

Consensus Statement
for
the Diagnosis and Treatment
of
Lysosomal Storage Diseases with Neurological
Manifestations

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Bulgarian Society of Paediatric Neurology, Psychiatry, and
Developmental Psychology

Today, on the 9th day of June 2026, we, the undersigned specialists have reached a consensus on the diagnosis and treatment of lysosomal storage diseases with neurological manifestations.

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ABBREVIATIONS:

AD — autosomal dominant

AR — autosomal recessive

ASMD — acid sphingomyelinase deficiency

BBB — blood-brain barrier

CK — creatine kinase

ERT — enzyme replacement therapy

FVC — forced vital capacity

GD1 — Gaucher disease type 1

GD2 — Gaucher disease type 2

GD3 — Gaucher disease type 3

GL3 — globotriaosylceramide

Gb3 — globotriaosylceramide

MPS — mucopolysaccharidoses

MRI — magnetic resonance imaging

NCL — neuronal ceroid lipofuscinosis

NPA — Niemann-Pick disease type A

NPB — Niemann-Pick disease type B

NPC — Niemann-Pick disease type C

SRT — substrate reduction therapy

XR — X-linked recessive

6-MWT—6-minute walk test

Introduction

Lysosomal storage diseases involve about 50 rare genetic metabolic diseases engaging various mutations/pathological variants that cause enzyme deficiency and lysosomal dysfunction due to the accumulation of certain substrates in them: lipids, glycoproteins, and mucopolysaccharides. These diseases induce multiple organ involvement and have a progressive course. They are mainly inherited in an autosomal recessive (AR) manner, e.g. Niemann-Pick disease type C, and, in rare cases, in an X-recessive (XR) (Fabry disease and Hunter disease (MPS II)) or an autosomal dominant (AD) manner (neuronal ceroid lipofuscinosis type 4 (NCL4)). Disease incidence is about 1/7,700 births. Disease prevalence is about 1:100,000 but occasionally reaches 1:5,000–1:10,000. The onset is usually in childhood, however infantile, late infantile, pediatric, adolescent, and adult disease forms have also been identified. Clinical syndromes in the presence of neurological manifestations depend on the site of substrate accumulation and most often impair the central nervous system as well as, less commonly, the peripheral nervous system, sometimes—the muscles, while multiple organ involvement (heart, vessels, kidneys, liver, spleen, etc.) is also possible.

These diseases are classified as:

- **Mucopolysaccharidoses**
- **Mucolipidoses and oligosaccharidoses**
- **Pompe disease**
- **Sphingolipidoses** - Gaucher disease, Fabry disease, other sphingolipidoses (GM1 gangliosidosis, Tay-Sachs disease, Sandhoff disease, Krabbe disease, and metachromatic leukodystrophy, Niemann-Pick disease type A, type B, type A/B and type C)
- **Neuronal ceroid lipofuscinoses (NCL 1–15) (*Table 1*)**

Their ICD-10 codes are: E75 Lipid storage disorders — Sphingolipidoses, incl. Gaucher disease and Niemann-Pick disease (E75.2); Gangliosidoses, incl. Tay-Sachs disease (E75.0-E75.1); Leukodystrophies; E76.0 Mucopolysaccharidoses, incl. Hunter disease and Hurler disease; E77 Glycoprotein storage disorders; E77.0–E77.1 Mucolipidoses.

When the CNS is affected, lesions according to the type of the disease are found on brain MRI - rapidly progressive cerebral and cerebellar atrophy due to neuronal death and hypomyelination in neuronal ceroid lipofuscinoses, general cerebral atrophy in mucopolysaccharidosis type III, multiple cerebrovascular lesions in Fabry disease, vessel

dolichoectasia in Pompe and Fabry diseases. X-ray examinations reveal characteristic bone changes depending on the type of accumulation of different substrates in cells, most commonly in mucopolysaccharidoses and mucolipidoses.

Pathogenic treatment with proven therapeutic efficacy is administered to alter the natural course of disease in some types of diseases and in certain enzyme deficiency: enzyme replacement therapy (ERT), substrate-reducing therapy (SRT), chaperones that can bind and help proper configuration or maturation, and transportation of enzymes to the right places. Chaperones are currently used in lysosomal storage diseases such as Gaucher disease and Fabry disease. Attempts for such treatment of Pompe disease are in experimental stage. Stem cell administration has been shown to be effective only in mucopolysaccharidosis type I, in the early stages of the disease. Attempts to employ gene therapy using viral vectors and nanoparticles for gene delivery are also in an experimental stage.

Table 1. Lysosomal Storage Diseases

Disease	Inheritance/gene/locus	Enzyme defect	Lysosomal storage
Mucopolysaccharidoses (MPS): Hurler disease (I), Hunter disease (II), Sanfilippo disease (III), Morquio disease (IV), Maroteaux-Lamy disease (VI), Sly disease (VII), MPS IX	AR/MPS I- <i>IDUA</i> ; MPL II- <i>IDS</i> ; MPL IIIA- <i>SGSH</i> ; MPL IIIB- <i>NAGLU</i> ; MPL IIIC- <i>HGSNAT</i> ; MPL IIID- <i>GNS</i> ; MPL IVA- <i>GALNS</i> ; MPL IVB- <i>GLBI</i> ; MPS VI- <i>ARSB</i> ; MPS VII- <i>GUSB</i> ; MPS IX- <i>HYAL1</i> XR/Xq28 (Hunter disease)	α -L-iduronidase (Hurler disease, Hunter disease), heparan N-sulfatase (Sanfilippo), galactose 6-sulfate sulfatase (Morquio), β -glucuronidase (Sly)	Glycosaminoglycans
Mucolipidoses (sialidoses): - Mucopolipidosis I - Mucopolipidosis II/III - Mucopolipidosis IV - Mannosidosis - Fucosidosis - Galactosialidosis	- AR/ <i>NEU1</i> /6p21.33 - AR/ <i>GNPTAB</i> , <i>GNPTG</i> / - <i>MCOLN1</i> - <i>MAN2B1</i> , <i>MANBA</i> - <i>FUCA1</i> - <i>CTSA</i>	- α -neuraminidase - UDP-N-acetylglucosamine-1-phosphotransferase - Mucopolipin-1 - α - and β -mannosidase	Mucopolysaccharide, sphingolipids, and glycolipids

- Salla disease - Schindler disease Aspartylglucosaminuria	- <i>SLC17A5</i> - <i>NAGA</i> - <i>AGA</i>	- Fucosidase - Cathepsin A - Sialin - α -N-acetylgalactosaminidase - Aspartylglucosaminidase	
Pompe disease	AR/ <i>GAA</i> /17q25	Acid α -glucosidase	Glycogen
Gaucher disease	AR/ <i>GBA</i> /xp1	Acid β -glucocerebrosidase	Glucocerebrosides
Fabry disease	XR/ <i>GLA</i> /X21.33-q22	α -galactosidase A	Globotriaosylceramide (Gb3)
Tay-Sachs disease	AR/ <i>HEXA</i> /15q23-q24; 5q11.2-q13.2.3.	Hexosaminidase A	G _{M2} gangliosides
Late infantile and pediatric G _{M1} gangliosidosis	AR/ <i>GLB1</i> / <u>3p22.3</u>	β -galactosidase 1	G _{M1} gangliosides (glycosphingolipids)
Niemann-Pick disease type A, type B and type A/B ASMD	AR/ <i>NPA</i> /11p15.1	Sphingomyelinase	Sphingomyelin, impaired intracellular cholesterol transport
Niemann-Pick disease type C	AR/ <i>NPC1</i> /18q11; <i>NPC2</i> /14q24.3		Impaired cholesterol intracellular transport of glycosphingolipids, sphingosine and cholesterol
Neuronal ceroid lipofuscinosis (NCL 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14)	AR • <i>CLN1/PPT</i> /1p32 • <i>CLN2/TPP1</i> /11p15.5 • <i>CLN3</i> /16p12.1 • <i>CLN5</i> /13q21.1-q32 • <i>CLN6</i> /15q21-q23 • <i>CLN7/MFSD8</i> /4q28.1-q28.2	• Palmitoyl protein thioesterase (NCL1); • Tripeptidyl peptidase (NCL2)	Ceroid and lipofuscin

	• CLN8/8p23 • CLN9 • CLN10/<i>CTSD</i>/11p15.5 • CLN11/<i>GRN</i> • CLN12/<i>ATP13A2</i> • CLN13/<i>CTSF</i> • CLN14/<i>KCTD7</i> • <i>SGSH</i>		
	AD/CLN4/ <i>DNAJC5</i>		

1. MUCOPOLYSACCHARIDOSES

Mucopolysaccharidoses (MPS) are diseases with mucopolysaccharide storage in lysosomes of various tissues, such as skin, cartilage, cornea, liver, spleen, and vessels due to degrading enzyme deficiency (*Table 2*). They are inherited in an autosomal recessive (AR) pattern and only MPS II (Hunter disease) inheritance pattern is XR.

Table 2. Mucopolysaccharidoses, gene defects, and enzyme deficiency

Disease	Gene defect	Enzyme deficiency
MPS I (Hurler and Scheie syndromes)	<i>IDUA</i>	Alpha-L-iduronidase
MPS II (Hunter syndrome)	<i>IDS</i>	Iduronate 2-sulfatase
MPS IIIA (Sanfilippo syndrome)	<i>SGSH</i>	Heparan N-sulfatase
MPS IIIB (Sanfilippo syndrome)	<i>NAGLU</i>	N-acetylglucosaminidase
MPS IIIC (Sanfilippo syndrome)	<i>HGSNAT</i>	Acetyl-CoA glucosamine N-acetyltransferase
MPS IIID (Sanfilippo syndrome)	<i>GNS</i>	N-acetylglucosamine-6-sulfatase
MPS IVA (Morquio syndrome)	<i>GALNS</i>	N-acetylgalactosamine-6-sulfate sulfatase
MPS IVB (Morquio syndrome)	<i>GLB1</i>	β -galactosidase
MPS VI (Maroteaux-Lamy syndrome)	<i>ARSB</i>	Arylsulfatase B
MPS VII (Sly syndrome)	<i>GUSB</i>	β -glucuronidase
MPS IX	<i>HYAL1</i>	Hyaluronidase

MPS I and MPS II

The most common types of MPS are MPS I (Hurler syndrome or Scheie syndrome depending on the clinical presentation severity, with alpha-L-iduronidase deficiency) and MPS type II (Hunter syndrome, with iduronate-2-sulfatase deficiency).

Clinical presentation: Classical form presentation includes delayed development, short stature, recurrent otitis and respiratory infections, hepatosplenomegaly, macrocephaly, coarse facial features with thick eyebrows, lips, and nose, gingival hyperplasia, and macroglossia. There is progressive development of hearing loss, cardiac valve defects, obstructive pulmonary disease, joint contractures, and intellectual regression. In untreated patients, IQ is < 70 in 61% and borderline (IQ 70–85) in 25% at 2–3 years. Other complications include corneal clouding, carpal tunnel syndrome, hydrocephalus, cervical instability and spinal compression, cardiac arrhythmias, and glaucoma. There are characteristic radiographic findings - dysostosis multiplex, changes in sella turcica, ribs, proximal metacarpal and metatarsal bones, and hip dysplasia. Life expectancy in untreated patients is up to the second or third decade of life. **In mild forms of MPS I and II**, there are mild somatic manifestations, with no CNS involvement and normal intellect.

Diagnosing:

- *quantitative urinary mucopolysaccharide analysis* is the initial screening test in patients with suspected MPS I and II
- *enzyme activity assay in dried blood spots* when increased urinary excretion of mucopolysaccharides is present — decreased enzyme activity confirms the diagnosis. *Genetic testing* is required to prove a mutation/pathological variant.
- *X-ray examination* — dysostosis multiplex supports the diagnosis.

Treatment: *Enzyme replacement therapy (ERT) with laronidase* for MPS I and idursulfase for MPS II delays disease progression, i.e. changes its natural course but does not cure it. These enzymes do not cross the BBB and do not affect neurological symptoms. *Hematopoietic stem cell transplantation has been administered in MPS I* patients less than 2 years old and stabilises neurocognitive functions. There are some positive results in cases of MPS II. Follow-up of patients should be performed by multidisciplinary teams.

MPS III includes 4 subtypes with progressive heparin sulphate storage expressed in CNS neurons, with MPS IIIA being the most common subtype (Table 2). Compared to other MPS, the most common symptoms of MPS III are neuropsychiatric ones with early

manifestation of delayed neuropsychiatric development and mental retardation, progressive spastic quadriparesis, symptomatic epilepsy in 60–70% of cases, insomnia, dementia, behavioural disorders with aggression, anger reactions, destructive behaviour, hyperactivity, and attention deficit. In advanced stages, patients have encephalopathy and reach a chronic vegetative state in adolescence. Diffuse atrophy is found on brain CT and MRI scans. Hepatosplenomegaly, cardiac valvular involvement, dysostosis multiplex, and facial dysmorphism are not severely manifested.

Diagnosis is based on proven elevated urinary excretion of mucopolysaccharides, proven enzyme deficiency, and genetic testing.

Treatment: There is no reliable treatment available for MPS III. ERT is being experimented with, but no crossing of the blood-brain barrier (BBB) and penetration into the CNS has been identified.

MPS type IV (Morquio syndrome) is caused by 2 enzyme deficiencies (Table 2) and is characterised mainly by skeletal dysplasia: short stature, pectus carinatum, forearm deformity, genu valgum, scoliosis, hip dysplasia, atlanto-occipital instability, and dental abnormalities. Non-skeletal manifestations involve corneal clouding, hearing loss, obstructive or restrictive lung diseases, and cardiac dysfunction. Intellect is normal.

