIM 300011	
BAG3	AD	●			Myofibrillary myopathy, cardiomyopathy	OMIM 603883	
BSCL2	AD	●			Distal sections of lower limbs, spastic paraparesis	BSCL2-linked neurological diseases / sepsinopathies	dHMN5A
CNTNAP1	AR	●	●		Arthrogryposis, leukodystrophy	OMIM 602346	
COA7	AR	●				Higuchi et al [2018]	
DCTN1	AD				Distal sections of lower limbs	OMIM 601143	dHMN7B
DCTN2	AD	●			Vocal cords paresis[4]	OMIM 607376	
DGAT2	AD	●				OMIM 606983	
DHTKD1	AD	●				OMIM 614984	CMT2Q
DNAJB2	AR	●			Distal motor neuropathy	Frasquet et al. [2016], Lupo et al. [2016]	DSMA5
DNMT1	AD	●			Deafness, dementia	DNMT1-linked dementia, deafness and	DMNT1

						sensory neuropathy	
DNM2	AD			●		DNM2-linked intermediary CMT neuropathy	CMT2M DI-CMTB
DRP2	X-linked			●	Autism	OMIM 300052	
DYNC1H1	AD	●			SMA	OMIM 600112	CMT2O
EGR2	AD		●			OMIM 129010	CMT1D
	AR		●				CMT4E
FGD4	AR		●			CMT neuropathy type 4H	CMT4H
FIG4	AR		●			CMT neuropathy type 4J	CMT4J
GARS	AD	●			Beginning in the hands	GARS-linked axonal neuropathy	CMT2D dHMN5A
GNB4	AD			●		OMIM 610863	DI-CMTF
HARS	AD	●	●			OMIM 142810	CMT2W
HSPB1	AD	●				OMIM 602195	CMT2F dHMN2B
HSPB3	AD					OMIM 604624	dHMN2C
HSPB8	AD	●			Later age onset	OMIM 608014	CMT2L dHMN2A
IGHMBP2	AP	●				OMIM 600502	CMT2S DSMA1
INF2	AD			●	Glomerulosclerosis	OMIM 610982	
KIF1B	AD	●				OMIM 605995	CMT2A1
KIF5A	AD	●			Spasticity	OMIM 602821	
LITAF	AD		●			OMIM 603795	CMT1C
LMNA	AR	●				OMIM 150330	CMT2B1
	AD						

LRSAM 1	AR	●				OMIM 610933	CMT2G CMT2P
MARS	AD	●				OMIM 156560	CMT2U
MCM3AP	AR	●	●		Infant age onset	OMIM 603294	
MED25	AR	●				OMIM 610197	CMT2B2
MME	AR AD	●				OMIM 120520	CMT2T
MORC2	AD	●				OMIM 616661	CMT2Z
MPV17	AR	●			Nephropathy	OMIM 137960	
MPZ	AD	●	●	●		OMIM 118200	CMT1B CMT2I/J DI-CMTD
MTMR2	AR		●		Vocal cords paresis	OMIM 603557	CMT4B1
NAGLU	AD	●				OMIM 609701	CMT2V
NDRG1	AR		●			OMIM 605262	CMT4D
NEFH	AD	●				OMIM 162230	
NEFL	AD, AR	●	●			CMT neuropathy type 2E/1F	CMT1F/2E
PDK3	X-linked	●				OMIM 300906	CMTX6
PLEKHG5	AR			●	Predominant distal involvement	OMIM 611101	DSMA4
PRPS1	X-linked				Retinopathy, deafness	CMT neuropathy X type 5	CMTX5
PRX	AR	●				OMIM 605725	CMT4F
PTRH2	AR				Impaired hearing	OMIM 608625	
RAB7A	AD	●			Expressed sensory disorder	OMIM 602298	CMT2B
SBF1	AR	●				OMIM 603560	CMT4B3

SBF2	AR		●			OMIM 607697	CMT4B2
SCO2	AR	●			Motor neuropathy		
SETX	AD				Distal parts of the limbs	OMIM 608465	FALS
SIGMAR 1	AR	●			Motor neuropathy	OMIM 601978	
SGPL1	AR	●			Recurrent polyneuropathies	OMIM 603729	
SPG11	AR	●			Spasticity, cognitive decline	OMIM 610844	CMT2X ALS5
SPTLC1	AD	●				OMIM 605712	HSAN1A
TRIM2	AR	●			Paresis of the vocal cords	OMIM 614141	CMT2R
TRPV4	AD	●			Paresis of the vocal cords, skeletal dysplasias	TRPV4-linked diseases	CMT2C
VCP	AD	●			Myopathy with inclusion bodies, dementia	Myopathy with inclusion bodies with Paget's disease of bone and / or fronto-temporal dementia	CMT2Y
WARS	AD	●			Motor neuropathy	OMIM 191050	dHMN9
YARS	AD			●		OMIM 603623	DI-CMTC
Unknown	X-linked		●		Rapid progression, severe	OMIM 302802	CMTX3

