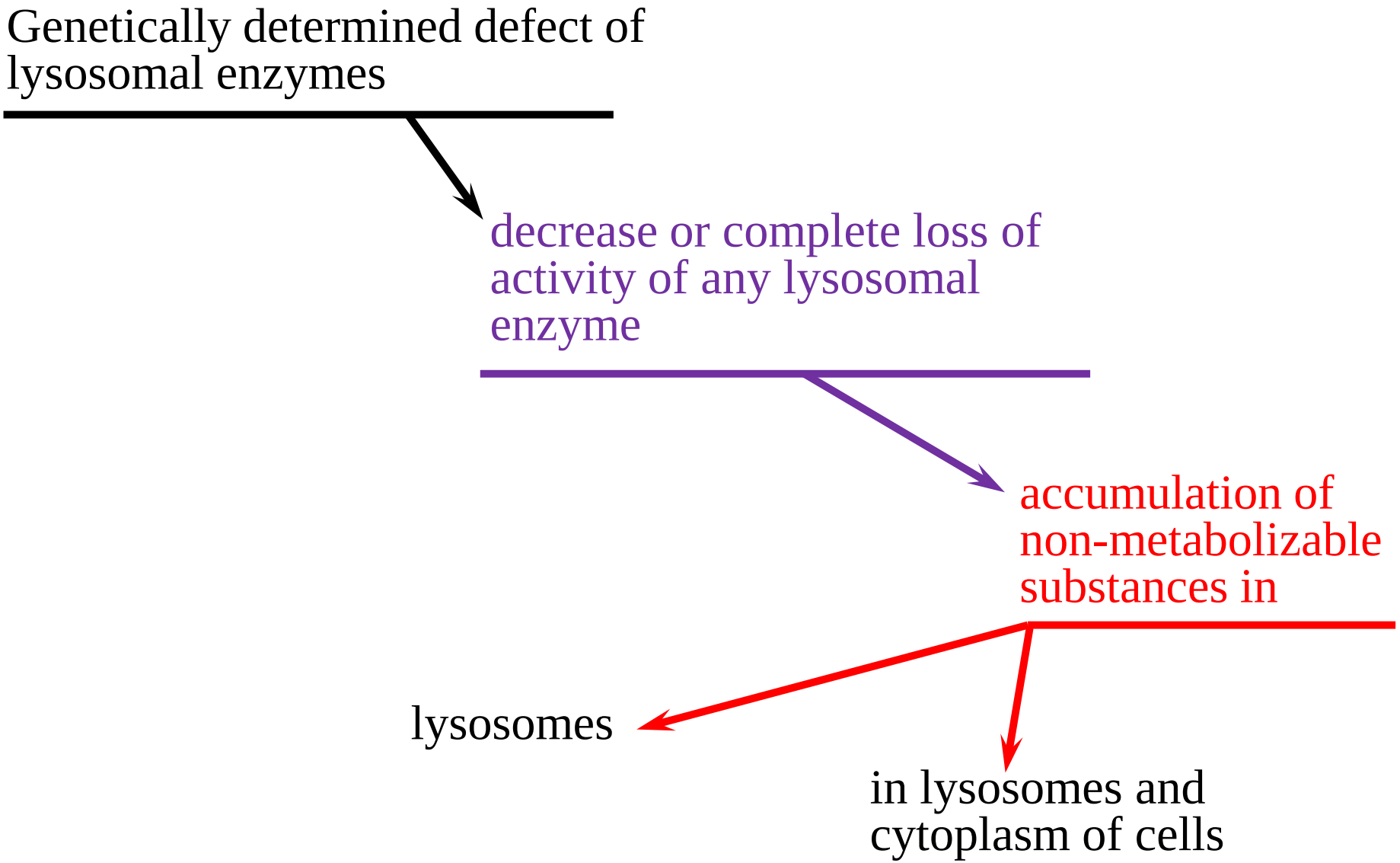
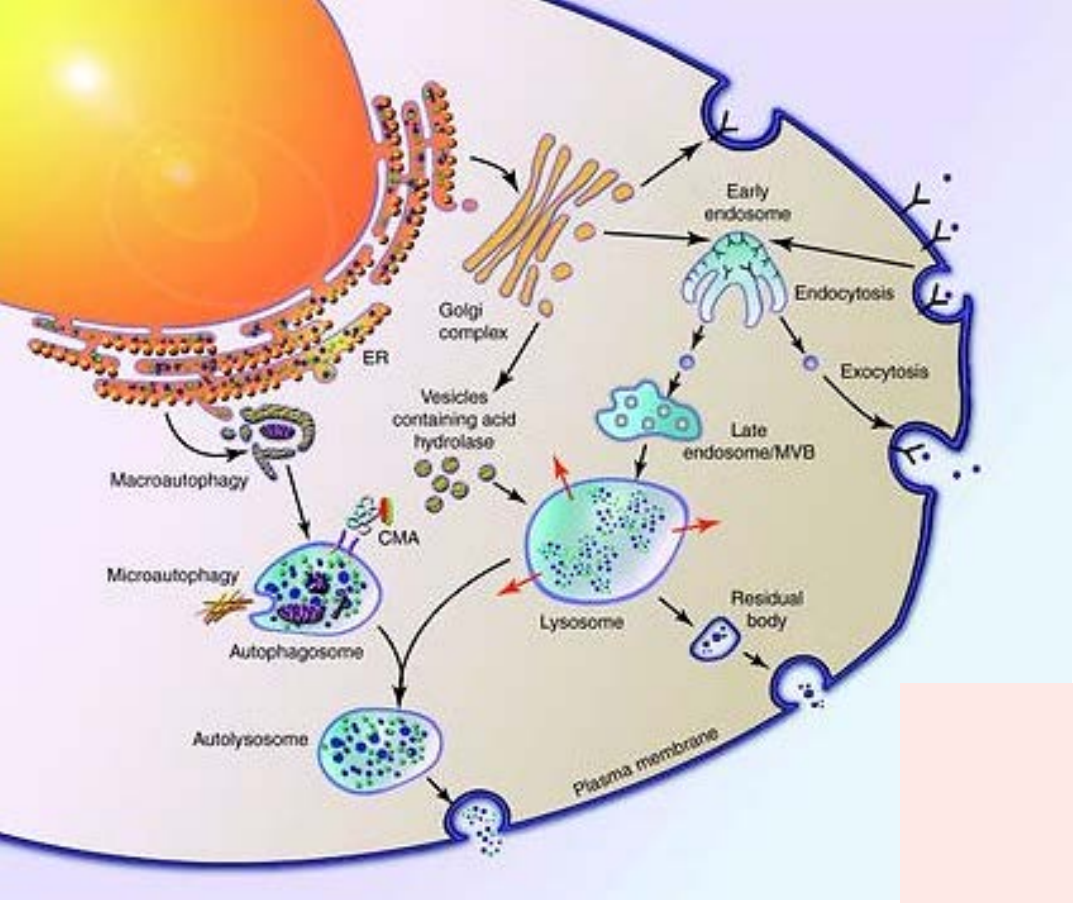