Diagnosing: Diagnosis is difficult because the amount of mucopolysaccharides in urine may be normal, especially in adult patients. Enzyme assays and genetic testing are needed to confirm diagnosis. Radiographs identifying dysostosis multiplex support the diagnosis.

Treatment: ERT with *Elosulfase alfa* is administered for MPS IVA but not for MPS IVB. Elosulfase alfa reduces keratan sulfate storage and improves 6-minute walk test (6MWT) results, pulmonary functions are slightly improved as well. Patient follow-up is performed by specialists: geneticist, orthopedist, otorhinolaryngologist, pulmonologist, cardiologist, neurologist, and dentist.

MPS VI is a rare disease (incidence of 0.36 to 1.30 per 100,000 live births). Similar to MPS I and II, dermatan sulphate is accumulated, but unlike the other two, heparan sulphate metabolism is not impaired. Intellect is usually normal. MPS VI clinical manifestations are similar to those in MPS I and II: short stature, facial dysmorphism with coarse features, corneal clouding, broncho-obstructive syndrome, hepatosplenomegaly, cardiac valve abnormalities, inguinal and umbilical hernias, dysostosis multiplex, joint contractures, hip dysplasia, and carpal tunnel syndrome.

Diagnosis: Proven *increased urinary excretion of mucopolysaccharides, low arylsulfatase B enzyme activity in urine, and genetic testing to prove a mutation/pathological variant in the ARSB gene.*

Treatment: ERT with *galsulfase* is administered in MPS V to improve growth, reduce cardiac hypertrophy, and slow progression of cardiac valve changes and joint disorders. Treatment must be initiated as early as possible.

MPS VII is a very rare disease (0.05–0.29 per 100,000 live births). In 40–45% of patients with MPS VII *nonimmune fetal hydrops* is manifested, which is rarely found in other MPS and therefore its presence suggests MPS VII. MPS VII is associated with *mental retardation* (86%), *coarse facial features* (87%), *dysostosis multiplex* (90%), *joint contractures* (84%), *hepatosplenomegaly* (75%), *scoliosis* (69%), *corneal clouding* (63%), *obstructive pulmonary disease* (44%), *cardiac valve disease* (50%), and *cardiomyopathy* (37%). **Diagnosis** of MPS VII is based on evidence of elevated urinary mucopolysaccharide excretion, measurement of β -glucuronidase enzyme activity in blood, and genetic testing. Treatment with ERT with intravenous *vestronidase alfa*, a recombinant form of β -glucuronidase, has a proven effect on motor activity with an improvement of 6MWT result, fine motor skills, and fatigue.

2. MUCOLIPIDOSES AND OLIGOSACCHARIDOSES

Mucolipidoses and oligosaccharidoses (*Table 3*) are relatively rare progressive diseases that resemble MPS because of developmental delay, organomegaly, and dysostosis multiplex.

Table 3. Mucolipidoses and oligosaccharidoses - identified genes and enzyme deficiency

Disease	Gene	Enzyme deficiency
Mucopolipidosis I (Sialidosis)	<i>NEU1</i>	α -neuraminidase
Mucopolipidosis II/III	<i>GNPTAB, GNPTG</i>	UDP-N-acetylglucosamine-1-phosphotransferase
Mucopolipidosis IV	<i>MCOLN1</i>	Mucolipin-1
α -mannosidosis	<i>MAN2B1</i>	α -mannosidase
β -mannosidosis	<i>MANBA</i>	β -mannosidase
Fucosidosis	<i>FUCA1</i>	Fucosidase
Galactosialidosis	<i>CTSA</i>	Cathepsin A

Salla disease	<i>SLC17A5</i>	Sialin
Infantile sialic acid storage disease	<i>SLC17A5</i>	Sialin
Aspartylglucosaminuria	<i>AGA</i>	Aspartylglucosaminidase
Schindler disease	<i>NAGA</i>	α -N-acetylgalactosaminidase

Sialidoses type 1 and type 2 (also known as mucopolidosis I) are caused by a mutation in *NEU1* gene located at 6p21.33, which leads to alpha-neuraminidase and beta-galactosidase deficiency, intracellular storage and high urinary excretion of sialooligosaccharides. More than 40 mutations in *NEU1* have been identified. They are **clinically** manifested by *progressive blindness, characteristic retinal degeneration called cherry-red spot, progressive myoclonic epilepsy, ataxia, hearing loss, and intellectual regression*. **Sialidosis type 1** with later onset and **Sialidosis type 2** — severe, with early-onset (**congenital, infantile and juvenile form**) — characterised by rapidly progressive blindness in case of cherry-red spot retinal degeneration, progressive myoclonic epilepsy, ataxia, hearing loss and intellectual regression have been described.

2.1. POMPE DISEASE

Pompe disease (glycogenosis type II, acid maltase deficiency or acid alpha-glucosidase deficiency (GAA)) (OMIM # 232300) is a rare autosomal recessive metabolic disease with glycogen storage in lysosomes of various organs and systems. It has the most severe clinical presentation of the 12 known glycogenoses. The disease is caused by over 558 mutations (genetic defects) in the GAA gene localised at 17q25 causing varying degrees of deficiency of acid alpha-glucosidase enzyme, resulting in lack of glycogen degradation. It is clinically manifested by a decrease of more than 25% of the average normal enzyme activity of GAA.

Pathogenesis and pathologic morphology. The disease has progressive multiple organ involvement due to glycogen storage in lysosomes of various organs and systems, but the main clinical manifestation of myopathic syndrome is a result of the involvement of muscle cells, liver cells, motor neurons of the anterior horn of the spinal cord, CNS neurons and other structures.

Epidemiology. Pompe disease incidence varies in different populations from 1:40,000 to 1:300,000; the incidence of late-onset form is 1:57,000, and the incidence of infantile-onset

form ranges from 1:33,000 to 1:158,000. In Southern China and Taiwan, incidence reaches 0.5–1% of the total population wherefore mass neonatal screening is conducted.

Clinical presentation. The disease is classified into 2 main clinical forms according to the age of onset and the level of GAA enzyme deficiency: *infantile-onset form with significant enzyme deficiency* (GAA deficiency < 1% in the classical form, GAA deficiency > 2% in the non-classical form) and *late-onset forms* — *paediatric and juvenile* with GAA deficiency between 2% and 6% as well as an *adult form* with GAA deficiency > 40%. In all forms, the progressive *myopathic syndrome* is the main clinical syndrome together with respiratory failure, heart failure with pronounced cardiomyopathy is manifested in infantile forms; hepatic failure is possible, while vascular and cerebrovascular injuries have been rarely observed.

Early-onset (infantile) forms (Table 4). The **infantile (classical) form** has an early onset (average 1.5 months of age) with a clinical presentation of the so-called ‘floppy baby’. The disease progresses with: severe *progressive myopathic syndrome*; rapid development of *hypertrophic cardiomyopathy* with a typical ECG with short P-R intervals and large QRS complexes as well as *heart failure*; frequent lung infections and *respiratory failure* requiring artificial lung ventilation at an average age of 5.9 months; *hepatomegaly and splenomegaly*, macroglossia; lethal outcome at about 6.3 months (up to 7–8 months); complete *absence of alpha-glucosidase enzyme* (< 1%), increased serum creatine kinase (CK). The **infantile (non-classical) form** is milder than the classical one, having a slightly later age of symptom onset (about 5 months of age) and an average survival of 19 months.

Table 4. Clinical manifestations of infantile form of Pompe disease

Organs/systems	Symptoms
Muscular	- Progressive muscle weakness - Marked hypotension, 88% - Inability to hold head up - Failure to master motor skills - Areflexia - Macroglossia
Respiratory	- Progressive respiratory failure, 78% - Frequent respiratory infections

	Death due to cardiac and respiratory failure
Heart	Cardiomyopathy (massive), 88% Left ventricular hypertrophy, 92%
Digestive	Difficulty sucking, swallowing (hypotrophy), 57% Hepatomegaly

Differential diagnosis of infantile forms of Pompe disease includes spinal muscular atrophy, muscular dystrophies, mitochondrial diseases, heart diseases, etc. (*Table 5*).

Table 5. Differential diagnosis of infantile form of Pompe disease

Differential diagnosis	General signs and symptoms
Spinal muscular atrophy type I (Werdnig-Hoffmann disease)	Hypotension, progressive limb-girdle muscle weakness, loss of reflexes, feeding difficulties, elevated creatine kinase (CK)
Congenital muscular dystrophy	Severe hypotension and muscle weakness
Mitochondrial diseases	Hepatomegaly, cardiomyopathy, myopathy, elevated creatine kinase (CK)
Idiopathic hypertrophic cardiomyopathy	Biventricular hypertrophy
Danon disease	Hypertrophic cardiomyopathy, skeletal muscle myopathy, glycogen storage, elevated CK
Myocarditis	Myocardial inflammation leading to heart enlargement
Glycogenosis type III and IV	Hepatomegaly, hypotension, cardiomegaly, muscle weakness, elevated CK
Endocardial fibroelastosis	Shortness of breath, feeding difficulty, cardiomegaly, heart failure
Carnitine deficiency	Cardiomyopathy, muscle weakness

Hypothyroidism	Hypotension, macroglossia
Paroxysmal disorders	Hypotension, hepatomegaly

Late-onset forms of Pompe disease. Paediatric, juvenile, and adult forms begin after 1 year of age. There is a *progressive myopathic syndrome of limb-girdle type with proximal localization*, but cardiomyopathy is rare and is not identified in juvenile and adult forms. The age of onset and severity of myopathy correlate with *the deficiency of GAA enzyme activity, and in paediatric and juvenile forms the available enzyme activity is 2–6% of normal, while in adult forms — from 7 to 40%.* In paediatric and juvenile forms, this progressive myopathic syndrome has a *proximal localisation*, more pronounced in *the lower extremities*, with difficulty to inability to stand up from squatting position, difficulty climbing stairs, and a “swaying” gait. *Axial muscle weakness* makes it difficult to rise from a lying position, *scoliosis and winged scapula* are formed, *spinal rigidity, myalgias, and asymptomatic increase in creatine kinase (CK) (20%)* are possible. *Respiratory muscle* involvement initially causes nocturnal hypoventilation with a morning headache, fatigue, and, subsequently, respiratory failure (Table 6). There are cardiac arrhythmias and conduction disorders with no hypertrophic cardiomyopathy typical of the infantile form.

Table 6. Symptoms and syndromes in late-onset form of Pompe disease

Organs/systems	Symptoms
Musculoskeletal	- Progressive proximal muscle weakness (legs and axial muscles) - Low back pain - Difficulty climbing stairs - Scapulae alatae - Gowers’ sign - Delayed motor development (children) - Lordosis, scoliosis, spinal rigidity

Lungs	• Progressive respiratory failure • Orthopnea • Sleep apnoea • Dyspnoea, intolerance to physical exertion • Frequent respiratory infections, mild cough
Digestive	• Feeding difficulty, reduced body weight • Difficulty chewing, swallowing • Hepatomegaly
Other	• Morning headache • Daytime somnolence

Pompe disease in childhood and adolescence has a broad clinical spectrum, in which the phenotype is partially explained by the genotype. *Differential diagnosis* includes other muscular dystrophies, congenital or metabolic myopathies, motor neuron diseases or impaired neuromuscular transmission (*Table 7*). Algorithms for disease diagnosis have been adopted. In case of unclear myopathic syndrome or only persistently elevated CK levels with EMG evidence of myogenic impairment, especially if CK is above 2,000 U, the diagnosis is likely to be late-onset Pompe disease with GAA deficiency, progressive Becker muscular dystrophy or limb-girdle muscular dystrophy, myotonic dystrophy type 2, mitochondrial myopathies, endocrine myopathies, and polymyositis.

Table 7. Differential diagnosis of Pompe disease with onset in childhood and adolescence — types of diseases

Type of impairment	Disease
Dystrophies	• Limb-girdle • Dystrophinopathies (Duchenne/Becker muscular dystrophy) • Myofibrillar myopathy • Myotonic dystrophy type 2 • Scapuloperoneal syndromes • Danon disease

	• X-linked myopathy with excessive autophagy • Facioscapular muscular dystrophy
Inflammatory myopathies	• Polymyositis • Inclusion body myositis
Congenital myopathies	• Nemaline myopathy • Central core myopathy • Centronuclear myopathy • Hyaline body myopathy • Other congenital myopathies
Other metabolic myopathies	• McArdle disease (late-onset) • Mitochondrial myopathies • Myopathies associated with lipid diseases
Motor neuron diseases	• Spinal muscular atrophy type I–III • Kennedy disease • Amyotrophic lateral sclerosis
Impaired neuromuscular transmission	• Myasthenia gravis • Congenital myasthenic syndromes • Lambert-Eaton syndrome

Diagnosis of Pompe disease is based on: 1) clinical presentation of *progressive myopathic syndrome* with or without *cardiomyopathy* (mandatory only in the infantile form) and *respiratory disorders* assessed by forced vital capacity (FVC) measurement, oximetry, capnography, and polysomnography; 2) EMG findings of myogenic impairment; 3) elevated creatine kinase (CK) values, but 5% of patients have normal values; 4) disease *confirmation is done by evidence of alpha-glucosidase deficiency in dried blood spot on a filter paper* and is *genetically verified* (muscle biopsy is optional).