					weakness in the hands		

Dejerine-Sottas syndrome is less often perceived as separate CMT form, as molecular genetic studies have shown that it can be caused by a heterozygous and homozygous mutations in PMP22 and MPZ genes, heterozygous mutations in EGR2 gene and homozygous mutations in PRX and GDAP1 genes (the Inherited Peripheral Neuropathies Mutation Database). The same is valid for the congenital hypomyelinization syndrome (CHS).

Epidemiology. Charcot-Marie-Tooth's disease is the most common monogenic hereditary disease of the nervous system, affecting nearly 1-4 / 10,000 individuals. Worldwide, it is believed that the most dominant Type 1 CMT are prevalent. In Bulgaria, CMT prevalence ranges from 1 / 10,000 individuals in the total population to 3.5 / 10,000 individuals among Roma ethnicity with prevailing recessive forms.

Etiology. To date, more than 80 genes have been identified, various mutations in which lead to one or another form of HMCN. The most common mutation, which accounts for about 70% of all cases of HMCN1, is the duplication of the PMP22 gene in 17th chromosome. The second most frequent mutations are the conexine-based mutation of 32nd gene located on the X chromosome. Various mutations in the MPZ gene lead to a broad clinical spectrum of HMCN.

In Bulgaria, three new autosomal-recessive hereditary neuropathies specific to the Roma ethnicity are described: Clinical and genotyped three types of autosomal recessive hereditary neuropathies: HMCN type Roma, HMCN type Ruse and Congenital cataract, facial dysmorphism, neuropathy syndrome. For the first time, in Bulgarian and American families, the AD HMCN with intermediate ST - DM SMT C was described, with mutations in the YARS gene.

Pathogenesis. There is a wide variety of pathogenetic mechanisms leading to the development of HMCN, behind each of which there is a certain genetic defect. For example, the duplication of the PMP22 gene changes the gene dosage, increasing the amount of the protein product, thereby interfering with the interaction between axons and Schwann cells. Mutations in the MPZ gene cause disorder in the formation of compact multilamellar myelin. EGR2 is an important transcription factor, and the genetic defects in this gene affect the regulation of Schwann cells proliferation. Mutations in the NEFL gene lead to accumulation of neurofilamental proteins in the

cellular bodies and disrupt axonal transport, axonal regeneration and axonal life. Genotype-phenotype correlations reveal the complex pathogenesis of these diseases with a lighter or heavier, demyelinating or axonal phenotype, depending on the type of mutation. Some mutations, such as the 1.5 Mb deletion involving the PMP22 gene, lead to a specific clinical picture of hereditary neuropathy prone to palsy (HNPP). Mutations in the same gene can lead to a different phenotype - e.g. SHMT 1A and DCC at PMMP22 mutations, SMT1 and SMT2 in mutations in the MPZ and NEFL genes. The same phenotype - e.g. DSS may be the result of mutations in different genes.

Clinical picture

The demyelinating HMCN (type 1) is the most common hereditary peripheral neuropathy and is a genetically heterogeneous disease. Inheritance is most often AD and, more rarely, X-dominant or AR. Molecular genetic studies have found that these genetic forms represent separate nosological units caused by mutations in different genes. In general, HMCN type 1 is characterized by a slowed rate of motor and sensor fibers transmittance and signs of demyelination of the neural biopsy.

Autosomal-dominant demyelinating HMCN type 1 (AD HMCN 1)

The clinical picture is identical to the classic phenotype. The onset of complaints is usually between 5 and 25 years of age. The main features are distal weakness, starting with the peroneal muscles and possibly other distal muscles of the legs and arms. Tendon reflexes are usually absent or weakened. Often, at the beginning of the disease there is a deformity of pes cavus type. Occasionally palpable, subcutaneous, thickened peripheral nerves. Sensory disorders are discrete and may remain unrecognized in routine neurological examination. The severity is relatively mild and the patients remain ambulatory even in later age.

X- dominant demyelinating HMCH- connoxinopathy (HMCN X) is a motor-sensory neuropathy that affects men more often.

