Disorders of lysosome metabolism/Lysosomal hydrolase deficiency

- Lysosomes contain different hydrolases depending on which stored substrate they are cleaving. Disturbances in the function of these enzymes lead to accumulation of the substrate in the lysosomal apparatus of the cell. Is part of them:
  - **Lipidoses and Sphingolipidoses**
  - **Mucopolysaccharidoses**
  - **Mucopolysaccharidoses and glycoproteinoses**
  - **Glycogenosis**
  - **Proteinoses**

Lipidoses are **congenital disorders** of enzymes (enzymopathy) of lipid metabolism. These are primarily lysosomal hydrolases, which break down complex lipids - characterized by the accumulation (accumulation, hoarding) of lipids in the lysosomal apparatus. Degradation of sphingolipid glycoconjugates takes place in lysosomes by gradual cleavage of sugar units from the non-reducing end of the chain by specific exohydrolases down to **ceramide** . Similarly, **sphingomyelin** is degraded by cleavage of phosphorylcholine. Ceramide is further deacylated to **sphingosine**. These end products leave the lysosome and are used again for biosynthesis or are further degraded. **Cholesterol esters** are hydrolyzed, **cholesterol** is transported to the cytosol and esterified.

Due to the involvement of the nervous system, **lipidoses** are sometimes also referred to as **neurolipidoses**.

Microscopy

Hypertrophy of lysosomes – microvacuolar, foamy to honeycomb appearance of cells. Subsequently, regressive changes including the secondary formation of lipopigments (ceroid and lipofuscin). Stored lipids tend to be **gangliosides**, **cerebrosides**, **sphingomyelin**, **ceramide**, **cholesterol** and its **esters**. They primarily affect RES histiocytes, but also epithelium and endothelium (visceral lipidosis) or ganglion cells (neuronal lipidosis).

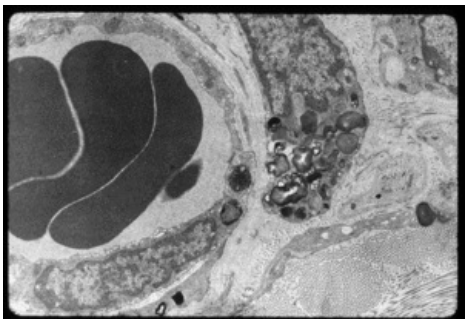
Distribution

According to the location of the disability

- Neuronal;
- visceral;
- neurovisceral;
- **according to stored lipid** (and defective enzyme).

CNS lysosomal diseases have two forms:

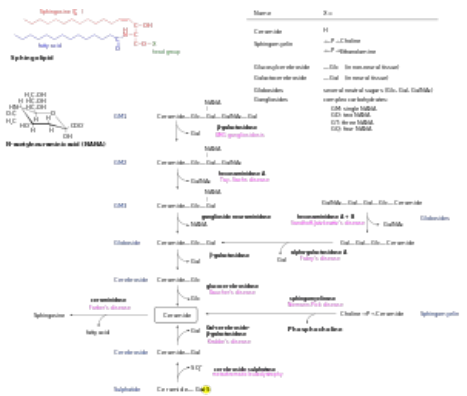
1. **ganglion cell** involvement – hoarding disease;
2. **white matter** impairment – leukodystrophy (disorders of myelin metabolism)



Biopsy from the conjunctiva of a patient with Fabry disease. Laminar structures - lysosomes storing ceramide trihexoside are visible in pericytes

Simplified distribution of complex lipids

- **Phospholipids** :
  - *glycerophospholipids* – phosphatidic acid (3-phospho-1,2-diacylglyerol) + another component (choline, ethanolamine);
  - *sphingophospholipids* – ceramide (sphingosine + MK) + phosphate + another component (if it is choline, it is sphingomyelin).
- **Glycolipids** – contain ceramide (sphingosine + MK) with a bound sugar component:
  - *cerebrosides* – binding of hexose (Glc, Gal) to ceramide;
  - *gangliosides* – binding of oligosaccharide with sialic acid (N-acetylneuraminic) to ceramide.