Tests required to confirm diagnosis:

- X-ray examination: to prove cardiomegaly in the infantile form;
- ECG: findings suggestive of conduction disorders;
- Echocardiography: evidence of hypertrophic cardiomyopathy in infantile form;

- EMG: findings suggestive of *myogenic impairment*, but *denervation potentials may also be seen* as in spinal muscular atrophies due to glycogen deposition in motor neurons of anterior horns;
- FVC, oximetry and capnography, polysomnography;
- blood tests: elevated CK, AST, ALT, LDH;
- **quantitative determination of GAA enzyme activity in dried blood spots (DBS)** is the main informative rapid diagnostic method with evidence of quantitative reduction: < 1% in the classical infantile form; < 2% in the non-classical infantile form; 2–6% in paediatric and juvenile forms; 7–40% in adult forms;
- **genetic verification of the GAA gene.**

Screening programs by testing GAA enzyme activity in dried blood spots (DBS), including in Bulgaria, are used to diagnose the disease in patients with unclear myopathic syndromes and asymptomatic persistently elevated CK levels, or with normal CK levels and disproportionate axial and respiratory muscle weakness in comparison with limb muscle involvement. *Next-generation sequencing (NGS) genetic testing is needed* in case of suspected Pompe disease.

Clarification through *screening tests* is necessary when considering Pompe disease in unexplained cases of a myopathic syndrome with proximal muscle weakness, disproportionate axial and respiratory muscle weakness in comparison with limb muscle involvement or unclear elevated CK levels as well as possibly normal CK levels.

Pompe disease treatment is complex: *medication enzyme replacement therapy and symptomatic treatment*—cardiac treatment; treatment of lung inflammation and respiratory care (nasal CPAP—in obstructive sleep apnea, BiPAP—in nocturnal hypoventilation, O₂—at night or persistent administration in hypoxia); moderate rehabilitation; general social and psychological care; genetic counselling, prenatal diagnosis, and screening. There are no reliable findings on the therapeutic effect of substrate-reducing therapies, viral vector-based gene therapy, and hematopoietic stem cell transplantation.

ERT treatment with alglucosidase alfa and avalglucosidase alfa:

- ***alglucosidase alfa*** is approved for all disease forms in Europe and the United States. ERT treatment with alglucosidase alfa is started at an early stage before irreversible tissue changes occur. The treatment is administered by intravenous infusion every two weeks at the recommended dose of 20 mg/kg body weight. Results have been published, incl. from double-blind, placebo-controlled

multicenter trials on ERT with aglucosidase alfa in various forms of Pompe disease, which demonstrate the effect of stabilising and delaying the development of main syndromes - cardiomyopathy in infantile forms and myopathy and respiratory disorders in infantile and late-onset forms - and delaying the need for respiratory care, especially in early treatment. In *infantile forms*, the best results are achieved when treatment is initiated before 6 months of age. In *the late-onset form* of Pompe disease, treatment is found to improve striated muscle functions and cardiac function as well as to stabilise and increase tidal volumes showing a better effect in early therapy. Treatment alters the natural course of the disease because in untreated patients the risk of loss of independent gait increases by 13% each year and the risk of respiratory failure requiring ventilation increases by 8% each year, whereas in treated patients motor activity is improved or stabilised, there is a functional improvement in daily activities, respiratory stabilisation is achieved, the need for breathing device is reduced, and the risk of lethal outcome is reduced by 59%. The long-term effect of alpha glucosidase has been analysed in a large study of 438 patients followed up for an average of 45.7 months and described in 22 publications (pertaining to 19 clinical studies). Survival, motor and respiratory functions (mortality, % FVC, and 6MWT) have been evaluated in treated and untreated patients. Patients treated with aglucosidase alfa were found to have 5-fold lower mortality; % FVC increased rapidly by 1.4% after 2 months of treatment and demonstrated a slow regression back to baseline over 3 years. In untreated patients, a decrease in % FVC by 2.3% after 12 months and by 6.2% after 48 months was measured. In the 6MWT, the most significant improvement was observed over the first 20 months — a 50-meter increase over baseline and stabilisation over time. Untreated patients did not show a 6MWT improvement. The study concluded that aglucosidase alfa improved survival, ability for self-care, and respiratory functions. The conclusions from follow up of paediatric patients were similar.

avalglucosidase alfa has been approved for all forms in Europe and USA. Avalglucosidase alfa is a recombinant human acid α -glucosidase (rhGAA) that provides an exogenous source of GAA. The recommended dose of avalglucosidase alfa is 20 mg/kg of body weight administered once every 2 weeks. For patients with infantile-onset Pompe disease (IOPD) who experience lack of improvement or insufficient response in cardiac, respiratory, and/or

motor function while receiving 20 mg/kg, a dose increase to 40 mg/kg every other week should be considered in the absence of safety concerns (e.g., severe hypersensitivity, anaphylactic reactions, or risk of fluid overload). Avalglucosidase alfa is a modification of alglucosidase alfa in which approximately 7 hexamannose structures each containing 2 terminal mannose-6-phosphate (bis-M6P) moieties are conjugated to oxidised sialic acid residues on alglucosidase alfa. Avalglucosidase alfa has a 15-fold increase in mannose-6-phosphate (M6P) moieties compared with alglucosidase alfa. Binding to M6P receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalised and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity to degrade glycogen. The higher affinity to M6P receptors results in clinically significant advantages in terms of disease severity compared with alglucosidase alfa, when used as a comparator in COMET - the pivotal Phase 3 study. A clinical study in patients with LOPD (EFC14028/COMET), comparing the efficacy and safety of *avalglucosidase alfa* and alglucosidase alfa, which included an open-label, long-term, follow-up phase of up to 5 years for all patients, showed statistical non-inferiority in terms of change in FVC % predicted in the upright position from baseline and numerical improvement in the 6-minute walk test (6MWT) with *avalglucosidase alfa* compared with alglucosidase alfa. The study demonstrated maintenance of effect during the long-term treatment with *avalglucosidase alfa* 20 mg/kg every other week for up to 6 years in patients with LOPD in terms of FVC% predicted and 6MWT. A clinical trial in patients with IOPD (ACT14132/mini-COMET), was a multi-stage, Phase 2, open-label, multicentre, multinational, repeated ascending dose cohort of *avalglucosidase alfa* in paediatric IOPD patients (1-12 years of age), who demonstrated either clinical decline or sub-optimal clinical response while on treatment with alglucosidase alfa. In paediatric IOPD patients (<18 years of age) treated with *avalglucosidase alfa* at 40 mg/kg every other week who have demonstrated either clinical decline (cohort 2) or sub-optimal clinical response (cohort 3) while on treatment with alglucosidase alfa, the mean percentage (SD) change in urinary hexose tetrasaccharides from baseline was -40.97% (16.72) and -37.48% (17.16), respectively, after 6 months. In patients previously deteriorating treated with *avalglucosidase alfa* at 20 mg/kg every other week, mean (SD) percentage change was 0.34% (42.09). In IOPD patients with IOPD previously deteriorating with alglucosidase alfa, the efficacy on specific parameters of worsening, including motor function, cardiac left ventricular mass, and eyelid position measurements, was sustained up to 2 years.

Consensus has been reached on enzyme replacement therapy based on patient follow-up for more than 10 years, incl. in Bulgaria, according to which ERT is to be administered when there are clinical manifestations (Table 8).

Recommendations for the treatment of Pompe disease include:

1. In the infantile form of Pompe disease: ERT at a dose of 20 mg/kg every 14 days.

- Before ERT, CRIM (cross-reactive immune material) status should be determined and ITI (immune tolerance induction) should be included in the treatment plan. The treatment should be carried out at a centre with experience in the treatment of the infantile form of Pompe disease.
- After diagnosis and before starting ERT a respiration assessment is to be performed and, if necessary, non-invasive support should be provided.
- Chewing difficulties should be assessed by using methods of adequate nutrition and height.

2. In the late-onset form of Pompe disease:

- ERT at a dose of 20 mg/kg every 14 days should be administered to mobile patients, who are not mechanically ventilated in wakefulness and do not use breathing assistance during sleep.

- ERT at a dose of 20 mg/kg every 14 days should be administered to disabled patients with breathing assistance in wakefulness and sleep, with an improvement of functional status shown by testing; ERT interruption should be considered in case of lack of efficacy.

3. Patients with the late-onset form of Pompe disease should be monitored for respiratory complications by regular functional assessment of respiration.

- **Patients with the late-onset form of Pompe disease with poor response to ERT for months/years should be evaluated for presence of high sustained antibody titres (HSAT) and, if present, treatment attempts should be made to reduce them.**

- **Patients with the late-onset form of Pompe disease should be on a diet with adequate protein and energy intake.**

- **Vitamin D levels should be evaluated and vitamin D supplements should be added to reach a level of at least 75 nmol/L.**

- **Patients with late-onset form of Pompe disease should receive recommendation on individually tailored exercises.**

- **Periodic assessment of QoL and/or motor functions should be performed.**

- **If assessment shows lack of efficacy**, ERT should be discontinued and patient should be switched to supportive and palliative care.

Table 8. Recommendations for ERT according to the stage and severity of the late-onset form of Pompe disease

Condition	Recommendation
Asymptomatic patients without objective disorders (carriers)	• Should be followed-up every year, incl. by neurological status evaluation, manual muscle testing, functional assessment of respiration, ECG, assessment of activities of daily living • ERT should be initiated at onset of clinical manifestations
Asymptomatic patients with objective disorders	ERT should be initiated immediately at onset of clinical manifestations: abnormalities in manual muscle testing or changes in respiratory function—decreased FVC in supine position
Symptomatic patients	ERT should be initiated immediately
Patients with severe symptoms	For patients confined to wheelchairs and on a 24-hour mechanical pulmonary ventilation: • ERT should be administered for 1 year and the patient's response to treatment should be assessed • Treatment should be continued if clinical progression is slowed and patient's condition stabilises
Duration of ERT	This is a long-term treatment. Its effect is assessed after at least 1 year.
Follow-up	Symptomatic patients: Patients should be followed-up every 6 months, incl. by neurological status evaluation, manual muscle testing, functional assessment of respiration, ECG, assessment of activities of daily living Asymptomatic carriers of Pompe disease: should be followed-up every year, incl. by neurological

	status evaluation, manual muscle testing, functional assessment of respiration, ECG, assessment of activities of daily living
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The need for treatment of presymptomatic patients with Pompe disease should be discussed as it is known that the disease begins at an earlier age in males than in females and with the same mutations within a family, sometimes including a long period with no clinical symptoms. For this reason, follow-up of asymptomatic carriers with mutations of Pompe disease by assessment of muscle strength, ECG, EchoCG, and FVC every 12 months is recommended.

The follow-up of asymptomatic carriers of mutations of Pompe disease includes: *manual muscle testing; 6MWT; time tests* (for walking 10 m, climbing 4 steps, getting up from a lying position, and standing up from a chair); ventilatory capacities: *FVC* in sitting and supine position, maximum inspiratory/expiratory pressure; *ECG, EchoCG*

3. SPHINGOLIPID METABOLISM DISEASES

3.1. GAUCHER DISEASE

The most common lysosomal storage disease with a prevalence of 1/40,000, however in the Ashkenazi Jewish population its prevalence is 1/1,000. Gaucher disease is caused by a *GBA* mutation and an enzyme deficiency of glucocerebrosidase. Glucosylceramide is stored in macrophage lysosomes, reticuloendothelial system, liver, spleen, and bone marrow.

3 clinical types are described: *Gaucher disease type 1 (GD1)*, which does not involve the nervous system, is characterised by a specific *GBA* mutation in the p.N370S allele in homozygous or double-heterozygous carriers; *Gaucher disease type 2 (GD2) and 3 (GD3)*, the so-called “neuronopathic forms”, with neurological involvement: in homozygotes of the p.L444P allele and these mutations are common in the Ashkenazi Jewish population.

Gaucher disease type 1 (GD1) or “non-neuronopathic” type is the most common one (in 90% of cases) and presents with hepatosplenomegaly, thrombocytopenia, anaemia, leukopenia, bone pain, and short stature. “Bone crises” (33%), osteopenia (42%), femoral infiltrates (40%), avascular necrosis (25%), pathological fractures (15%), and lytic lesions (8%) have been described. The age of disease onset varies from childhood to 70 years.

Gaucher disease type 2 (GD2) in homo- or heterozygous carriers of alleles L444P is characterised by severe neuropsychiatric retardation, cachexia, spastic quadriparesis, epileptic seizures, horizontal gaze palsy, opisthotonus, and fetal hydrops. Survival duration is up to 2 years.

Gaucher disease type 3 (GD3) presents with hepatosplenomegaly, anaemia, respiratory disorders, and manifestations of the CNS including epileptic seizures, discoordination syndrome, oculomotor apraxia, esotropia, hearing loss, and cognitive decline. Patients survive for more than 10 years and into adulthood.

Diagnosing Gaucher disease: 1. Demonstrating the reduced glucocerebrosidase activity in leukocytes. 2. Demonstrating 2 pathogenic variants of the *GBA* gene. 3. In some cases, a bone marrow biopsy with evidence of characteristic “Gaucher cells”.

Treatment for Gaucher disease type 1 and type 3 includes *ERT or substrate reduction therapy (SRT)*.

3 medicinal products for **ERT** have been authorised by EMA in Europe and by FDA in the United States: *imiglucerase* and *velaglucerase alfa* have been proven for long-term treatment in patients with a confirmed diagnosis of non-neuronopathic (type 1) or chronic neuronopathic (type 3) form with clinically pronounced non-neuropathic manifestations of the disease, and *taliglucerase alfa* is for adult patients. **Substrate reduction therapy (SRT)** for adult patients is based on 2 authorised medicinal products: *miglustat* for Gaucher disease type 1 in mild to moderate form and *eliglustat* for long-term treatment of adult patients with Gaucher disease type 1 (GD1). Oral SRT inhibits the enzyme glucosylceramide synthase, the first step in glycosphingolipid synthesis. ERT with *imiglucerase or velaglucerase alfa* should be initiated immediately after diagnosis, and taliglucerase alfa, miglustat, and eliglustat should be used for the patients aged over 18 years. ERT and SRT for Gaucher disease type 1 and type 3 increase platelet and haemoglobin concentrations, decrease liver and spleen volume, and reduce Gaucher disease biomarkers such as chitotriosidase, but do not have effect on neurological impairment and syndromes of Gaucher disease type 3.