Molecular genetic studies detect mutations in the connexin gene 32, found on the Xq13.1 chromosome. Connexin 32 is a gap-junction membrane protein, localized in the Ranvier nodes and in the Schmidt-Lanterman peripheral nerve incisures. It is thought to be structurally and functionally involved in the intracellular and the cellular transport of ions, nutrients and other small molecules around and through the compact myelin to the innermost myelin layers, possibly indirectly feeding the axon. This could

explain the combination of myelin damage and axonal degeneration observed in Cx32 mutations.

The clinical phenotype of men with HMCN X is usually more severe than in patients with HMCN 1A duplication, but the age of onset is later - usually in the second decade. The manifestations in the affected women range from missing to mild, or moderately severe, due to the presence of one normal allele. Clinical symptoms may vary considerably, even in individual families. The SP study shows variations from almost normal to moderately low, most often in the 30-40 m / s range. In men, they are generally lower and the electrophysiological trend is for HMCN 1 or HMCN 2. In HMCN X, age-related penetrance has been established.

Hereditary neuropathy prone to paralysis when compressing (HNPP) is an AD disease.

It is characterized by a variety of localized recurrent peripheral nerve paresis or sensory disturbances without pain, often provoked by mild trauma or compression. Usually the onset is acute, but there can also be chronic progression. In most cases, patients recover for days or weeks, but recurrences often take place, and weakness may persist for a long time. Some have signs of symmetrical distal neuropathy without acute paresis. In 50-80% of patients, Achilles areflexia was detected and in 15-30% - diffuse hyporeflexia. A small number (10-15%) of patients with mutations may be clinically asymptomatic, indicating incomplete penetrance.

Autosomal recessive demyelinating HMCN are rare, pathological and genetically heterogeneous diseases, usually more severe than AD HMCN.

In each of the forms of HMCN 4, there are characteristic ethnic, pathoanatomic and clinical features. The clinical phenotype is, as a rule, heavier than that of AD HMCN 1, bone-skeletal deformities are often found. 7 genes and 1 locus associated with HMCN type 4 were identified. HMCN 4A and 4C forms were observed in patients with different ethnicity. The HMCN 4E and 4F forms indicate severe recessive neuropathies with mutations in the EGR2 and PRX genes and a phenotype as in CX and DSS.

HMCN 4D – HMCN type Lom is described for the first time in Bulgarian Roma ethnicity and was later identified in a number of European countries.

The disease is mapped on the 8q24 chromosome. It was found to be due to the mutation C → T transition in exon 7 and nucleotide position 564 in the NDRG1 gene. It is suggested that the NDRG1 protein plays a role in limiting growth and in cell differentiation, probably as a signal protein between the cytoplasm and the nucleus.

Particularly high expression of the protein in Schwann cells, probably playing signaling functions for the survival of the axon.

Demyelinating neuropathy with poorly formed bulbs, which in the later stages degenerates, is pathoanatomically established. Non-compact myelin, pleomorphic material in the Schwann cell cytoplasm, as well as intra-axonal inclusions, are noticed ultrastructurally.

The onset is usually in the first decade with progressive distal weakness in the lower limbs. In the second decade, hands are also affected. There are also sensory disturbances and deformation of the feet. A characteristic feature is the senso-neural deafness that usually manifests in the third decade. The motor velocities are greatly reduced (average 12.5 m / s of n. medianus and SANPs are not obtained. Abnormal are auditory evoked potentials.

Congenital cataract, facial dysmorphism, neuropathy (CCFDN) syndrome is a complex inherited multisystem disorder, affecting both the developing eye, the peripheral and central nervous system and the gonads. The disease was first discovered among Bulgarian Roma. Later, it was also found among Roma ethnicity around the world.

It is caused by a mutation in the CTDP1 gene located on the 18q chromosome. The CTDP1 gene encodes acid phosphatase of RNA polymerase II, the transcription enzyme. Therefore, the disease refers to the group of "transcription syndromes" and is the first "pure" defect of polymerase II-mediated transcription in man.

The main clinical signs are bilateral congenital cataract and microcornea, facial dysmorphism and short stature, mental retardation, peripheral neuropathy and hypogonadism. The most characteristic manifestation of the disease is neuropathy, which is predominantly motor and hypomyelinizing / demyelinating. CNS involvement is manifested by the presence of cognitive impairment in most patients, symptoms of cortico-spinal pathway involvement and mild chorea, found in about 1/3 of patients. This is confirmed by abnormal neuroimaging and electroencephalographic findings. The presence of spinal cord atrophy also suggests thinning of the spinal cerebral tract. The facial dysmorphism is more pronounced in later childhood and is more demonstrative in men. There are no gender differences in neurological manifestations. Some patients experience mild ataxia unrelated to the proprioceptive sensory disorder. The presence of mild cerebral involvement is supported by electro-histographical examinations and by the presence of quadrangle twitching of the ocular apples during

tracking movements in individual patients. Cerebellar manifestations are not significant and not found in all patients. Light hypogonadism is found in both sexes. Although external secondary gender characteristics appear to be normal, ultrasound examination revealed diminished ovarian and uterine sizes. Almost all women report irregular menstrual cycles, progressing to secondary amenorrhea. The somatotropic hormone values are low and correspond to decreased growth. All patients studied showed reduced bone density in both compact and trabecular bones at age at which peak bone mass was to be achieved.