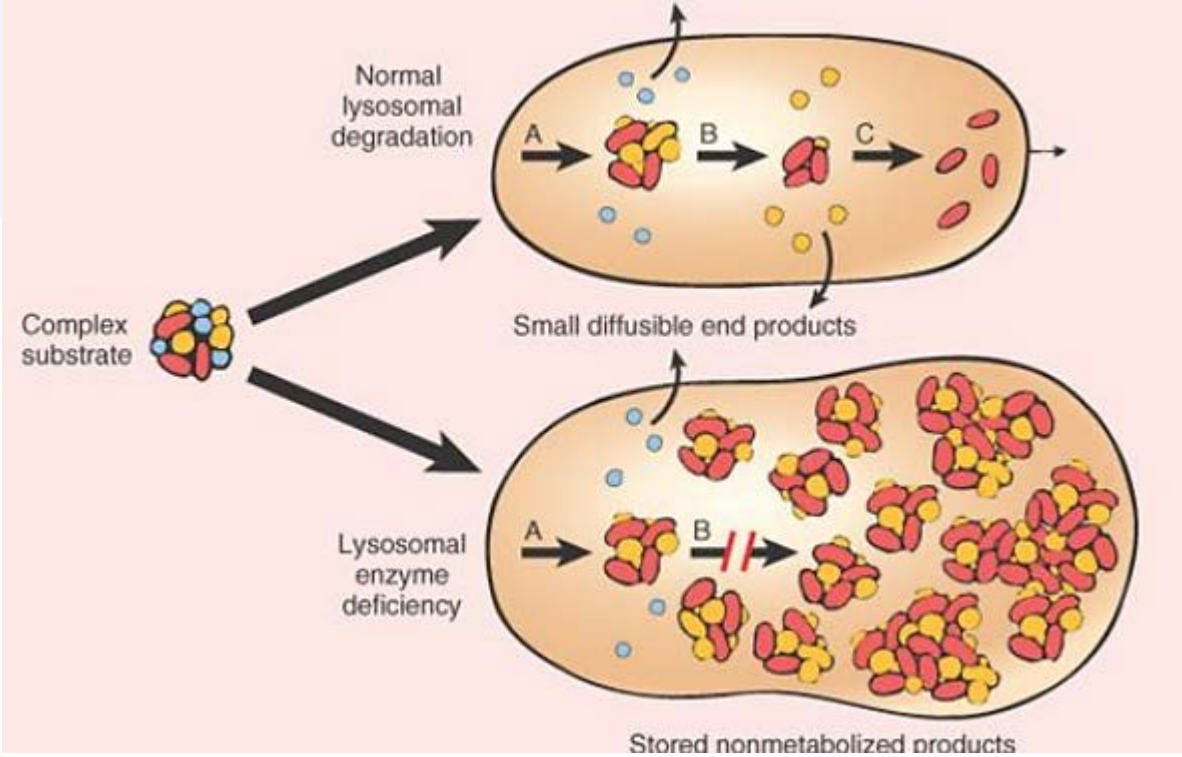
Lecture 4.