Sphingolipidosis

Gaucher disease

🔎 *For more information see Gaucher disease.*

- **Defect: glucocerebrosidase** deficiency causes accumulation of glucocerebrosides in the spleen (RES) and CNS.
- **Clinical signs:**
  - **type 1:**
    - the onset of the disease is in childhood, full manifestation in adulthood

        - splenomegaly is typical, hepatomegaly is only mild, but the development of cirrhosis is possible
        - bone marrow infiltration, pathological fractures and aseptic necrosis occur
        - massive involvement of the lungs can lead to *cor pulmonale* ; skin hyperpigmentation and coincidences with various malignancies are also known
    - **type 2:**
        - basic features include hepatosplenomegaly and severe neurological symptomatology (trismus, strabismus, retroflexion of the head, progressive spasticity, hyperreflexia and emergence of pathological reflexes, in the terminal stage hypotonia)
    - **type 3:**
        - longer course of the disease and neurovisceral symptomatology around 1-3 years of life, hepatosplenomegaly and later neurological symptomatology - ataxia and spastic paresis, eye motility disorders, mental retardation and seizures (often myoclonus)
- **Microscopy**: the characteristic finding is the so-called *Gaucher cells* – large lipid-storing macrophages, with "wrinkled" cytoplasm, first appearing in the bone marrow, later also elsewhere (similar cells, the so-called gaucheroid cells, occur in the bone marrow in CML)
- **Diagnosis**: is confirmed by determining the deficiency of b-glucosidase activity in leukocytes isolated from peripheral blood or cultured skin fibroblasts ; DNA analysis is an additional examination in cases with a confirmed diagnosis
- **Prenatal diagnosis**: in families with enzymatically proven diagnosis, analysis of native and cultured chorionic villi or cultured amniocytes is possible
- **Treatment**: even by supplying the missing enzyme, inhibition of glucocerebroside biosynthesis

Farber's disease

- it is an **AR disease**
- **Defect**: deficiency of acid **ceramidase activity**
- **Clinical symptoms:** damage to the subcutaneous tissue and mucous membranes by deforming nodes caused by the granulomatous scarring process - the maximum changes are in the joints and around the tendon sheaths
    - involvement of the larynx leads to hoarseness up to aphonia
    - involvement of heart valves, mild hepatosplenomegaly, retinal changes similar to the so-called "cherry spot" were also described
    - neurological involvement is less common - hypotonia, denervation atrophy and myopathic changes
    - the basic features of the late-onset forms include a mitigated disability with a protracted course (clinically similar to classic Farber's disease)
- **Diagnosis**: is confirmed by determining the deficiency of acid ceramidase activity in leukocytes isolated from peripheral blood or cultured skin fibroblasts
- **Prenatal diagnosis:** in families with enzymatically proven diagnosis, analysis of native and cultured chorionic villi or cultured amniocytes is possible
- **Treatment**: not available

Niemann-Pick disease

🔎 *For more information see Niemann-Pick disease.*

An autosomal recessive hereditary storage disorder, it belongs to the so-called **lipidoses** - lipid metabolic disorders. It arises on the basis of the deposition **of sphingomyelin** in the macrophages of the reticuloendothelial system - mainly in the liver, spleen and bone marrow.

This is a heterogeneous group of diseases **of type A, B, C,** which differ in a metabolic disorder - **acid sphingomyelinase deficiency** (type A, B) vs. **lipid transport disorder** (type C).

Acute forms, typical for childhood, affect the nervous system, chronic forms are manifested later by cholestatic liver disease, progressing to cirrhosis. Secondarily, there is an increase in the concentrations of non-esterified cholesterol.