The axonal HMCN (type 2) are genetically heterogeneous and are inherited most often in the AD path. In some families with Cx32 mutations, some patients have the HMCN 2 phenotype, but there is no male-to-male transmission. Cases of MPZ mutations and HMCN 2 phenotype have also been reported.

Clinically resembles HMCN1 and is characterized by a typical syndrome of peroneal muscular atrophy. The onset of the disease is later, the CNR types are relatively more preserved, and weakness and atrophy, especially in the distal parts of the lower limbs, are more pronounced. Extensions of the feet and fingers, as well as the small muscles of the feet, are usually affected earlier and heavier than the muscles of the lower legs. However, these differences are insufficient to make a convincing differentiation in the individual patient. In some forms of HMCN1, there are associated signs.

*HMCN 4 type Ruse (*HMCNR*)* was described in 2000 and 2001 in Bulgarian Roma and later - in Roma in the Czech Republic, Spain, in and France. It is due to a mutation in the gene, responsible for hexokinase 1. Loss of large myelinized fibers, pronounced regenerative activity, and evidence of hypomyelinization were found pathoanatomically.

The onset of the disease (with distal muscular weakness in the legs) is between 8 and 16 years of age, and in upper limbs - between 10 and 43 years, at 22 years average. The disease progresses to severe generalized weakness in lower extremities and severe distal upper limbs up to the 4th-5th decade. Significant sensory disorders are observed for all modalities and pronounced deformations of the feet.

Tests. Electrophysiologically characterized by normal or slightly reduced motor and sensory SC, reduced amplitudes of the SMAP and sensory nerve action potential (SNAP). Needle EMG establishes data for denervation.

HMCN 2 is differentiated from distal spinal muscular atrophy (DSMA) by the presence of sensory disorders or changes in SNAP in the ENG study.

Autosomal recessive axonal neuropathy with neuromyotonia is a new nosological disease in the framework of the myotonic syndromes, which should be clinically and genetically differentiated from myotonic dystrophy and channelopathies, causing non-demyelinary forms of myotonia. Recently, mutations in HINT1 have been found to be a major cause of AR axonal neuropathy with neuromyotonia. The most common mutation in the entire cohort is R37P, which is found to be homozygous in 4 Bulgarian non-related patients and 2 sibs, and one family of two affected sibs are double heterozygotes of mutations R37P / H112N. HINT1 mutations were responsible for 11% of autosomal recessive neuropathy and 76% of cases with concomitant neuromyotonia.

HMCN with intermediate speeds of conducting (SC) in the range of 25 - 45 m / s, overlapping with that of SMT 1 and SMT 2. Mixed demyelinating and axonal changes are found pathoanatomically. Mutations in the genes MPZ, Cx32, NEFL and GDAP1 may lead to both HMCN type 1 or 2 and to HMCN with intermediate SC. Three specific AD forms with intermediate SC (DM SMT) are also differentiated: The DM SMTA form has an established locus of locus 10q24; DM SMTB is due to mutations in the DNM2 gene. DM SMTS was first described in 2003 with Bulgarian and American families. Various mutations in the YARS gene have been identified.

The age at onset of the disease is highly variable - from 7 to 59 years, and the SC is in the range of 25 - 50 m / s. Invalidation is usually not severe and patients go alone until late.

Determination of the intermediate type of HMCN is only possible if a larger number of family members are examined, individual patients may exhibit axonal or demyelinating type based on electrophysiological criteria.

Diagnosis of the different HMCN is based on data, obtained from clinical, electrophysiological, neuropathological and genetic studies. They should be differentiated from:

- Acquired, non-genetic causes of peripheral neuropathy: inflammatory, autoimmune neuropathies such as Guillain-Barre Chronic Demyelinating Polyneuritis and Multifocal motor neuropathy; ethylism; vitamin B12 deficiency; thyroid disease; diabetes mellitus, AIDS, vasculitis, leprosy, neurolues, amyloidosis, ocular neoplasms, heavy metal intoxication.