There is no ERT for Gaucher disease type 2. Patients receive symptomatic treatment, incl. respiratory care as needed.

Follow-up: MRI is used to monitor abdominal structures, the degree of bone marrow infiltration, osteosclerosis and osteonecrosis; bone marrow mineral density is measured.

3.2. FABRY DISEASE

Fabry disease (OMIM #301500) is a rare X-linked progressive genetic disease with multiple organ involvement caused by a pathological variant (mutation) in the GLA gene in Xq21.3-q22 resulting in α -galactosidase (GalA) enzyme deficiency and glycosphingolipid globotriaosylceramide (Gb3) storage in the lysosomes of different types of cells of the skin, eyes, kidneys, central and peripheral nervous system. Accumulation of Gb3 in the vessels secondarily increases endothelial proliferation and leads to vascular occlusions, ischemia, and infarction associated with the most common involvement of the vertebral and basilar arteries, and small cerebellar vessels. Prothrombotic mechanisms with low levels of thrombomodulin (TM) and elevated levels of plasminogen activator inhibitor (PAI) linked to nitric oxide and non-nitric oxide-dependent endothelial proliferation and dilation are also involved in the development of stroke in young patients with Fabry disease. Gb3 accumulation in autonomic ganglia and spinal ganglia is associated with neuropathic manifestations and autonomic dysfunction. Accumulation in the renal glomerular, tubular, and interstitial cells cause chronic-progressive kidney disease with early proteinuria and polyuria as well as subsequent chronic renal failure. Involvement of cardiac muscle cells, vascular smooth muscle cells, valvular fibrocytes together with conduction system involvement cause cardiomyopathies, arrhythmias, conduction disorders, and heart failure. Due to the multiple organ glycosphingolipid accumulations, life-threatening clinical disorders develop as a result of renal, cardiac or cerebrovascular and peripheral nerve complications. Enzyme replacement therapy (ERT) with α -GalA has been shown to reduce Gb3 accumulation in many different cell types, including endothelial and parenchymal cells, and alters the natural course of the disease. Migalastat is the first chaperone therapy authorised by EMA and in Canada. Experimental viral vector-based gene therapies and mRNA therapy using lipid nanoparticles are being studied.

Epidemiology. Disease prevalence is 1:40,000–60,000 men. Fabry disease prevalence in Caucasian males is about 1:17,000 to 1:117,000. Classical Fabry disease mutations are found in 1:22,000 to 1:40,000 males while atypical presentations exist in 1:1,000 to 1:3,000 males and 1:6,000 to 1:40,000 females.

Clinical characteristics. The main clinical manifestations of Fabry disease — nephrological, cardiological, neurological, ophthalmological, and dermatological — are related to the lysosomal sphingolipid storage of globotriaosylceramide (Gb3) mainly in different cell types: vascular endothelial cells, podocytes, tubular cells, glomerular endothelial

cells, cardiomyocytes, and neurons. The age of onset of Fabry disease can range: from childhood to the 5th decade of life or later, but the early clinical manifestations are *neurological, gastrointestinal, and cutaneous*. Some mutations determine the classical clinical manifestations with an early onset and a severe course, while others lead to a milder course with a later onset. According to its clinical course, Fabry disease is divided into ***classical and non-classical phenotypes***. The classical form of Fabry disease has a severe phenotype and α -galactosidase enzyme activity is practically absent or severely reduced (less than 5%) while in late-onset and “non-classical” phenotype single organs are affected and α -galactosidase enzyme activity is increased.

The classical form of Fabry disease is described in males due to its X-linked inheritance. Symptoms develop from early childhood: *neuropathic pain, gastrointestinal manifestations with disturbed gastrointestinal motility, and hypohidrosis* caused by disorders of the peripheral nervous system and autonomic nervous system. Presentations include *angiokeratomas and corneal opacities*. *The disease progresses with multiple organ damage: of the kidneys (albuminuria, decreased glomerular filtration rate (GFR), and renal failure), of the heart (left ventricular hypertrophy, heart failure, arrhythmias, and conduction disorders), hearing impairments with hearing loss, vestibular symptoms, and CNS disorders with strokes* at a relatively young age. In the advanced stages of the disease, renal failure, ischemic strokes, cardiomyopathy, arrhythmias, and conduction disorders are immediate causes of death. **Fabry disease in females**: Current data conclusively demonstrate that women with pathogenic variants in the GLA gene are not merely asymptomatic carriers but may develop clinically significant and progressive disease.

Pathophysiological features and clinical variability

The clinical presentation in women is highly variable and is determined primarily by the process of random X-chromosome inactivation (lyonization). As a result, a mosaic population of cells is formed – some with an active normal GLA allele and some with a mutated allele, which leads to a varying degree of α galactosidase A (α Gal A) deficiency in tissues.

This mosaicism gives rise to a broad spectrum of manifestations – from an asymptomatic course to severe organ complications comparable to those in men. In rare cases, homozygous women are described, in whom the phenotype is similar to the classical severe form in men.

Clinical manifestations

Women with Fabry disease may present with either a classical or a late-onset (atypical) form, the latter being more common. The clinical picture is often milder, fragmented or organ-specific, which leads to significant diagnostic delay.

A broad spectrum of organ manifestations is observed, including:

- Neurological symptoms: neuropathic pain in 43–77% of patients
- Cerebrovascular complications: in 4–25%
- Cardiac involvement: left ventricular hypertrophy in 18–26%
- Renal involvement: proteinuria in 35–39%

The frequency and severity of organ damage underscore the need for active follow-up of women with a confirmed GLA variant.

The non-classical form of the disease has a milder course and patients develop single symptoms, most often **left ventricular hypertrophy and/or cardiomyopathy, the so-called cardiac form**, with only a discrete proteinuria.

The classic form of Fabry disease in males begins with neurological symptoms affecting the peripheral nervous system (painful polyneuropathy with small fibre involvement and autonomic dysfunction) and, subsequently, the central nervous system (ischemic and hemorrhagic strokes, epilepsy as well as cognitive and behavioural disorders). This form of the disease is characterised by neuropathic pain and acroparesthesias (burning pain, attacks of tingling in hands or feet) as well as autonomic dysfunction with hypohidrosis. Later, due to Gb3 accumulation in the cerebral vessels, transient ischemic attacks (TIA) and stroke develop in 12% of males relatively early—at an average age of 28.8 years. Hearing impairments, corneal opacities, cornea verticillata, changes in mood such as anxiety and depression are possible.

Neuropathies in Fabry disease are initial clinical manifestations due to the thin myelinated A δ and unmyelinated C fibre damage of peripheral and autonomic nerves. This is caused by the accumulation of Gb3 and its deacylated form in neurons, dysfunction of intracellular proteins and ion channels, occlusion of the vasa nervorum of the peripheral nerves by Gb3, impaired vasoconstriction and vasodilation, increased platelet aggregation, increased peripheral nerve excitability and central sensitisation, and functional disruption of the axons of the affected neurons.

Neuropathic pain is the main initial symptom observed in 70% of children and adolescents with Fabry disease, with a mean age of onset of 9 years in boys and 16 years in girls. The pain in the area of palms and soles is chronic, burning, nagging and is combined

with dysesthesias and paresthesias. Attacks of burning pain radiating from the distal to the proximal parts of the limbs and provoked by fever, exercise or stress are also possible. Distal thermal hypesthesia is identified. With disease progression and loss of small nerve fibres the painful sensations decrease, but in some cases intensify. Neuropathic pain in childhood and adolescence is misdiagnosed as rheumatoid pain, growing pain in bones, psychogenic pain, etc.

Clinical manifestations of autonomic dysfunction include mainly hypohidrosis, pupillary abnormalities, hyposalivation, hypolacrimation, altered gastrointestinal motility with stomach pain, diarrhoea, and nausea.

Compression of n. medianus in the carpal tunnel caused by Gb3 accumulation is found in about 25% of patients.

In the early stages of Fabry disease, electromyography (EMG) shows no abnormalities as the thick myelinated nerve fibres A α and A β associated with motor functions and deep sensation are not affected. However, the disease progression leads to their involvement resulting in a reduction of the compound motor action potential and, less frequently, of the conduction velocity.

The most common *otoneurological manifestations* are progressive sensorineural hearing loss mainly at high frequencies, sudden hearing loss, tinnitus, and dizziness, which increase with age.

Ophthalmological manifestations of the disease include cornea verticillata, subcapsular cataract as well as tortuosity of conjunctival and retinal blood vessels.

Central nervous system (CNS) involvement. It is comprised of *transient ischemic attacks (TIA) and ischemic or hemorrhagic cerebral infarctions*. Patients with Fabry disease have a 12-fold higher risk of ischemic stroke (IS) compared to the general population and mainly vertebrobasilar arterial system is involved. Fabry disease is one of the causes of ischemic stroke (IS) at a young age and was found in 4.9% of males and 2.4% of females in a screening study of 721 young patients with IS aged 18–55 years. The mean age of the patients with Fabry disease in this study at which their first IS occurred was 39 years for males and 45.7 years for females. IS develop as a result of vascular autonomic dysfunction and impaired vascular autoregulation, hypercoagulability due to increased vascular adhesion molecules and decreased thrombomodulin, a proliferation of smooth muscle cells due to accumulation of lyso-Gb3 in the media, thromboembolism due to cardiac arrhythmias, and arterial

hypertension. Ischemic or hemorrhagic cerebral infarctions precede renal or cardiac involvement in 6.9% of males and 4.3% of females with Fabry disease.

Cognitive disorders with more severely impaired attention and executive functioning have also been found in patients with Fabry disease. In 60% of those affected, there are depressive symptoms that may be provoked by a reaction to the chronic multisystem disease.

Magnetic resonance imaging (MRI) of the brain in Fabry disease reveals cerebral white matter lesions, mainly in the posterior periventricular areas and centrum semiovale, cerebral infarctions, incl. thalamic infarction, and vertebrobasilar dolichoectasia. The number of cerebral white matter lesions increases with age and may precede neurological symptoms. In female carriers, the MRI changes may be identical to those in males.

Differential diagnosis of Fabry disease **involving the CNS and PNS** includes: vasculitis and collagenosis (SLE, Behçet disease, Sjögren syndrome, rheumatoid arthritis, antiphospholipid syndrome), hereditary thrombophilia, CADASIL, multiple sclerosis, Raynaud syndrome, fibromyalgia, chronic fatigue syndrome, chronic inflammatory polyneuropathy, diabetic polyneuropathy, uremic polyneuropathy, hereditary motor and sensory neuropathies, erythromelalgia, and dermatomyositis.

Gastrointestinal symptoms with abdominal pain and diarrhoea and **angiokeratomas** (clusters of purple, punctate lesions) are early manifestations of the disease beginning about 5–10 years of age.

Renal function progressively deteriorates due to GL3 accumulation in the kidneys, with the mean age of clinically evident nephropathy being about 27 years. Untreated patients develop end-stage renal disease at a mean age of about 47 years (between 21 and 56 years).

Cardiac involvement includes left ventricular hypertrophy, arrhythmias, myocardial fibrosis, syncope as well as exercise intolerance. Left ventricular hypertrophy develops between the ages of 40 and 50. Before the introduction of enzyme replacement therapy, the disease was fatal at an age of about 45.5 years as a result of renal failure.

An obstructive type of lung disease also develops.

Fabry disease is diagnosed based on clinical, biochemical, genetic, and pathological criteria. Clinical criteria such as nephropathy, hypertrophic cardiomyopathy, and stroke are nonspecific and require a broad differential diagnosis, therefore a combination of clinical symptoms and additional biochemical and genetic tests, in some cases histopathological, are used to prove the diagnosis. Cornea verticillata and biopsy evidence of angiokeratomas are more specific but are of diagnostic importance in combination with other clinical criteria.

Clinical criteria for diagnosing Fabry disease:

Major criteria: Family history of Fabry disease; angiokeratoma; kidney disease (renal failure or isolated proteinuria); corneal opacities; acroparesthesias in the palms and soles of the feet; hypertrophic cardiomyopathy or diastolic filling abnormalities; early TIA or ischemic stroke (IS). In women, clinical suspicion is often based on organ-specific or atypical presentation, and the presence of one or more of the following criteria warrants referral for diagnosis:

- Family history of Fabry disease, including male relatives with a severe course
- Unexplained left ventricular hypertrophy, often as an isolated manifestation or at a later age
- Early cerebrovascular event (stroke/TIA), including in the absence of classical risk factors
- Proteinuria or chronic kidney damage of unclear etiology
- Neuropathic pain (acroparesthesias), which may be less pronounced or intermittent

Minor criteria: chronic gastrointestinal disorder; hypohidrosis; heat intolerance; lymphedema; hearing impairment; tinnitus and postural hypotension; cardiac criteria (minor): increased left atrial size, AV block conduction abnormalities, short PR interval in the absence of Wolf-Parkinson-White syndrome, ventricular and atrial tachyarrhythmia, left bundle branch block; moderate mitral or aortic insufficiency in the absence of other known valvular abnormalities; unexplained MRI changes in the cerebral white matter; vertigo; monocular blindness (optic neuropathy); joint pain (arthralgia/arthritis). In women these manifestations are often mild, nonspecific or fragmented, which contributes to the diagnostic delay:

- Hypohidrosis/anhidrosis (often underestimated)
- Gastrointestinal symptoms with a chronic course
- Sensorineural hearing loss or tinnitus
- Angiokeratomas, which may be limited and difficult to recognize
- Generally reduced quality of life and multisystem but nonspecific complaints

A characteristic feature in women is that the disease may run a monosystemic course (e.g. only cardiac or only renal involvement), as well as with later onset, which requires a high index of suspicion even in the absence of a classical picture.