Storage diseases

Lysosomal storage disease




Early endosome
Endocytosis
Golgi complex
ER
Exocytosis
Vesicles containing acid hydrolase
Late endosome/MVB
Macroautophagy
CMA
Microautophagy
Lysosome
Residual body
Autophagosome
Autolysosome
Plasma membrane


Normal lysosomal degradation
A
B
C
Complex substrate
Small diffusible end products
Lysosomal enzyme deficiency
A
B
Stored nonmetabolized products

Lysosomal storage disease

There are three groups of diseases

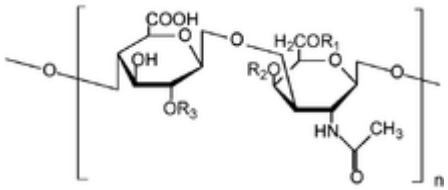
1. Mucopolysaccharidosises

2. Sphingolipidosis

3. Mucolipidosises

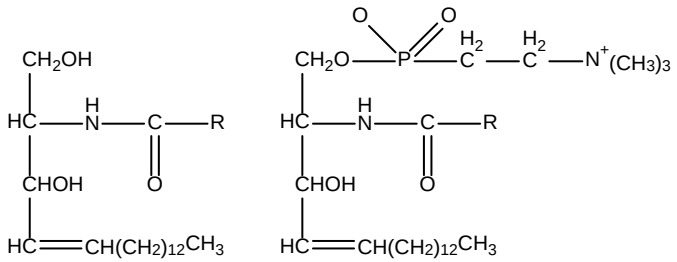
STORAGE

mucopolysaccharides



in the body they are covalently bound to the protein part of proteoglycans and do not occur in free form

sphingolipids



sphingosines and their N-acylated derivatives of ceramides

acid lipids and other chemicals

Clinically storage diseases are divided into two types

with a primary lesion

nervous system

muscular system

leukodystrophies
(degenerative diffuse brain sclerosis)
generalized demyelination of the nervous system-loss of nerve fibers of their myelin sheaths

Mucopolysaccharidosis
es violation of the cleavage of mucopolysaccharides-generalized glycogenosis

Diseases, associated with sphingolipid metabolic disorders

Tay-Sachs Disease

272800 15q23 Autosomal recessive disease
β-hexosaminidase a deficiency
Accumulating substance-GM2-ganglioside

Three types

Acute infantile
the most common Symptoms occur a few months after birth. For progressive: motor skills deteriorate rapidly, develops blindness, deafness, paralysis.
Death within 2-3 years.

