Lysosomal Diseases

Lysosomal diseases ("storage diseases“) are rare, heritable conditions leading to substrate accumulation in lysosomes as a result of insufficient activity of some of the lysosomal enzymes or associated transport proteins. These are **multisystemic condition with permanent progression** that can manifest at any age. Most affected are metabolically active organs and tissues (bone marrow, bones, sceletal musles, myocardium and CNS). More than 60 different lysosomal defects have been described. Early-onset forms typically have more serious presentation with rapid progression and unfavourable prognosis. The incidence is estimated as 1 affected per 8200 live births. The inheritance is most often **autosomal recessive**, but there are also rare X-linked recessive forms (Fabry disease and mucopolysaccharidosis type II). Lysosomal enzymes, so called acidic hydroxylases, allow for gradual breakdown of large complex molecules (sphingolipids, glycoproteins či mucopolysaccharides) from cell membranes of senescent cells. Insufficient level or insufficient enzymatic activity leads to accumulation of substrate in lysosomes of various cells. Some diseases can me treated by substituting missing enzyme - **enzyme replacement therapy** (in Gaucher, Fabry and Pompe disease and in mucopolysaccharidoses type I, II and VI) or by reducing amount of accumulated substrate - **substrate reduction therapy** (in Gaucher disease, Niemann-Pick disease type C). In rare cases, bone marrow transplant can be also indicated (mucopolysaccharidosis type I).[1]

Division

- Lysosomal diseases from *defects in lysosomal transport proteins*
- Lysosomal diseases from *deficiency of lysosomal membrane proteins*
- Lysosomal diseases from *deficiency of lysosomal hydrolases*
- Lysosomal diseases from *deficiency of enzyme activators of lysosomal hydrolases*

Pathophysiological mechanisms of lysosomal diseases and their examples

- **Accumulation of secondary products**
  - Cholesterol (NPC C)
  - Sphingomyelin (NPC A, NPC B)
  - Mucopolysaccharides
- **Neuroinflammation**
  - as induced through microglia which work as phagocytes in CNS. These become swollen (just like foam cells in atheroma) as result of material building up in their lysosomes. Eventually they „burst“ (undergo lysis) releasing lytic enzymes into the surroundings.
- **The defect in calcium metabolism**
  - includes Gaucher disease which is a defect in enzyme **glucosylcerebrosidase** which modulates function of ryanodine receptors in endoplasmic reliculum. These regulate the calcium balance inside the cell. When their function is compromised, there is a calcium eflux from ER leading to activation of lytic enzymes and caspases (apoptosis).
- **Oxygen radicals**
  - arise probably as a result of mitochondrial and ER damage, especially in brain
- **Increased autophagy**
  - increased autophagy for multiple reasons ultimately leads to apoptosis. . One of them is defective circulation of plasma membrane components which leads to damage of cell and its chemical and electrical gradients, opening path for apoptosis.

Lysosomal diseases from defects in lysosomal transport proteins

I-cell disease (mucolipidosis II)

- Deficiency in **GlcNAc-1-phosphotransferase**.
- Man-6-P serve as a chemical marker tagging enzymes which are to be transported into lysosomes.
- Inclussion cell disease is caused by defect in lysosomal transport of proteins tagged by Man-6-P. This is caused by mutation in N-acetylglucosamin 1-phosphotransferase.
- Receptor for Man-6-P is not affected; enzyme-bound Man-6-P doesn’t form at all.
- This all leads to increased activity of lysosomal proteins in extracellular liquid and plasma, but decreased activity of many lysosomal enzymes in tissues.
- Lysosomal are enlarged due to substrate accumulation.
- As a result of accumulating lysosomes, lymphocyte became vacuolisated („inclusion cells“).
- Pacients have: rough facial features, thickened gingiva, mild hepatomegaly and splenomegaly, bone disease – dysostosis multiplex, psychomotoric retardation, increased activity of lysosomal hydroxylases in plasma, but decreased activity in tissues.

Lysosomal diseases from deficiency of lysosomal hydrolases

Dannon's disease

- Deficiency in **LAMP2** (Lysosomal-associated membrane protein 2)

Cystinosis

- Deficiency in **cystinosin**
- **Clinical presentation:**
- Kidney disease with Fanconi's syndrome
- Renal failure requiring kidney transplant
- Crystals in cornea, photophoby
- Growth retardation
- Normal intelligence

Sialuria

- Deficiency in **sialin**

Lysosomal diseases from deficiency of enzyme activators of lysosomal hydrolases

- Lysosomes contain diffent hydrolases depending on where the sustrate is degraded. Defect in funtion of these enzymes leads to accumulation of substrate in the lysosomal apparatus of the cell. They include:
- **Lipidoses a Sphingolipidoses**
    - **Mucopolysaccharidoses**
    - **Mucopolysaccharidoses and glycoproteinoses**
    - **Glycogenoses (this includes only glykogenosis II - Morbus Pompe)**
    - **Proteinoses**

Lipidoses

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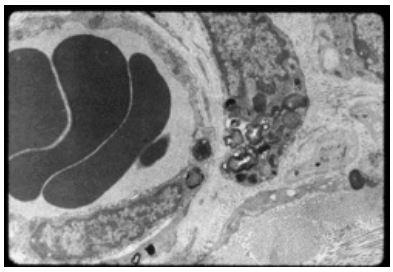
Lipidoses are **congenital disorders of enzymes** (enzymopathy) of lipid metabolism. These are mainly lysosomal hydrolases that break down complex lipids - characterized by the accumulation (accumulation, hoarding) of lipids in the lysosomal apparatus. Degradation of sphingolipid glycoconjugates takes place in lysosomes by gradual cleavage of sugar units from the non-reducing end of the chain by specific exohydrolases up 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 into the cytosol and esterified.