Adults fulfilling one major and one minor or three minor criteria should be further examined.

Fabry disease should be considered *in children under 16 years of age* fulfilling one major or three minor criteria.

Biochemical criteria:

- **Decreased enzyme activity of α -galactosidase A (α -GalA)** in leukocytes or dried blood spots is **the gold standard for diagnosing Fabry disease in males, as it is reduced below 5% or absent.** In women, the enzyme activity of α Gal A shows wide variability – from markedly reduced to completely normal. This is due to the random X-chromosome inactivation (lyonization), leading to mosaic expression of the mutant and the normal GLA allele in the different tissues.

As a result, the values of enzyme activity:

- do not reliably correlate with clinical severity,
- may be normal even in the presence of advanced organ involvement,
- have limited sensitivity as a screening method in women.

Owing to these features, measurement of α Gal A activity should not be used as a standalone diagnostic criterion in women, but has a supporting role in combination with clinical, biochemical and genetic data.

- **Biomarkers in urine and plasma:** elevated **globotriaosylceramide (Gb3) and sphingosine globotriaosylceramide (Lyso-Gb3).** Elevated Gb3 in plasma and urine is indicative of initial diagnosis and long-term follow-up, as well as of the effect of treatment. Gb3 is elevated 200–400 times in males with classical Fabry disease. In women with a pathogenic variant in the GLA gene (heterozygous carriers), the values of these biomarkers show considerable variability, due to the random inactivation of the X-chromosome and the consequent mosaic expression of the enzyme deficiency in the different tissues.

In this population:

- LysoGb3 may be elevated, normal or only minimally elevated, with elevated values supporting the presence of active disease and often correlating with organ involvement;
- Normal values of LysoGb3 are common, including in symptomatic patients and in the presence of organ damage;
- Gb3 (in plasma/urine) has lower diagnostic sensitivity in women and may remain within normal limits or be slightly elevated, without a clear correlation with clinical severity.

Therefore:

- Normal values of Gb3 and/or LysoGb3 do not exclude the diagnosis of Fabry disease in women, especially in late-onset or organ-specific forms;
- **Molecular genetic testing of the *GLA* gene** is required for females suspected of having Fabry disease, in family screening, and for genetic counselling. The known mutations are reported in databases with well-proven mutations/pathological variants (<http://www.galafoldamenabilitytable.com/hcp/>). Variants of uncertain significance (VUS) are not accepted for diagnostic purposes, and a biopsy is performed to prove the diagnosis when appropriate clinical manifestations exist. In the presence of a variant of uncertain clinical significance (VUS) in the *GLA* gene, the diagnosis of Fabry disease may be accepted in the presence of corresponding clinical symptoms, including organ or subclinical (suborgan) involvement. In these cases mandatory histological confirmation by renal biopsy is not required, especially in the absence of renal involvement. The diagnostic decision should be based on an integrated assessment of the clinical manifestations, the family history and the supporting biochemical markers, with the genetic finding serving as the principal element in the algorithm.

Genetic testing for Fabry disease as part of panel screening is recommended for patients with hypertrophic cardiomyopathy, but in the event of Fabry disease with hypertrophic cardiomyopathy, other causes should be ruled out as well (other mutations are possible).

- **Anatomical pathology criteria:** The pathological diagnosis of Fabry disease is based on demonstrating the characteristic accumulation of glycosphingolipids, mainly globotriaosylceramide (Gb-3), in various tissues, including kidneys, heart, skin and other organs. This can be established by immunohistochemical methods, as well as by electron microscopy.

Electron microscopy (EM) is a highly specific method for the morphological confirmation of the disease, visualizing the typical lysosomal deposits in the form of lamellar, concentric structures – the so-called zebra bodies or myelin-like inclusions. They are localized in podocytes, endothelial, mesangial and tubular cells in the kidney, as well as in cardiomyocytes and other cell types.

However, the role of biopsy should be considered in the context of the contemporary diagnostic approach, as complementary rather than mandatory.

In men with Fabry disease, the presence of a pathogenic or likely pathogenic variant in the GLA gene, in combination with significantly reduced α -galactosidase A activity and a characteristic clinical presentation, is sufficient to establish the diagnosis, without the need for histological confirmation.

In these cases, tissue biopsy is not mandatory and should not be used routinely.

The role of biopsy in men is selective and is limited to situations of diagnostic uncertainty, including in the presence of a variant of uncertain clinical significance (VUS) without typical symptoms, a discrepancy between clinical, biochemical and genetic data, as well as in atypical or organ-specific presentation. Biopsy may also be useful when differential diagnosis is needed or to assess the degree and character of organ damage, especially in renal involvement.

Therefore, despite its high diagnostic specificity, tissue biopsy does not constitute a mandatory element of the diagnostic algorithm in men, but should be applied at clinical discretion in selected cases.

In women, owing to the mosaic character of the disease determined by X-inactivation, the morphological findings may be heterogeneous, focal or in some cases absent in the examined material, despite the presence of clinically significant organ involvement. In this regard

- a negative electron microscopy result does not exclude the diagnosis of Fabry disease;
- the absence of characteristic histological findings does not rule out the disease in the presence of genetic and clinical data.

In view of this, in women with a confirmed pathogenic variant or VUS in the GLA gene and corresponding organ or subclinical symptoms, biopsy is not necessary to establish the diagnosis, especially in the absence of renal involvement.

In contemporary practice, the diagnosis of Fabry disease is based predominantly on clinico-genetic correlation, with biopsy retaining its place mainly in:

- diagnostic uncertainty
- need for differential diagnosis
- assessment of the degree and character of organ involvement

Therefore, biopsy should not be routinely included as a mandatory diagnostic criterion, but should be used selectively and at clinical discretion.

For a definite diagnosis, it is assumed that patients should have 3 points according to the following criteria (Table 9):

Table 9. Diagnostic criteria

Criteria	Findings identified	Points towards diagnosis	Comments
Clinical features	Cornea verticillata or a biopsy-proven angiokeratoma	Presence of either or both: 1 point	Need to exclude other diseases
Alpha-galactosidase in plasma or leukocytes	Below 5%	1 point	Activity may not be reduced in females, but low activity in a male member of the family contributes towards the diagnosis
Elevated plasma or urine biomarkers	Gb3, lyso-Gb3 is preferred	1 point	Diseases other than Fabry disease can elevate biomarkers
Genetic testing	Mutations defined in literature as disease-causing	1 point	Variants of uncertain significance (VUS) are not used to contribute towards the diagnosis
Anatomical pathology findings	Presence of accumulations typical of Fabry disease	2 points for typical target organs (kidneys and heart)	Should be interpreted by a pathologist with expertise in Fabry disease

		1 point for other organs (skin)	
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When screening patients with unclear kidney disease with persistent proteinuria or $\text{eGFR} < 90 \text{ mL/min/1.73 m}^2$ in males under 50 years of age or females regardless of age who have a history of hypohidrosis, cold or heat intolerance, acroparesthesia, family history, proven angiokeratomas, measurements of α -galactosidase enzyme activity in males or *lyso-Gb3* in females are performed along with genetic testing to make a diagnosis.

Differential diagnosis of Fabry disease: *In the event of the CNS and PNS involvement, differential diagnosis* includes: vasculitis and collagenosis (SLE, Behçet disease, Sjögren syndrome, rheumatoid arthritis, antiphospholipid syndrome), hereditary thrombophilia, CADASIL, multiple sclerosis, Raynaud syndrome, fibromyalgia, chronic fatigue syndrome, chronic inflammatory polyneuropathy, diabetic polyneuropathy, uremic polyneuropathy, hereditary motor and sensory neuropathies, erythromelalgia, and dermatomyositis; celiac disease, irritable bowel syndrome, and lactose intolerance; Differential diagnosis in case of cardiac involvement: idiopathic cardiomyopathy, etc. Differential diagnosis in case of renal involvement requires the exclusion of many causes of renal failure.

Follow-up of patients with Fabry disease is performed by multidisciplinary teams by regular monitoring of renal function (urine for proteinuria, sediment, creatinine clearance (24-hour), creatinine, urea, Gb3 level); serum lyso-Gb3 is monitored once per year, cardiac status by using ECG and EchoCG is monitored once a year or more often. In case of CNS involvement, follow-up with CT angiography, magnetic resonance angiography is performed at a 3-year interval or as needed; neuropathy monitoring is conducted. Hearing and vision are monitored once a year. In paediatric patients, follow-up is done annually or more often as needed, including renal function (general examination, creatine clearance), ECG, Echo-CG, ocular status, gastroenterological status, MRI and magnetic resonance angiography as needed.

Treatment. Fabry disease is treated with **ERT** with recombinant *agalsidase alfa* (authorised in Europe, Asia, Australia, and Canada) and *agalsidase beta* (authorised in Europe and the United States) administered intravenously every 14 days, regardless of the mutation type and pegunigalsidase alfa - the first PEGylated α -galactosidase A, designed for better stability, a longer half-life (~80 hours) and a low level of treatment-induced

ADAs compared with the existing ERTs for Fabry disease, with an amino acid sequence similar to the naturally occurring human enzyme, authorized for use by the FDA and EMA. **Chaperone** therapy has also been authorised: oral *migalastat* for patients aged 12 years and older with certain mutation types. Options for substrate-reducing therapy, viral vector-based gene therapy or mRNA delivery by nanoparticles are being studied.

ERT with agalsidase beta, agalsidase alfa and pegunigalsidase alfa is the main maintenance therapy for Fabry disease. It is initiated in all symptomatic male and female patients, regardless of their age, who have a definite diagnosis and treatment criteria, regardless of the mutation type, when other causes of symptoms have been ruled out. Asymptomatic boys with a classic mutation for Fabry disease are recommended to initiate ERT at 8–10 years of age. Asymptomatic girls should be followed-up.

ERT with agalsidase alfa (1 mg/mL concentrate for solution for infusion, 3.5 ml vial) is administered at a dose of 0.2 mg/kg body weight every other week by intravenous infusion over 40 minutes). The safety and efficacy of *agalsidase alfa* at enrolment have been evaluated in 2 randomized, double-blind, placebo-controlled, open-label extension studies in a total of 40 patients diagnosed with Fabry disease based on clinical and biochemical findings.

ERT with *agalsidase beta* is recommended for patients with a confirmed diagnosis of Fabry disease who are adults, children and adolescents aged 8 years and older. The therapy is to be administered every 14 days at a dose of 1 mg/kg by intravenous infusion. The initial infusion rate should not exceed 0.25 mg per minute (15 mg per hour) to minimise the risk of infusion-related adverse reactions. For authorisation purposes, Fabrazyme has been tested in three studies involving a total of 73 adults, incl. in 2 double-blind, placebo-controlled studies and in an open-label extension clinical trial where 58 patients were enrolled.

ERT with *pegunigalsidase alfa* is indicated for long-term enzyme-replacement treatment of adult patients with a confirmed diagnosis of Fabry disease. The efficacy and safety of Pegunigalsidase alfa were evaluated in 142 patients (94 men and 48 women), of whom 112 received Pegunigalsidase alfa 1 mg/kg weekly. The recommended dose of Pegunigalsidase alfa is 1 mg/kg body weight, administered once every two weeks. The treatment may also be administered at a dose of 2 mg/kg body weight, once every four weeks, in patients stable on treatment with ERT. The efficacy and safety of Pegunigalsidase alfa for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease, has been demonstrated in one large-scale controlled study with an active-comparator arm (BALANCE) and the open-label studies in patients previously treated with another ERT

(BRIDGE, BRIGHT), or in patients who had not been on enzyme replacement treatment (at all / until at least 6 months prior). These clinical trials include a sufficiently large number of patients, considering the rarity of the disease FD (112 patients treated with the approved dose of 1 mg/kg, out of a total population of 142 patients) and were accepted by the CHMP / EMA in the approval procedure for Pegunigalsidase alfa

ERT with agalsidase alfa, agalsidase beta and pegunigalsidase alfa had a proven effect in stabilising renal and cardiac function, reducing myocardial hypertrophy, and improving neuropathic in patients. *In summary, those clinical studies revealed evidence of improvement* in patients with Fabry disease *receiving ERT* with agalsidase alfa, agalsidase beta and pegunigalsidase alfa by stabilising nephropathy (effect on proteinuria and glomerular filtration) and cardiomyopathy along with stabilising or reducing left ventricular cardiomyopathy (decreased left ventricular mass index (LVMI), reduced thickness of the left ventricle, and improved PR interval on ECG); improvement of diarrhoea syndrome, spasms, pain, nausea, and vomiting. There is no definite effect of ERT on tachy- or bradyarrhythmia, stroke and TIA, depression, and hearing loss. ERT has been shown to significantly lower the level of globotriaosylceramide (Gb3) in plasma and urine and its accumulation in various kidney cells proven by renal biopsy, incl. lyso-GL3 accumulation, by reducing proteinuria and albuminuria and delaying the progression of glomerular filtration decrease; reduces accumulations in myocardial cells and skin; improves left ventricular myocardial hypertrophy and cardiac conduction as measured by QRS duration; there is also improvement in hypohidrosis, and in most cases in body temperature, pain sensitivity and quality of life due to the smaller frequency of pain crises, decreased need for analgesics and a smaller number of absences from work or school. There are no reliable data suggesting a reduction of MRI lesions in the cerebral white matter, dolichoectasias of cerebral vessels, and cerebral haemorrhages. There were no significant differences reported in the efficacy of agalsidase alfa and agalsidase beta at standard doses: agalsidase alfa (0.2 mg/kg) and agalsidase beta (1.0 mg/kg) based on 5- and 8-year follow-up — the CFDI data revealed the same treatment outcome. A meta-analysis identified stable renal function and cardiac parameters in patients treated with agalsidase beta followed by agalsidase alfa. According to CFDI data from a 10-year follow-up, changes in renal function in males with the classical form of the disease treated with agalsidase beta and agalsidase alfa were not statistically significant. There was no difference between the 2 groups - females and males with the nonclassical phenotype.