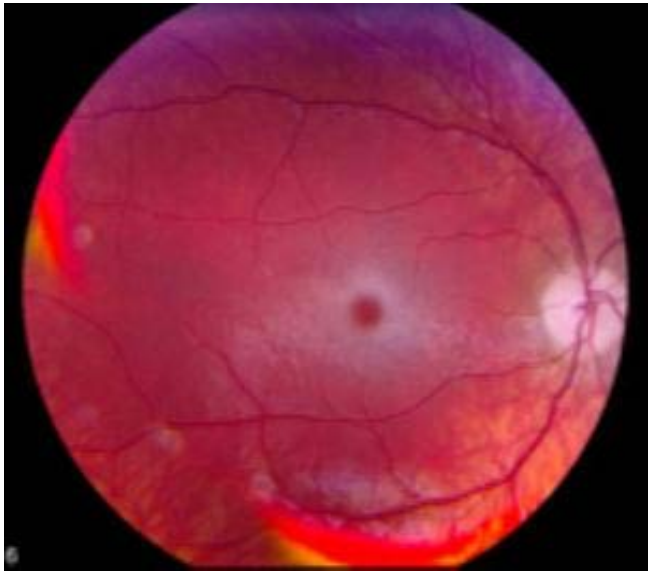
Late juvenile
Is extremely rare. The first manifestations in the period from 2 to 10 years. Gradually disintegrate acquired complex skills-walking, speech, writing. Average life expectancy – 15 years

Chronic adult
Isolated cases of this form, which begins at 25-30 years, are described. Violation of speech, arbitrary motor acts, mental disorders (psychosis). The prognosis of mortality is unknown.

Tay-Sachs Disease

Symptoms:

Newborns with this disease develop normally in the first months of life. At the age of about six months there is a regression in mental and physical development. The child loses sight, hearing, the ability to swallow. There are seizures. The muscles atrophy and paralysis sets in. Tay-Sachs Disease is characterized by the presence of a red spot (a symptom of a "cherry stone") located on the retina opposite the pupil. This spot can be seen with an Ophthalmoscope.



Gaucher Disease

Three main types

Аутосомно-рецессивное заболевание

Type I

Gaucher disease I (neuronopathic) occurs with a frequency of 1/50000. Most often – among Ashkenazi Jews (incidence 1/450)

230800

1q22

Deficiency of acid β-glucocerebrosidase

Glucosylceramide accumulation

Type II

Gaucher disease II (neuronopathic infantile form)

The incidence is 1/100000, ethnic predisposition does not have

230900

1q22

Deficiency of acid β-glucocerebrosidase

Accumulation glucosylceramide

Type III

Gaucher disease III (subacute neuronopathic (juvenile) form)

