Disorders of lysosomal metabolism / Lysosomal hydrolase deficiency

- Lysosomes contain different hydrolases depending on which stored substrate cleaves. Disorders of these enzymes lead to substrate accumulation in the lysosomal apparatus of the cell. Some of them are:
  - **Lipidoses and Sphingolipidoses**
  - **Mucopolysaccharidoses and glycoproteinoses**
  - **Glycogenoses**
  - **Proteinoses**

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

Lipidoses are sometimes referred to as **neurolipidoses** due to the nervous system.

Microscopy

Lysosome hypertrophy - microvacuolar, foamy to honeycomb appearance of cells. Subsequent regressive changes, including secondary lipopigment formation (ceroid and lipofuscin). The stored lipids are usually **gangliosides**, **cerebrosides**, **sphingomyelin**, **ceramide**, **cholesterol** and its **esters**. They mainly affect RES histiocytes, but also epithelium and endothelium (visceral lipidoses) or ganglion cells (neuronal lipidoses).

Types

According to the place of damage

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

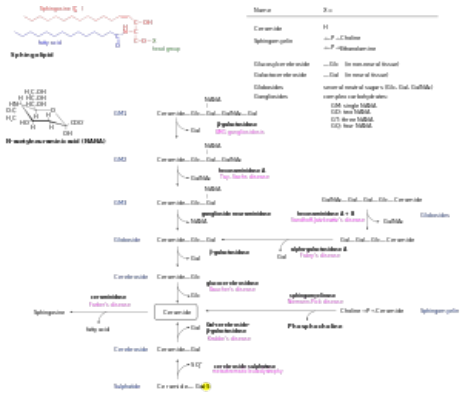
Lysosomal diseases of the CNS have two forms:

1. **ganglion cell** involvement - a thesaurative disease;
2. **white matter** involvement - leukodystrophy (disorders of myelin metabolism).

Simplified distribution of complex lipids

- **Phospholipids**:
  - *glycerophospholipids* - phosphatidic acid (3-phospho-1,2-diacylglyerol) + other component (choline, ethanolamine);
  - *sphingophospholipids* - ceramide (sphingosine + FA) + phosphate + other component (if it is choline, it is sphingomyelin).

- **Glycolipids** - contain ceramide (sphingosine + MK) with bound sugar component:
  - *cerebrosides* - binding of hexose (Glc, Gal) to ceramide;
  - *gangliosides* - binding of oligosaccharide with sialic acid (N-acetylneuraminic acid) to ceramide.



Sphingolipidosis

Gaucher's disease

More on Gaucher's disease

- **Defect**: **glucocerebrosidase** deficiency causes glucocerebrosid accumulation in the spleen (RES) and CNS.
- Clinical signs:
  - **type 1**:
    - the onset of the disease is in childhood, full of manifestations in adulthood
    - splenomegaly is typical, hepatomegaly is only mild, but cirrhosis is possible
    - bone marrow infiltration, pathological fractures and aseptic necrosis occur
    - massive lung involvement can lead to *cor pulmonale*; cutaneous hyperpigmentation and coincidence with various malignancies are also known

    - **type 2**:
        - the basic features include hepatosplenomegaly and severe neurological symptoms (trismus, strabism, retroflexion of the head, progressive spasticity, hyperreflexia and the emergence of pathological reflexes, in the terminal stage of hypotension)
    - **type 3**:
        - longer course of the disease and neurovisceral symptomatology around 1 - 3 years of age, 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 macrophages storing lipids, with "wrinkled" cytoplasm, first appear in the bone marrow, later 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**: i.v. delivery of the missing enzyme, inhibition of glucocerebroside biosynthesis

Farber's disease

- **AR disease**
- **Defect**: deficit of acid ceramidase **activity**
- **Clinical symptoms**: damage to the subcutaneous tissue and mucous membranes by deforming nodules caused by granulomatous scarring process - maximum changes are on the joints and around the tendon sheaths
    - the laryngeal disease leads to hoarseness and aphonia
    - heart valve disease, mild hepatosplenomegaly, retinal changes similar to the so-called "cherry spot" have also been described
    - neurological impairment is less common - hypotension, denervation atrophy and myopathic changes
    - the basic features of late-onset forms include a mitigated disorder with a prolonged 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

More on Niemann-Pick disease

Autosomal recessive hereditary storage disorder is one of the so-called **lipidoses** - lipid metabolic disorders. It is based on 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, and C**, which differs in metabolic disorder - **acid sphingomyelinase deficiency** (type A, B) vs. **lipid transport disorder** (type C).

Acute forms typical of childhood affect the nervous system, chronic ones manifest later in cholestatic liver disease, which progresses to cirrhosis. Secondary concentrations of non-esterified cholesterol increase.

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

- **type A** - the basic features include **neurovisceral damage** with death under 1-3 years of age (specifics increased incidence in the ethnic group of Ashkenazi Jews);
    - the problems appear in the first weeks of life
    - manifests itself in vomiting, diarrhea and general neonatal malnutrition to cachexia; within a few months it progresses to lymphadenopathy and hepatosplenomegaly (rarely to cholestatic icterus)
    - muscle weakness, hypotension, psychomotor retardation appear, there is a gradual loss of motor functions, spasticity and muscle rigidity; brown-yellow xanthomas may appear on the skin
    - about half of the patients have a so-called **cherry spot** on the retina
    - patients usually die by the age of 3