Migalastat is a pharmacological chaperone that binds the active site of alpha-galactosidase and stabilises the mutant protein. It is authorised by FDA and EMA and is indicated for long-term treatment of adults and adolescents aged 12 years or older with confirmed Fabry disease diagnosis (α -galactosidase deficiency) and a sensitive mutation. The recommended dose regimen is 123 mg migalastat (1 capsule) once every other day, at the same time of the day. It is administered orally as an alternative therapy for patients with Fabry disease who are not treated with ERT due to antibody formation, side effects or other reasons. *Migalastat* is not intended for concomitant use with ERT. *Migalastat* is not recommended for use in patients with severe renal failure defined as estimated GFR less than 30 mL/min/1.73 m². Migalastat has a better effect on renal function, left ventricular hypertrophy, and diarrhoea syndrome than placebo in patients who have an amenable mutation (<https://www.galafoldamenabilitytable.com/hcp/>). Clinical studies were performed in patients with mild clinical manifestations (eGFR of 89–94 mL/min/1.73 m², LVMI of 94–97 g/m²) and did not include patients with high proteinuria (mean albumin/creatinine ratio of 13–27 and no evidence of nephrotic syndrome), which is a risk factor for adverse cerebrovascular and renal impairment in Fabry disease. Moreover, the studies were short (18–24 months).

Symptomatic treatment: In addition to ERT, patients with Fabry disease receive treatment for complications:

Acroparesthesia is treated with *gabapentin*, *pregabalin*, and *carbamazepine*. Opioid analgesics should be avoided.

Microalbuminuria is treated with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).

Aspirin or *clopidogrel* is administered for *TIA* or *stroke*. Management of major vascular risk factors, such as arterial hypertension and dyslipidemia, is important for the prevention of vascular accidents.

Interdisciplinary care: a neurologist specialised in the field of cerebrovascular disease and Fabry disease; a cardiologist specialised in the field of heart attacks as well as rhythm and conduction disorders; a nephrologist for diagnosis and follow-up of kidney disorders.

3.3. NIEMANN-PICK DISEASE TYPE A, TYPE B AND TYPE A/B with acid sphingomyelinase deficiency (ASMD)

In Niemann-Pick disease type A and type B with acid sphingomyelinase deficiency, sphingomyelin accumulates in the tissues of the spleen, liver, lungs, bone marrow, and, rarely, the brain.

Niemann-Pick disease type A (ASMD type A) is known as a “neuronopathic” or “infantile neurovisceral” form associated with severe course in infancy with hepatomegaly, jaundice, vomiting, diarrhoea, respiratory infections, macular degeneration, neuropsychiatric regression, and survival up to 2–3 years of age. It is found in Ashkenazi Jews and is caused by a founder mutation in *SMPD1*.

Niemann-Pick disease type B (ASMD type B) is known as “non-neuronopathic”. Its progression involves hepatomegaly, frequent lung infections in > 80% of patients, thrombocytopenia in > 50% of patients, dyslipidemia, heart valve damages, osteopenia or osteoporosis in adults.

An intermediate chronic neurovisceral form (type A/B) with acid sphingomyelinase deficiency has also been described, which is characterised by hepatosplenomegaly in childhood, elevated transaminases, fibrosis, and cirrhosis. Development is normal until 5–7 years of age, then neurological syndromes manifest - hearing loss, hypotension, hyporeflexia, ataxia, cognitive impairment, and pareses. Survival duration varies.

Diagnosis is made by evidence of sphingomyelinase deficiency in lymphocytes or cell cultures, genetic testing to detect a mutation/pathological variant in the *SMPD1* gene. Elevated levels of oxysterols in plasma, especially lyso-sphingomyelin, have been detected, and lipid-containing macrophages (“foamy” cells) have been found on bone marrow biopsy.

More than 30 patients with intermediate phenotype of Niemann-Pick type B disease have been diagnosed in Bulgaria. The disease is genetically homogeneous in the Bulgarian population. All diagnosed patients are Roma and have the same mutation - transversion c.1711T>G in *SMPD1* gene, which leads to substitution of conservative tryptophan by glycine at position 391. There is significant variability with respect to the clinical phenotype.

Treatment: *Olipudase alpha* is the first and only indicated as an enzyme replacement therapy for the treatment of manifestations of acid sphingomyelinase deficiency (Niemann-Pick type A, type B and type A/B) with no CNS involvement in paediatric and patients. *Olipudase alpha* is a recombinant human acidic sphingomyelinase that reduces the accumulation of sphingomyelin (SM) in organs in patients with acid sphingomyelinase deficiency (ASMD). The recommended starting dose of *olipudase alfa* in adults is 0.1 mg/kg,

and the recommended maintenance dose is 3 mg/kg every 2 weeks. The recommended starting dose of olipudase alfa in paediatric patients is 0.03 mg/kg, and the recommended maintenance dose is 3 mg/kg every 2 weeks.

The efficacy of olipudase alfa has been evaluated in 3 clinical studies (ASCEND study in adult patients, ASCEND-Peds study in paediatric patients and extension study in adult and paediatric patients).

In the ASCEND study, neurological manifestations were seen at baseline in 9 out of 36 adult patients (25%) consistent with a clinical diagnosis of ASMD type A/B. The remaining 27 patients had a clinical diagnosis consistent with ASMD Type B. Improvements in mean percent change in % predicted DLco, spleen volume, as well as in mean liver volume and platelet count were observed in the olipudase alfa group as compared to the placebo group. In addition, lyso-sphingomyelin, which is substantially elevated in plasma of ASMD patients, declined significantly, reflecting reduction of sphingomyelin content in tissue. The LS mean percentage change from baseline to week 52 (SE) in pre-infusion plasma lyso-sphingomyelin level was 77.7 % (3.9) in the olipudase alfa treatment group compared to 5.0% (4.2) in the placebo group. The liver sphingomyelin content, as assessed by histopathology, decreased by 92.0% (SE: 8.1) from baseline to week 52 in the olipudase alfa treatment group (compared to +10.3% (SE: 7.8) in the placebo group). Sustained improvements in % predicted DLco, spleen and liver volumes, and platelet count, compared to baseline, were observed in adults over the course of the study.

The ASCEND-Peds study enrolled 20 patients aged <18 years. Neurological manifestations were seen at baseline in 8 out of 20 paediatric patients (40%) consistent with a clinical diagnosis of ASMD type A/B. In ASCEND-Peds, treatment with olipudase alfa resulted in improvements in mean percent change in % predicted DLco, spleen and liver volumes, platelet counts, and growth in height (as measured by Height Z-scores) as compared to baseline. In addition, LS mean pre-infusion plasma ceramide and lyso-sphingomyelin levels were reduced by 57% (SE: 5.1) and 87.2% (SE: 1.3), respectively, compared to baseline after 52 weeks of treatment. The effects of olipudase alfa on spleen and liver volumes, platelets and height Z-scores were seen across all paediatric age cohorts included in the study. The most frequently reported adverse drug reactions (ADRs) were headache (31.7%), pyrexia (25%), urticaria (21.7%), nausea (20%), vomiting (16.7%), abdominal pain (15%), myalgia (11.7%), pruritus (10%) and C-reactive protein increased (10%).

3.4. NIEMANN-PICK DISEASE TYPE C

It is pathogenetically induced by impaired lipid and cholesterol intracellular transport due to mutations in the *NPC1* or *NPC2* genes and therefore differs from Niemann-Pick disease A and B, which are sphingomyelinase deficiencies.

Nieman-Pick disease type C is a progressive autosomal recessive disease with mutations in the *NP1* gene, in 18q11-q12 (in 95% of patients) and, rarely, in the *NP2* gene, in 14q24.3 (in 5% of patients), which are homozygous or double heterozygous mutations. These mutations cause a disorder in cholesterol and glycosphingolipid cell transport and lysosomal cholesterol export. The *NPC1* protein is involved in the transport of glycosphingolipids, sphingosine, and cholesterol between the inner and peripheral parts of the cell, while the *NPC2* protein is a soluble glycoprotein located in lysosomes that also binds cholesterol and other sterols. The two proteins function in a common complex and ensure the export of lysosomal cholesterol. In patients with NPC, abnormal lipid transport results in accumulation of GM2 and GM3 gangliosides in the central nervous system as well as of unesterified cholesterol, sphingomyelin, glycosphingolipids, and sphingosine in the spleen, liver and other tissues, and causes programmed cell death (apoptosis). Some structures of the central nervous system are damaged earlier and more severely in patients with NPC, which correlates with the main clinical manifestations. Decreased Purkinje cell count is an early manifestation of the disease associated with locomotor ataxia, dysarthria, and dysphagia. Neurofibrillary degeneration, ectopic dendritogenesis, and meganeuritis formation in the cerebral cortex result in epileptic seizures and cognitive deficit. The pronounced neuronal loss in the rostral interstitial nucleus of the fasciculus longitudinalis medialis, which controls vertical eye movements, causes early vertical palsy.

Epidemiology: The disease incidence ranges from 1/100,000 to 1/150,000 live births, while its prevalence varies across countries from 0.47, 0.35 to 2.20/100,000. The disease has a heterogeneous clinical manifestation due to the combined progressive involvement of internal organs to varying degrees (mainly the spleen and liver) and the central nervous system involvement with the manifestation of neurological and psychiatric syndromes. Depending on the age of NPC onset, *early childhood form* (early and late infantile forms with an onset before the age of 6), *late childhood form* with an onset between 6 and 11 years of age, *juvenile form* and *adult form* have been described, but the most common are childhood forms.

Clinical presentation: The clinical manifestations of the disease are characterised by extreme heterogeneity in terms of age of onset (from the perinatal period until the seventh

decade of life) and life expectancy (from a few days after birth to over 70 years of age). The clinical presentation leading to diagnosis of the disease is based on a combination of syndromes, including hepato- and/or splenomegaly, vertical gaze palsy, cataplexy, ataxia and/or dystonia, delayed development, cognitive disorders, dementia, and psychiatric disorders of varying frequency (*Table 10*) and in varying degree of severity depending on the clinical form (age of onset) and stage of the disease (*Table 11 and Table 12*).

Table 10. Clinical symptoms of Niemann-Pick disease type C

Visceral manifestations	Neurological manifestations	Psychiatric manifestations
Splenomegaly, hepatosplenomegaly	Vertical gaze palsy	Retarded neuropsychological development/dementia
Prolonged neonatal jaundice	Cataplexy	Psychotic manifestations
Hydrops foetalis	Ataxia	Aggressive behaviour
	Dystonia	Medication-resistant psychiatric symptom progression
	Dysarthria	Retarded neuropsychological development/dementia
	Dysphagia	Psychotic manifestations
	Hypotension	Aggressive behaviour
	Clumsiness	Medication-resistant psychiatric symptom progression
	Epileptic seizures	
	Sensorineural hearing loss	

Table 11. Incidence of the most common syndromes in Niemann-Pick disease type C

Symptoms in patients with Niemann-Pick disease type C	%
Clumsiness	87
Learning difficulties	87
Ataxia	83
Vertical gaze palsy	81
Dysphagia	80
Dysarthria	70

Cataplexy with laughter	52
Epilepsy	52
Respiratory disorders	52
Sleep problems	42
Mental disorders	28
Auditory problems	15

Table 12. Progression of Niemann-Pick disease type C (disease stages)

Stages	Clinical presentation
Stage 0	The disease has been diagnosed using biochemical, histological or molecular genetic testing, but so far there has been no impairment or typical symptoms of the disease
Stage 1	Initial symptoms, such as discrete motor disorders or cognitive disorders are identified only by careful examination • Unstable gait in rare cases, but patients can climb stairs and walk long distances without support • Mild dystonia or ataxia • Horizontal saccadic eye movements are slowed down • Vertical supranuclear gaze palsy not fully manifested (only up or down) • Delayed speech, but the patients conduct a differentiated conversation (speech using correct grammar, emotions, and abstraction)
Stage 2	Pronounced progressive cognitive deficiency, easily noticeable motor disorders • Manifested instability of gait with balance issues, with their feet spaced widely apart, but patients can walk short distances (over 100 m) without support; they need support when climbing stairs • Movements associated with athetosis, dystonia or apraxia • Vertical supranuclear gaze palsy • Dysarthria; unclear, delayed speech; conversation is possible, but patients have articulation difficulties and problems with verbal expression (agrammatism, reduction in the number of words)
Stage 3	Significant cognitive deficiency and motor dysfunction requiring medical

	care • Walking only a short distance (several meters) with assistance • Need for assistance with eating, dressing and personal hygiene • Incontinence • Permanent impairment due to dystonia, ataxia or athetosis • Very limited speech: sentences of only 1–2 words; severely limited verbal and emotional expression, impossible abstract thinking
Stage 4	Severe neurological deficiency with inability to walk and speak; vegetative state

In the **early infantile form**, neonatal cholestasis and prolonged jaundice are possible, patients have splenomegaly or hepatosplenomegaly, muscular hypotension, and delayed motor development, while in the **late infantile form**, there are changes in gait, delayed speech development, rare manifestations of cataplexy and epilepsy, and peripheral neuropathy in very rare cases.