- Other forms of hereditary peripheral neuropathies: hereditary motor neuropathies (HMN, distal spinal muscular atrophy), where clinical and electrophysiological sensory disorders are absent; hereditary sensory and autonomic neuropathies (HSAN); hereditary neuralgic amyotrophy.
- Hereditary diseases in which peripheral neuropathy can be observed as part of the clinical phenotype: metachromatic leukodystrophy, adrenomyelophobia, Pelizaeus-Merzbacher disease, spinocerebellar ataxias with neuropathy.

Treatment and prophylaxis. The therapy of all forms of HMCN is symptomatic for the time being. Nivalin regimen is recommended, vitamins, peripheral vasoactive medicines. Especially important for delaying the development of the disease is the systemic conduction of physical therapy and neurorehabilitation - electrical stimulation of the parietal muscles, Nivalin electrophoresis, massage and healing physics. When developing deformities in the feet, it is recommended to wear orthotics or orthopedic corrections. In childhood, before bone growth is complete, soft tissue operations are performed with elongation of the Achilles tendon, and in adult age bone arthrodeses.

2. Hereditary motor neuropathies (HMN) - clinically and genetically heterogeneous diseases occurring with distal muscular weakness without sensory involvement. Table 9 presents the underlying forms of the disease with the underlying genes.

Table 10. Forms and clinical features of hereditary motor neuropathies

Disease	**Way of inheritance**	**Phenotype**	**Gene**	**Locus**
HMN type I	AD	Onset in adolescence, distal weakness and atrophy	HSPB1 HSPB8 GARS DYNC1H1	-
HMN type II	AD	Later age onset, distal weakness and atrophy	HSPB1 e HSPB8 e BSCL2 HSPB3	-
HMN type III	AR	Slowly progressing	Unknown	11q13

		weakness and atrophy		
HPN type IV	AR	Slow progressive weakness and diaphragm paresis	Unknown	11q13
HMN type V	AD	Affects mainly upper limbs	GARS BSCL2	-
HMN type VI	AR	SMA c respiratory distress Type 1	IGHMBP2	-
HMN type VII	AD	Late onset with vocal cord paresis	DCTN1 is TRPV4	-
X-linked HMN	X-linked	distal weakness and atrophy	ATP7A	-
HMN with pyramidal signs	AD	Pyramidal signs	SETX* BSCL2	- 4q34-q35 7q34-q36
HMN Jerash from Jordan	AR	Pyramidal signs	Unknown	9p21.1-p12
Congenital spinal muscular atrophy	AD	Distal weakness with arthrogryposis	TRPV4	-

3. Hereditary sensory and autonomic neuropathies (HSAN) may be characterized by mild, moderate or severe sensory deficits without muscle weakness or atrophy. Table 10 presents the main forms of the disease and the additional clinical manifestations.

Table 11. Forms of hereditary sensory and autonomic neuropathies

Gene	**Way of inheritance**	**Disease**	**Other manifestations**
ATL1	AD	HCAH1D	
ATL3	AD	HCAH1F	
DNMT1	AD	HCAH1E	Deafness, dementia
DST	AR	HCAH6	

RETREG1	AR	HCAH2B	Hyperlordosis, urinary disorders
ELP1	AR	HCAH3	Episodic hypertension, hyperhydrosis, cyclic vomiting
KIF1A	AR	HCAHC	
NGF	AR	HCAH5	
NTRK1	AR	HCAH4	
PRDM12	AR	HCAH8	
SCN11A	AD	HCAH7	Gastrointestinal dysfunction
SCN9A	AR	HCAH2D	Loss of pain sensation, erythromelalgia
SPTLC1	AD	HCAH1A	Perforating ulcers
SPTLC2	AD	HCAH1C	
WNK1	AR	HCAH2A	

D. The prophylaxis of neuro-muscular diseases involves the following stages

• Clarify the genetic defect responsible for the disease.

• Medical-genetic counseling of the affected family.

• Prenatal diagnosis of pregnancies in affected families.

• Selective screening for certain neuro-muscular diseases in high-risk groups.

E. Targeting national clinical registers for neuromuscular diseases and patient organizations.

From 2016 to the Clinic of Nervous Diseases, the University Hospital for Active Treatment "Alexandrovska" has established an Expert Center for Hereditary Neurological and Metabolic Diseases. Registers have been developed for these diseases. Information on available registers in the country and clinical centers for diagnosis and treatment can be found on the site of the Bulgarian Society of Neuromuscular Diseases www.nmd-bg.com.