- **type B - chronic** disease (more common in southern Europe and northern Africa), can occur at any time from late childhood to adulthood
    - usually manifested by **splenomegaly** or **hepatosplenomegaly** (more severe liver disease is rare)
    - **reticulonodular X-ray infiltration of the lungs** is often associated with interstitial involvement, which can manifest itself in varying degrees of exertional dyspnea
    - it also slows growth, delays bone age and puberty
    - the intellect and nervous system are not affected
    - adults have a pathological lipid profile, thrombocytopenia and increased liver transaminases
    - there are various serious 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 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 an enzymatically proven diagnosis, analysis of native and cultured chorionic villi or cultured amniocytes is possible; an additional examination is the analysis of the ultrastructure of chorionic villi

- **Treatment**: recombinant enzyme therapy is being prepared

Krabbe disease (leukodystrophy)

- **Defect**: deficiency of **galactocerebroside β-galactosidase** activity
- **Clinical signs**: the basic signs include half-yearly manifestations and a rapid course
  - at first there is increased irritability, hyperesthesia, hyperacusis and increased photosensitivity, gradually there is psychomotor retardation, hypertonia and tonic and clonic seizures
  - in the final stage is decerebration, opisthotonus, blindness, or deafness
  - exitus letalis occurs around 2 years
  - a laboratory finding of increased levels of cerebrospinal fluid protein (especially albumin and alpha-2-globulin) at normal cell numbers, optic atrophy and signs of peripheral neuropathy (reduced peripheral nerve conduction velocity); EEG can be abnormal, often with focal seizures; on CT and NMR is the diffuse atrophy of the white matter of the brain
  - in forms with late onset of clinical symptoms are among the basic features - mental retardation, pyramidal disorders, reaction disorders, visual impairment
  - the protein in the cerebrospinal fluid may not be increased, the rate of peripheral nerve conduction may be normal or decreased
- **Diagnosis**: is confirmed by determination of galactocerebroside-b-galactosidase deficiency 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 disorders, mental regression, ataxia, speech loss, peripheral neuropathy, quadriparesis, optic nerve atrophy, macular gray discoloration
  - the disease lasts for several months
  - a laboratory finding of increased levels of cerebrospinal fluid protein (especially albumin and alpha-2-globulin) at normal cell numbers, optic atrophy and signs of peripheral neuropathy (reduced peripheral nerve conduction velocity); EEG can be abnormal, often with focal seizures; on CT and NMR is the diffuse atrophy of the white matter of the brain
  - in forms with late-onset of clinical symptoms, the basic features include mental retardation, psychotic symptoms, pyramid disorders, reaction disorders, visual impairment
  - the protein in the cerebrospinal fluid may not be increased, the rate of peripheral nerve conduction may be normal or decreased
  - in the urine is a many-fold increased concentration of sulfatide

- **Diagnosis**: is confirmed by determination of arylsulfatase A deficiency 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 signs**: 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 symptoms, hypotony, myoclonus, convulsions, as well as a cherry spot on the back of the eye, progressive psychomotor deterioration, macrocephaly, and exitus within 2-4 years; the incidence is high among Ashkenazi Jews
  - in the *infantile type with a later onset*, the basic symptoms include central neurological symptomatology and thesaurus retinopathy
    - neurological disability is very variable - it can be dominated by classic CNS involvement (dystonia, extrapyramidal symptoms, ataxia), but there may also be a picture of juvenile spinal muscle atrophy (Kugelberg-Welander type), systemic atrophy close to amyotrophic lateral sclerosis or progressive spinocerebellar ataxia Friedreich
  - accumulation of GM2 ganglioside in the brain is typical

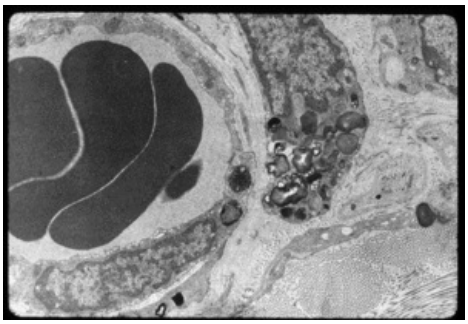
- **Diagnosis**: is confirmed by determining the deficiency of N-acetyl-beta-D-glucosaminidase A activity in leukocytes isolated from peripheral blood or cultured skin fibroblasts

- **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

More on Fabry disease

- it is an **X-linked** disease, frequency 1:40 000
- **Defect**: **alpha-galactosidase A** activity deficiency
- **Clinical signs**: basic features in hemizygotes (men) include persistent or episodic acroparesthesia or burning pain of varying intensity, slight fever and sedimentation
  - sowing of skin angiokeratomas, corneal opacity and deformities of retinal and conjunctival vessels are characteristic
  - renal impairment includes lipiduria, proteinuria and progressive insufficiency
  - cardiovascular disease includes hypertension (renal), myocardial hypertrophy (cardiomegaly) and ischemic changes in various organs, especially the brain
  - central neurological symptomatology may be present
  - in heterozygotes (women) the disability is different - fully developed symptoms to their complete absence
  - urinary concentrations of globotriaosylceramide are many times increased



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

- **Diagnosis**: is confirmed by determination of α-galactosidase A deficiency in leukocytes isolated from peripheral blood or in cultured skin fibroblasts; DNA analysis is an additional test in cases with a confirmed diagnosis, but it is necessary to confirm the heterozygous condition
- **Prenatal diagnosis**: in families with an enzymatically proven diagnosis, it is possible in native and cultured chorionic villi or cultured amniocytes; an additional examination is the analysis of the ultrastructure of chorionic villi
- **Treatment**: therapy is also possible by delivery of recombinant α-galactosidase A

Links

Related articles

- Glycogenosis
- Glycoproteinosis
- Mucopolysaccharidosis

References

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