The **juvenile form** combines ataxia, dystonia, dysarthria, vertical gaze palsy, epileptic seizures, cataplexy, cognitive disorders, expressive speech disorders, hyperkinetic disorder, and schizophrenic-like psychoses.

In **adults**, the leading manifestations include ataxia, dystonia, dysarthria, vertical gaze palsy, dementia and mental disorders (psycho-organic schizophrenia-like psychoses with visual hallucinations, cognitive regression, and therapeutic resistance up to 25%). Disease progression prognosis depends on the clinical form, and life expectancy varies widely. Early childhood forms (early and late infantile forms) have the fastest progression. Assessment based on disability scales also shows that progression depends on the age of diagnosis.

Diagnosis: The current recommendations for NPC diagnosis and treatment offer a further quantitative assessment of the constellation of clinical symptoms leading to diagnosis by using a scoring scale (www.NPC-SI.com) considering the age of disease manifestation: 1. A score of 40 points for vertical gaze palsy and cataplexy; 2. A score of 20 points for prolonged unexpected neonatal jaundice and splenomegaly and presenile cognitive decline and/or dementia; 3. A score of 10 points for ataxia, drop attacks, dysarthria and/or dysphagia, dystonia and psychosis with delirium, hallucinations, etc.; 4. A score of 5 points for acquired and progressive spasticity and psychosis; 5. A score of 1 point for hypotension,

delayed early development, partial or generalized epileptic seizures, and myoclonus.
(Table 13). Patients with a **score of ≥ 70 should be tested for NPC.**

Table 13. Niemann-Pick disease type C suspicion index

Criteria	Visceral	Neurological	Psychiatric
Very strong — 40 points each		Vertical gaze palsy	
		Cataplexy with laughter	
Strong — 20 points each	Prolonged unexpected neonatal jaundice or cholestasis		Cognitive regression or dementia
	Isolated splenomegaly		
Moderate — 10 points each		Ataxia, frequent falls (drop attacks)	Psychiatric syndromes: illusions, hallucinations and/or other
		Dysarthria and/or dysphagia	
		Dystonia	
Weak — 5 points each		Acquired and progressive spasticity	Treatment-resistant psychiatric syndromes
			Mental diseases
1 point each	Fetal hydrops	Hypotension	Behavioural disorders in childhood and adolescence
	Siblings with fetal ascites	Delayed development	
		Myoclonus	
1 point each	Visceral and neurological — 40 points Visceral and psychiatric — 40 points Neurological and psychiatric — 20 points		
Combinations	Visceral and neurological — 40 points Visceral and psychiatric — 40 points Neurological and		

	psychiatric — 20 points		
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Necessary tests

Main tests in patients with clinical manifestations to confirm NPC diagnosis:

1. Initial tests: *elevated serum chitotriosidase (non-specific), vacuolar cells in bone marrow or liver biopsy; plasma oxysterol-based testing; lyso-sphingomyelin-509 testing.*
2. *Skin biopsy and filipin staining of cultured fibroblasts (positive in 80–85%, but normal or slightly elevated in heterozygous carriers).*
3. *Genetic testing (mutations in the NP1 gene, in 18q11-q12 (in 95% of cases) or in the NP2 gene, in 14q24.3 (in 5% of cases)).* New biomarkers, highly specific for NPC — C chemokine in young patients and plasma oxysterols — have also been identified. *Prenatal diagnosis* of NPC is also possible.
4. *Neuroimaging examinations: MRI* reveals progressive brain atrophy in adults. In early infantile forms, T2 hyperintense lesions in the cerebral white matter and involvement of the hippocampus, thalamus, striatum, and corpus callosum are possible. Dynamics of change can be monitored with the help of various techniques, such as diffusion tensor imaging, magnetic resonance spectroscopy, and positron emission tomography.

Differential diagnosis: The diagnosis of Niemann-Pick disease type C, pathogenetically associated with impaired lipid transport and accumulation of cholesterol and glycosphingolipids in lysosomes, requires clinical, biochemical, and genetic differentiation from diseases with progressive neurological deficiencies and psychiatric symptoms in adolescence and adulthood, in some cases affecting the internal organs — *other lysosomal storage diseases* (neurolipidoses, the most common of which are the 10 known genetically identified types of neuronal ceroid lipofuscinosis) as well as different types of *leukodystrophies* (Table 14). Clinical presentations also impose differentiation from cataplexy and other common diseases in childhood such as epilepsy and expressive speech disorder. In the *early infantile forms*, some viral and autoimmune liver diseases are discussed in the presence of hepatosplenomegaly. In the *late infantile* and *late childhood forms*, in addition to other lysosomal storage diseases (most often neuronal ceroid lipofuscinosis types, leukodystrophies, and leukoencephalopathies), expressive speech disorder, learning difficulties, epilepsy and cataplexy are also discussed. In *juvenile forms and in adults* with NPC presenting with cognitive impairments, dementia and psycho-organic schizophrenia-like psychoses, the diagnosis of NPC is often delayed from 2 to 10 years and a number of

degenerative diseases, such as leukodystrophy and spinocerebellar ataxia, are considered. However, *vertical supranuclear gaze palsy* is an important clinical symptom of the disease.

Table 14. Diagnosis of neurolipidoses and some leukodystrophies (infantile, childhood, juvenile, and late forms) causing progressive neurological and psychiatric symptoms and dementia

Disease	Clinical presentation	Lipid accumulation	Diagnostic tests/ biochemical deficiency	Urinalysis findings	Gene defect/locus
GM2 gangliosidosis	Muscle weakness, epilepsy, ataxia, dementia	GM2 gangliosides	Hexosaminidase A and B	Oligosaccharides	HEXA in chromosome 15 HEXB in chromosome 5
Fabry disease	Acroparesthesias, renal impairment, cardiomegaly, neuropathy, ataxia, angiokeratomas, cataract, optic atrophy	globotriaosylceramide (Gb3) and sphingosine globotriaosylceramide (Lyso-Gb3)	Alpha-galactosidase	Globotriaosylceramide (Gb3)	GLA in Xq21.3-q22
Metachromatic leukodystrophy	Spastic quadriplegia, amblyopia, epilepsy; in adolescents and adults: dementia, mental disorders	Sulfatides	Arylsulfatase A	Sulfatides	22q13.31
X-linked adrenoleukodystrophy	Quadriplegia, amblyopia, amaurosis; in adolescents and adults: dementia, behavioural disorders	Very-long-chain fatty acids (VLCFA)	Long-chain acyl-CoA synthetase		ABCD1, in Xq28
Niemann-Pick disease type C	Children: speech and learning impairments, motor regression, ataxia/dystonia, vertical gaze palsy; Adolescents and adults: vertical gaze palsy,	Gangliosides, cholesterol, sphingomyelin	Filipin test: cholesterol accumulation in lysosomes	-	NP1 in 18q11-q12; NP2 in 14q24.3

	cognitive disorders, dementia, psychoses				
Ceroid lipofuscinoses types 1–14 (early and late infantile, juvenile, and late forms)	Children (CLN types 1–3, 5–10): quadriparesis, cerebellar ataxia, amblyopia, myoclonic epilepsy, intellectual regression; Adolescents and adults (Kufs disease, CLN type 4): ataxia, dementia	Autofluorescent ceroid and lipofuscin accumulations	Enzyme deficiency of PPT1 for CLN1, TPP1 for CLN2; genetic testing		<i>PPT1 for CLN1, TPP1 for CLN2, CLN3 for CLN6 and DNAJC5, CLN4, CLN5, CLN6 for CLN6, MFSD8 for CLN7, CLN8, CTSD for CLN10 CLN11/GRN CLN12/ATP13 A2, CLN13/CTSF CLN14/KCTD 7, SGSH</i>
Cerebrotendinous xanthomatosis	Progressive cerebellar ataxia, juvenile cataract, chronic diarrhoea	Cholesterol			<i>CYP27A1 in 2q33-qter</i>

Treatment:

- Disease-specific **pathogenetic therapy** is substrate-reducing and aims to inhibit glycosphingolipid synthesis. *Miglustat (100 mg tablet)*, a glucosylceramide synthase inhibitor, has been shown to improve the condition due to neurological syndrome stabilisation in placebo-controlled studies in adults and children and multicenter observational studies. Dosage is based on body weight (body surface area in m²) and possible gastrointestinal side effects: **In patients under 12 years of age — dose based on body surface area:** > 1.25 m² — 3 x 200 mg; > 0.88–1.25 m² — 2 x 200 mg; > 0.73–0.88 m² — 3 x 100 mg; > 0.47–0.73 m² — 2 x 100 mg; ≤ 0.47 m² — 100 mg; **in adolescents over 12 years of age and adults, the recommended dose is 200 mg three times a day.** Treatment duration from 6 months to 1 year is required to evaluate the efficacy of *Miglustat*.

- **Symptomatic treatment for neurological manifestations:**

- *Tricyclic antidepressants or CNS stimulants* to manage cataplexy

- *Anticonvulsants* (valproate, lamotrigine, and levetiracetam); carbamazepine, oxcarbazepine, and vigabatrin are avoided due to the risk of myoclonus induction; phenytoin is not used due to the risk of cerebellar symptom worsening
- For dystonia and tremor: *anticholinergic drugs, botulinum toxin*
- For insomnia: *melatonin*.

3.5. OTHER SPHINGOLIPIDOSES

Other sphingolipidoses - GM1 gangliosidosis, Tay-Sachs disease, Sandhoff disease, Krabbe disease, and metachromatic leukodystrophy associated with impaired metabolism caused by sphingolipid accumulation in the CNS neurons and other structures. They are characterised by progressive neurodegeneration. No specific treatment is known.

3.5.1. GM1 GANGLIOSIDOSIS

GM1 gangliosidosis is caused by a mutation in the **GLB1 gene/3p22.3** that results in a decreased **β-galactosidase** enzyme activity. More than 102 mutations are known. Clinical forms depend on the degree of enzyme deficiency and include varying degrees of neurodegeneration and skeletal abnormalities.

The most common is the infantile form of GM1 gangliosidosis (type 1) has its onset at birth with marked facial dysmorphism, macrocephaly, oedema, dysostosis multiplex, kyphoscoliosis, hepatomegaly, hypotension; epileptic seizures, progressive central quadriparesis with subsequent contractures, amaurosis, retinal changes of cherry-red spot type, hearing loss, and vacuolar lymphocytes are manifested. Patients survive for about 2 years. **GM1 gangliosidosis (type 2) is a late-onset infantile or juvenile form** has its onset at 1–3 years of age with epileptic seizures, incl. myoclonic ones, spastic quadriparesis progression, *extrapyramidal syndromes, intellectual regression*, retinal degeneration of cherry-red spot type, but with no hepatosplenomegaly. Life expectancy is about 10 years. **GM1 gangliosidosis type 3** has its onset at 3–30 years of age and presents with slowly progressive dysarthria, dystonia, rigidity, bradykinesia, and changes in gait. MRI of the brain reveals symmetrical T2 hyperintense lesions in the putamen and nucleus caudatus; the globus pallidus, cerebellum, and amygdala are also affected. There is no specific treatment. Symptomatic treatment is carried out.

3.5.2. TAY–SACHS DISEASE

Tay-Sachs disease is a GM2 gangliosidosis with hexosaminidase A deficiency and accumulation of GM2 gangliosides in neurons. The incidence of Tay-Sachs disease is about 1/112,000 and is significantly higher among Jews (1/3,900). There are 3 forms depending on the age of onset and neurological involvement. *The infantile form* typically begins at about 6 months of age with a violent reaction to noise known as a “startle response”. The disease progresses rapidly — patients develop central quadriparesis, epileptic seizures, blindness, and hearing loss and lethal outcome occurs before 4 years of age. *The juvenile form* begins between 2 and 10 years of age with regression in motor function and patients develop central quadriparesis, dysarthria, dysphagia, ataxia, and dementia, and lethal outcome occurs between 5 and 15 years of age. In *the late-onset form*, the first symptoms present from adolescence to 30 and 40 years of age with progressive impairment of gait and speech, cognitive regression as well as schizophrenic-like psychoses. There is no specific treatment. Patients receive symptomatic treatment.

4. NEURONAL CEROID LIPOFUSCINOSES

Neuronal ceroid lipofuscinoses are progressive neurodegenerative diseases with a histologically proven accumulation of lipid pigment-rich structures in brain neurons. They have an AR inheritance with the exception of CLN4, which pattern of inheritance is AD. Neuronal ceroid lipofuscinoses are the most common storage diseases with a prevalence of 0.56/100,000 to 5/100,000 where the most common form is the infantile one.

15 genetically distinct diseases have been described, which are grouped historically by age of onset as *early infantile form* (Santavuori disease with deficiency of palmitoyl protein thioesterase 1, PPT1), *late infantile form* (Jansky-Bielschowsky disease with deficiency of tripeptidyl peptidase 1, TPP1), *adolescent form* (Batten disease or Spielmeyer-Vogt-Sjögren disease), and an *adult form*. Subsequently, in the identification of 15 genetic types, it was found that each of them may determine a different age of onset (*Table 15*).