Niemann-Pick disease, type A and B: deficiency of acid **sphingomyelinase** activity (results from a mutation of the SMPD1 gene, more than 100 mutations are known)

- **type A** – the basic features include **neurovisceral disability** with death within 1-3 years of age (specifically increased incidence in the ethnic group of Ashkenazi Jews)
    - difficulties appear already in the first weeks of life
    - manifested by vomiting, diarrhea and general failure of the newborn to cachexia; within a few months it progresses to lymphadenopathy and hepatosplenomegaly (rarely to cholestatic icterus)
    - muscle weakness, hypotonia, psychomotor retardation appear, there is a gradual loss of motor functions, spasticity and muscle rigidity; xanthomas of brown-yellow spots may appear on the skin
    - in about half of the patients, a so-called **cherry spot** appears on the retina
    - patients usually die before the age of 3 years

- **type B** – **chronic** disease (more often in Southern Europe and North Africa), can appear at any time from late childhood to adulthood
    - usually manifests as splenomegaly or hepatosplenomegaly (more severe liver disease is rare)
    - there is often **reticulonodular X-ray infiltration of the lungs** associated with interstitial involvement, which may present with varying degrees of exertional dyspnea
    - growth retardation, bone age and puberty are also delayed

    - intellect and nervous system are not affected
    - adults tend to have a pathological lipid profile, thrombocytopenia and elevated liver transaminase activity
    - there are various severe forms of the disease, mostly with a normal life expectancy
- **The diagnosis of Niemann-Pick disease type A and B:** is confirmed by determining the deficiency of acid **sphingomyelinase** activity in leukocytes isolated from peripheral blood or cultured skin fibroblasts; DNA analysis is an additional examination in cases with a confirmed diagnosis
- **Prenatal diagnosis**: in families with enzymatically proven diagnosis, analysis of native and cultured chorionic villi or cultured amniocytes is possible; an additional examination is an analysis of the ultrastructure of the chorionic villi

- **Treatment**: recombinant enzyme therapy is under development

Krabbe disease (leukodystrophy)

- **Defect**: deficiency of **galactocerebroside b-galactosidase activity**
- **Clinical symptoms:** the basic features include manifestations after half a year of life and a rapid course
    - first there is increased irritability, hyperaesthesia, hyperacusis and increased photosensitivity, psychomotor retardation, hypertension and tonic and clonic seizures gradually occur
    - in the final stage there is decerebration, opisthotonus, blindness, or deafness
    - exitus occurs around 2 years
    - in the laboratory, there is a finding of an increased level of protein in the cerebrospinal fluid (especially albumin and alpha-2-globulin) with a normal cell count, optic atrophy and signs of peripheral neuropathy (reduced peripheral nerve conduction velocity); EEG may be abnormal, often with focal epileptic seizures; on CT and NMR there is diffuse atrophy of the white matter of the brain
    - in forms with a late onset of clinical symptoms, the basic features include - mental retardation, pyramidal disorders, reaction disorders, visual impairment
    - protein in the cerebrospinal fluid may not be elevated, peripheral nerve conduction velocity may be normal or decreased
- **Diagnosis**: is confirmed by determining the deficiency of galactocerebroside-b-galatosidase activity in leukocytes isolated from peripheral blood or cultured skin fibroblasts
- **Prenatal diagnosis:** in families with enzymatically proven diagnosis, analysis of native and cultured chorionic villi or cultured amniocytes is possible
- **Treatment**: not available