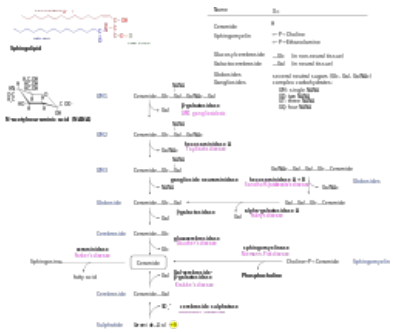
Due to the involvement of the nervous system, lipidoses are sometimes also referred to as **neurolipidoses**.



Conjunctival biopsy of a patient with Fabry disease. Laminar structures are visible in pericytes − lysosomes storing ceramide trihexoside

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).



Sphingolipidoses

Division

According to the place of 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).

Simplified breakdown 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 acid) to ceramide.

Gaucher disease

🔎 *For more information see Gaucher disease.*

- **Defect: glucocerebrosidase** deficiency causes accumulation of glucocerebrosides in the spleen (RES) and CNS.
- **Clinical symptoms:**
    - **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 the 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:** a characteristic finding is the so-called *Gaucher cells* - large lipid-storing macrophages, with "wrinkled" cytoplasm, first appear in the bone marrow, later also elsewhere (similar cells , so-called gaucheroid, 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, inhibiting glucocerebroside biosynthesis

Farber's disease

- this is **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 on 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" have also been described
    - neurological involvement is less common - hypotonia, denervation atrophy and myopathic changes
    - the basic features of late-onset forms include mitigated disability with a protracted course (clinically similar to classic Farber 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, belongs to the so-called **lipidoses** - lipid metabolic disorders. It arises from 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 **type A, B, C** , which differ in 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 damage, 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 in 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; progresses to lymphadenopathy and hepatosplenomegaly (rarely to cholestatic jaundice) within a few months
  - muscle weakness, hypotonia, psychomotor retardation appear, there is a gradual loss of motor functions, spasticity and muscle rigidity; xanthomay brownish-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 common 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 lung 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 activity of acid **sphingomyelinase** in leukocytes isolated from peripheral blood or cultured skin fibroblasts; a complementary examination in cases with a confirmed diagnosis is a DNA analysis
- **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 signs include manifestations after half a year of life and a rapid course
  - first there is increased irritability, hyperesthesia, 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
  - CSF protein 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 symptoms:** basic signs include gait disturbances, mental regression, and 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
  - CSF protein may not be elevated, peripheral nerve conduction velocity may be normal or decreased
  - the concentration of sulfatide in the urine is many times higher
- **Diagnosis:** is confirmed by determining the deficiency of arylsulfatase A activity in leukocytes isolated from peripheral blood or cultured skin fibroblasts; a complementary examination in cases with a confirmed diagnosis is a DNA analysis
- **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:** deficit activity 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 background of the eye, progressive psychomotor deterioration, macrocephaly, and exitus up to 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 - classic 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 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.*

- this is an **X-linked** disease, frequency 1:40,000
- **Defect:** deficiency in the activity of **alpha-galactosidase A activity**
- **Clinical symptoms:** basic signs include in hemizygotes (males) permanent or episodic acroparesthesia or burning pain of varying intensity, slightly 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 DNA analysis, however, it is necessary to confirm the heterozygous state
- **Prenatal diagnosis:** in families with enzymatically proven diagnosis 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 possible with the delivery of recombinant α-galactosidase A

Lysosomal diseases from deficiency of enzyme activators of lysosomal hydrolases

__ There are two types of activators:

- Saposins = SAP (sphingolipid activator protein) - these are several peptides, they contain about 80 amino acids
- GM2 activator (GM2A)

Saposins

Saposins are formed from a common precursor known as **prosaposin** (encoded by the PSAP gene), which is proteolytically cleaved into individual saposins in the early endosome phase - saposin A, B, C and D. Saposins are very stable proteins - resistant to strong proteases, high temperatures, extremely compact and rigid.

Saposins are sphingolipid-cleaving hydrolase activators

- **SAP A** - galactosylceramidase and lactosylceramidase enzyme activator
- **SAP B** - also known as GM1A, does not activate the enzyme directly, but reacts with the substrate; its function is to "pull" the glycolipid (substrate) from the lysosome membrane, i.e., without SAP B the hydrolase is active but has nothing to cleave
- **SAP C** - activates glycosylceramidase and galactosylceramidase; The function of SAP C is to activate and attach the enzyme to the membrane
- **SAP D** - participation in ceramide degradation

GM2A

The function of GM2A is to "pull" the glycolipid (GM2 ganglioside) from the membrane and allow contact of the substrate with β-hexosamidase; its function is therefore similar to that of SAP B (GM1A) - with the difference that it "pulls out" another substrate.

Diseases caused by a deficiency of lysosomal activators

In general, these diseases are very rare with the number of patients is in the tens. The deficit or mutation of activators causes the phenotype of the corresponding lysosomal sphingolipidosis.

- Prosaposin defect - there is a logical lack of all SAPs, i.e., very severe complete sphingolipidosis of the newborn, or the infant dies within 4 to 17 weeks; 6 cases described worldwide; AR disease
- **SAP A** deficiency or mutation causes the clinical picture of **Krabbe disease**
- **SAP B** deficiency or mutation causes the clinical picture of **Fabry disease** or **metachromatic leukodystrophy** (15 cases described worldwide)
- **SAP C** deficiency or mutation causes the clinical picture of **Gaucher disease** (3 cases described worldwide)
- **GM2** deficiency or mutation causes the clinical picture of **Sandhoff disease**
- **SAP D** deficit was not recorded

Activator deficiency is considered if the enzyme is functional, but there are still signs of lysosomal disease.

Links

References

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