- CLN1/PPT—mutations that cause NCL with onset in infancy or any age up to adulthood
- CLN2/TPP1—mutations that cause late infantile or later-onset NCL forms
- CLN3—mutations that cause NCL with onset in adolescence, most often with slow progression

- CLN4/*DNAJC5*—2 mutations causing late-onset AD NCL (Parry disease)
- CLN5—mutations that cause late infantile or later-onset NCL forms in adults
- CLN6—mutations that cause late infantile or later-onset NCL forms, incl. Kufs disease type A
- CLN7/*MFSD8*—mutations that cause late infantile or later-onset NCL forms
- CLN8—mutations that cause the late infantile NCL form or different diseases, incl. northern epileptic variant
- CLN10/*CTSD*—mutations that cause NCL with onset after birth, at an early age or later
- CLN11/*GRN*—mutations that cause adult NCL form
- CLN12/*ATP13A2*—mutations that cause juvenile NCL forms
- CLN13/*CTSF*—mutations that cause adult NCL forms, incl. Kufs disease type B
- CLN14/*KCTD7*—mutations that cause infantile NCL forms
- CLN9—NCL with onset in infancy, but not CLN3
- CLCN6—mutations in 2 patients with late-onset NCL
- SGSH—2 heterozygous mutations in 1 patient with late-onset NCL and other diseases (MPS IIIA).

Table 15. Neural ceroid lipofuscinoses, genes, phenotype, and encoded proteins

Gene	Disease/phenotype	Another name	Encoded protein
<i>CLN1/PPT1</i>	CLN1—infantile, but also late infantile, juvenile, in adults	Infantile form	Palmitoyl protein thioesterase 1, PPT1
<i>CLN2/TPP1</i>	CLN2—late infantile form; juvenile form	Late infantile form	Tripeptidyl peptidase 1, TPP1
<i>CLN3</i>	CLN3	Juvenile	CLN3 transmembrane protein/Battenin
<i>CLN4/DNAJC5</i>	CLN4	Adult AD Batten disease, Kufs disease, CLN—Parry type	Cysteine string protein α
<i>CLN5</i>	CLN5—late infantile form; CLN5—juvenile form; CLN5—adult form	The Finnish version, late infantile	Ceroid-lipofuscinosis neuronal protein 5

<i>CLN6</i>	CLN6—late infantile form; CLN6—juvenile form; CLN6—adult form	Early juvenile or late infantile variant	Ceroid-lipofuscinosis neuronal protein 6
<i>CLN7/MFSD8</i>	CLN7—late infantile	Late infantile variant	Major facilitator superfamily domain-containing protein 8
<i>CLN8</i>	CLN8—late infantile	Late infantile variant EPMR (progressive epilepsy with mental retardation)	Protein CLN8
<i>CLN10/CTSD</i>	CLN10—congenital; CLN10—late infantile form; CLN10—juvenile form; CLN10—adult form	Congenital, late infantile, juvenile, in adults	Cathepsin D
<i>CLN11/GRN</i>	CLN11—in adults	Adults—heterozygous mutation; it causes frontotemporal dementia	Progranulin
<i>CLN12/ATP13A2</i>	CLN12—adolescent	CLN12—adolescent (this mutation also causes Kufor-Rakeb syndrome)	ATPase type 13A2
<i>CLN13/CTSF</i>	CLN13—in adults	Kufs disease type B—adults	Cathepsin F
<i>CLN14/KCTD7</i>	CLN14—infantile	CLN14 disease, infantile	Potassium channel tetramerization domain-containing protein 7

Neuronal ceroid lipofuscinoses vary in age of onset (early or late infantile, juvenile, or adult forms), but are manifested with a combination of epileptic, mainly myoclonic seizures, progressive central quadriparesis, cognitive regression, dementia, ataxia, extrapyramidal syndrome, amblyopia and amaurosis, hearing loss, and psychiatric syndromes in adults (*Table 16*). The most common form is late infantile ceroid lipofuscinosis CLN2/TPP1, which has its onset at about 2 years of age with initial epileptic seizures —

generalized tonic-clonic, focal, epileptic statuses, but myoclonic seizures predominate. Ataxia, spastic quadriparesis, visual disturbances to blindness, cognitive regression as well as dementia progress rapidly. Survival duration is up to adolescence.

Table 16. Forms and variants of neuronal ceroid lipofuscinosis genes/loci and clinical characteristics: 4 phenotypic and 15 genetic forms, 2018

Forms/variants of NCL		Gene	Locus	Protein	Age of onset	Clinical presentation
1. NCL1 (PPT1-linked NCL, early infantile form of Santavuori disease)		<i>PPT1</i>	1p32	Palmitoyl-protein thioesterase 1 (PPT1)	6 months–2 years of age	Cognitive/motor regression, amblyopia → amaurosis, epileptic, mainly myoclonic seizures
2. Late infantile NCL	NCL 2 (TPP1-linked NCL, classical late infantile form, Jansky-Bielschowsky disease)	<i>TPP1</i>	11p15.5	Tripeptidyl peptidase 1 (TPP1)	2–4 years of age	Epileptic, mainly myoclonic seizures, motor/cognitive regression, ataxia, extrapyramidal syndrome, amblyopia → amaurosis
	CLN5-linked NCL (Finnish variant late infantile form)	<i>CLN5</i>	13q21.1-q32	CLN protein 5	4–7 years of age	Motor/cognitive regression, epileptic seizures, amblyopia → amaurosis
	CLN6-linked NCL (Indian variant late infantile form)	<i>CLN6</i>	15q21-q23	CLN protein 6	1.6–8 years of age	Amblyopia → amaurosis, epileptic seizures, ataxia, cognitive and motor regression
	MFSD8-linked NCL (Gypsy variant late infantile form)	<i>MFSD8</i>	4q28.1-q28.2	Transport protein 8	3 years of age	Amblyopia → amaurosis, epileptic seizures, myoclonus, cognitive and motor regression
	CLN8-linked NCL (Turkish variant late infantile form)	<i>CLN8</i>	8p23	CLN protein 8	2–7.5 years of age	Epileptic seizures, cognitive regression, sometimes amblyopia
	Other variants of late infantile NCL	<i>CTSD</i>	11p15.5	Cathepsin D	3–7.5 years of age	Cognitive and motor regression, epileptic seizures, amblyopia → amaurosis
		<i>PPT1</i>	1p32	PPT1	2–6 years	

					of age	
3. Juvenile form (Batten disease)	NCL 3 (<i>CLN3</i> -linked NCL, classical juvenile form, Batten disease or Spielmeyer-Vogt-Sjögren disease)	<i>CLN3</i>	16p12.1	Battenin	4–10 years of age	Epileptic seizures, cognitive and motor regression, cerebellar syndrome, amblyopia → amaurosis
	Juvenile NCL variants,	NCL 9 (unknown), <i>PPT1</i> , <i>TPP1</i>	unknown		4–10 years of age	Amblyopia → amaurosis, ataxia, motor/cognitive deficiency, stiffness
	Northern epilepsy variant of NCL (progressive epilepsy with mental retardation)	<i>CLN8</i>	8p23	<i>CLN</i> protein 8	5–10 years of age	Epileptic seizures, cognitive regression
4. Adult form (Kufs disease)	An adult form of Kufs disease (NCL4)	unclear gene defect			15–50 years of age	Epileptic seizures, cognitive and motor regression, behavioural disorders, amblyopia → amaurosis
	Adult form variants	<i>CTSD</i> , <i>PPT1</i> , <i>CLN3</i> , <i>CLN5</i>	11p15.5, 1p32, 16p12.1, 13q21.1-q32	Cathepsin D, <i>PPT1</i> , Battenin, <i>CLN</i> protein 5	15–50 years of age	Cognitive and motor regression, epileptic seizures, and behavioural disorders

Tests: *CT* and *MRI* show progressive cerebral and cerebellar atrophy at baseline and with T2 hyperintensity of the periventricular white matter, low thalamus and striatum signal as well as thinning of the corpus callosum. *EEG*: In the early infantile form, the main activity is not suppressed when eyes open, sleep spindles disappear between 1 and 2 years of age, and about the age of 3 years the wave amplitudes decrease to the isoelectric line. In the late infantile form, *EEG* shows high-amplitude occipital spikes in low-frequency photic stimulation (1 - 2 Hz). *Visually evoked potentials (VEP)* and *retinogram* are abnormal suggesting suppression to complete disappearance of normal potentials. In the late infantile form, there are giant VEP with flash stimulation. *The cerebrospinal fluid* has normal parameters. *Enzyme assays*: In the early infantile form with onset below 2 years of age, there

is an enzyme deficiency of *PPT1*, in rare cases—of *TPP1*; in the late infantile form—of *TPP1*. *Histological examination* of the skin, conjunctiva or rectal mucosa shows presence of autofluorescence, and *electron microscopic examination* shows granular osmophilic deposits in lysosomes.

The diagnostic algorithm for neuronal ceroid lipofuscinosis includes:

1. *For the onset below 2 years of age: testing for deficiency of PPT1 and TPP1* (possible in rare cases).
2. *For the onset between 2 and 4 years of age: testing for deficiency of TPP and PPT1* (possible in rare cases), and in the event of normal enzyme values—*electron microscopic examination of skin biopsy* to detect lysosomal storage and *genetic testing* of CLN5, CLN6, and CLN8.
3. *For the onset between 5 and 12 years of age: in the presence of vacuolar lymphocytes—genetic testing of CLN3 and testing for enzyme deficiency of PPT1 and TPP1* (possible in rare cases), and in the event of absence—*electron microscopic examination of skin biopsy to detect lysosomal storage*.
4. *In adults: electron microscopic examination of skin biopsy to detect lysosomal storage and genetic testing of CLN8* in Finnish and Turkish patients.

Treatment:

- *In late infantile ceroid lipofuscinosis (NCL 2 or TPP1-linked NCL) with deficiency of the CLN2 gene encoding the lysosomal enzyme tripeptidyl peptidase 1 (TPP1), enzyme replacement therapy with cerliponase alfa* authorised by FDA and EMA is administered to the cerebrospinal fluid intraventricularly every 7 days by infusion via a surgically implanted reservoir and catheter.

Conclusion

Diagnosis of the type of lysosomal storage diseases with neurological manifestations is based on:

- *The clinical presentation* with progressive quadriparesis, cerebellar, dementia syndrome, blindness, characteristic changes in the macula in some cases (cherry-red spot type), epileptic seizures, myoclonus and presence of hepatosplenomegaly in Nieman-Pick disease and Gaucher disease; renal impairment in Fabry disease; cardiac involvement in Pompe disease, Fabry disease, and some mucopolysaccharidoses.

- *Enzyme deficiency identified:* deficiency of hexosaminidase A in Tay-Sachs disease; deficiency of sphingomyelinase in Nieman-Pick disease; deficiency of glucocerebrosidase in Gaucher disease; deficiency of galactosidase A in Fabry disease; deficiency of palmitoyl protein thioesterase 1 and tripeptidyl peptidase 1 in neuronal ceroid lipofuscinoses; deficiency of α -neuraminidase or β -galactosidase in sialidoses.
- *Neurological imaging (CT and MRI)* - progressive cerebral atrophy is visualised.
- *Genetic testing* that proves characteristic gene defects.

Differential diagnosis—differentiation from:

- *Leukodystrophies.* Some of them have a specified metabolic defect. The MRI finding has extensive demyelination, which is specific and mainly occipital in X-linked adrenoleukodystrophy or frontal in Alexander disease. Polyneuropathic syndrome in metachromatic leukodystrophy and globoid cell leukodystrophy (Krabbe disease) has also been identified.
- *Chronic and persistent neuroinfections.* In subacute sclerosing panencephalitis (SSPE) and HIV encephalopathy, cerebrospinal fluid examinations show an increased intrathecal synthesis of IgG and antibodies against the viral agent.

Treatment:

Substrate reduction therapy (SRT): *miglustat* for Niemann-Pick disease type C patients at any age; *miglustat* for Gaucher disease type 1 patients over 18 years of age and *eliglustat* for Gaucher disease type 1 patients over 18 years of age.

Enzyme replacement therapy (ERT): *Laronidase* for MPS I and *idursulfase* for MPS II; *elosulfase alfa* for MPS IVA; *galsulfase* for MPS VI; *vestronidase alfa* for MPS VII; *alglucosidase alfa* and *avalglucosidase alfa* for Pompe disease; *imiglucerase* and *velaglucerase alfa* for Gaucher disease type 1, and *taliglucerase alfa* for patients over 18 years of age with Gaucher disease type 3; *olipudase alfa* for ASMD, *agalsidase alfa* and *agalsidase beta* for Fabry disease; *cerliponase alfa* for CL 2 or TPP1-linked NCL.

Chaperones: *migalastat* for patients aged 12 years and older with a confirmed diagnosis of Fabry disease who have amenable mutation.

Other gene therapies using viral vectors or nanoparticles—at experimental stage.

Hematopoietic stem cells: for mucopolysaccharidosis type 1 at an early stage.

Symptomatic treatment depending on clinical manifestations:

- Antiepileptic medications (see National Consensus Position Statement for the

Diagnosis and Treatment of Epilepsy, 2020).

- Muscle relaxants:
 - *Baclofen*: 0.4 to 2 mg/kg at a low initial dose divided in 3–4 intakes and increased every 3 days according to its effect. For children aged 1–2 years, the dose is 10–20 mg/day, 2–6 years: 20–30 mg/day, 6–10 years: 30–60 mg/day.
 - *Tetrazepam*: 50 mg/day, for adults: up to 150 mg/day.
 - *Botulinum Toxin A* administered locally into the spastic muscle sharply reduces spasticity for 4 to 8 months.
 - *Biperiden*: 0.5–1 mg/day for children aged 1–3 years, from 1 to 3 mg/day for children aged 3–15 years.
- **General care**