Metachromatic leukodystrophy

- **Defect**: deficiency **of arylsulfatase A activity**

- **Clinical signs:** basic features include gait disturbance, mental regression, ataxia, loss of speech, peripheral neuropathy, quadriparesis, optic nerve atrophy, macular graying
    - the disease lasts several months
    - in the laboratory, there is a finding of an increased level of protein in the cerebrospinal fluid (especially albumin and alpha-2-globulin) with a normal cell count, optic atrophy and signs of peripheral neuropathy (reduced peripheral nerve conduction velocity); EEG may be abnormal, often with focal epileptic seizures; on CT and NMR there is diffuse atrophy of the white matter of the brain
    - in forms with late onset of clinical symptoms, basic features include mental retardation, psychotic symptoms, pyramidal disorders, reaction disorders, visual impairment
    - protein in the cerebrospinal fluid may not be elevated, peripheral nerve conduction velocity may be normal or decreased
    - the concentration of sulfatide is increased many times in the urine
- **Diagnosis**: is confirmed by determining the deficiency of arylsulfatase A activity in leukocytes isolated from peripheral blood or cultured skin fibroblasts; DNA analysis is an additional examination in cases with a confirmed diagnosis
- **Prenatal diagnosis:** in families with enzymatically proven diagnosis, analysis of native and cultured chorionic villi or cultured amniocytes is possible
- **Treatment**: not available

Tay-Sachs disease (GM2 gangliosidosis)

- **Defect: deficiency of N-acetyl-beta-D-glucosaminidase A** activity
- **Clinical symptoms:** there are clinical variants according to the time of onset of the disease and the severity of the manifestation
    - in *the infantile form,* the basic features include progressive neurological symptomatology, hypotonia, myoclonus, convulsions, as well as a cherry spot on the eye background, progressive psychomotor deterioration, macrocephaly, and exitus by 2-4 years; the frequency of the disease is high among Ashkenazi Jews
    - in *the infantile type with later onset,* the basic symptoms include central neurological symptomatology and hoarding retinopathy
        - neurological involvement is highly variable - classical CNS involvement may dominate (dystonia, extrapyramidal symptoms, ataxia), but there may also be a picture of juvenile spinal muscular atrophy (Kugelberg-Walander type), systemic atrophy close to amyotrophic lateral sclerosis or progressive spinocerebellar ataxia of the Friedreich type
    - accumulation of GM2 ganglioside in the brain is typical

- **Diagnosis**: is confirmed by determining the deficiency of N-acetyl-beta-D-glucosaminidase A activity in leukocytes isolated from peripheral blood or cultured skin fibroblasts
- **Prenatal diagnosis:** in families with enzymatically proven diagnosis, analysis of native and cultured chorionic villi or cultured amniocytes is possible
- **Treatment**: not available

Fabry disease

🔎 *For more information see Fabry disease.*

- it is an **X-linked** disease, frequency 1:40,000
- **Defect:** deficiency of **alpha-galactosidase A** activity
- **Clinical signs:** in hemizygotes (males), the basic signs include permanent or episodic acroparesthesia or burning pain of varying intensity, mildly elevated temperature and sedimentation
  - skin angiokeratomas, corneal opacity and deformities of retinal and conjunctival vessels are characteristic
  - renal involvement includes lipiduria, proteinuria, and progressive insufficiency
  - cardiovascular involvement includes hypertension (renal), myocardial hypertrophy (cardiomegaly) and ischemic changes in various organs, especially the brain
  - central neurological symptomatology may be present
  - in heterozygotes (females), the disability is different - fully developed symptoms to their complete absence
  - the concentration of globotriaosylceramide is increased many times in the urine
- **Diagnosis**: is confirmed by determining the deficiency of α-galactosidase A activity in leukocytes isolated from peripheral blood or in cultured skin fibroblasts; an additional examination in cases with a confirmed diagnosis is a DNA analysis, however, it is necessary to confirm the heterozygous state
- **Prenatal diagnosis:** in families with enzymatically proven diagnosis, it is possible in native and cultured chorionic villi or cultured amniocytes; an additional examination is an analysis of the ultrastructure of the chorionic villi
- **Treatment:** therapy is also possible with the delivery of recombinant α-galactosidase A

Links

Related articles

- Glycogenosis
- Glycoproteinoses
- Mucopolysaccharidoses

Reference

References

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