Type 3 can begin in both childhood and adults with a incidence of 1/100000

231000

1q22

Deficiency of acid β-glucocerebrosidase

Accumulation glucosylceramide

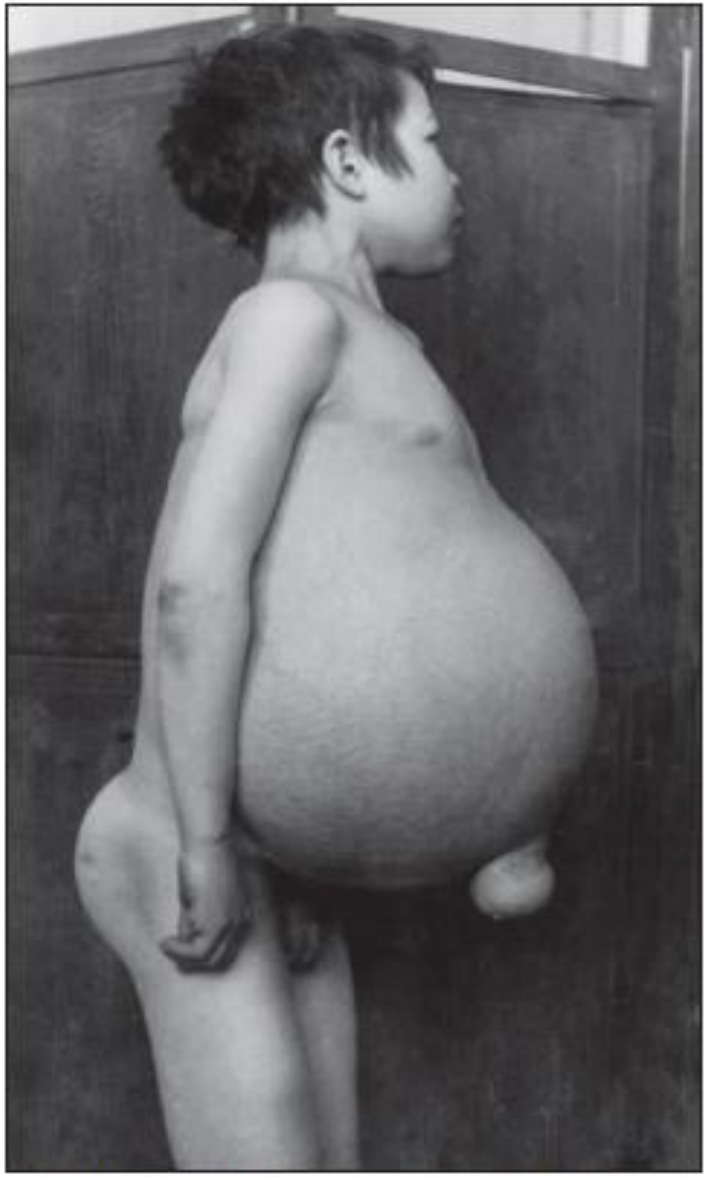


Рисунок 1. Пациент с болезнью Гоше (наблюдение проф. А.Я. Губергрица)

Gaucher Disease I

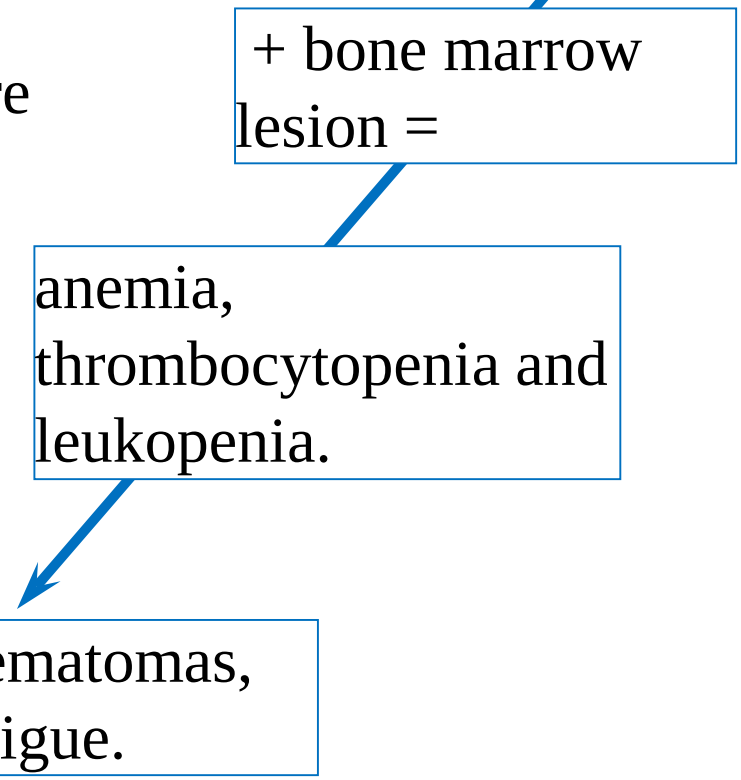
Begins in childhood or in adulthood.

Symptoms-enlarged liver and severely enlarged **spleen**

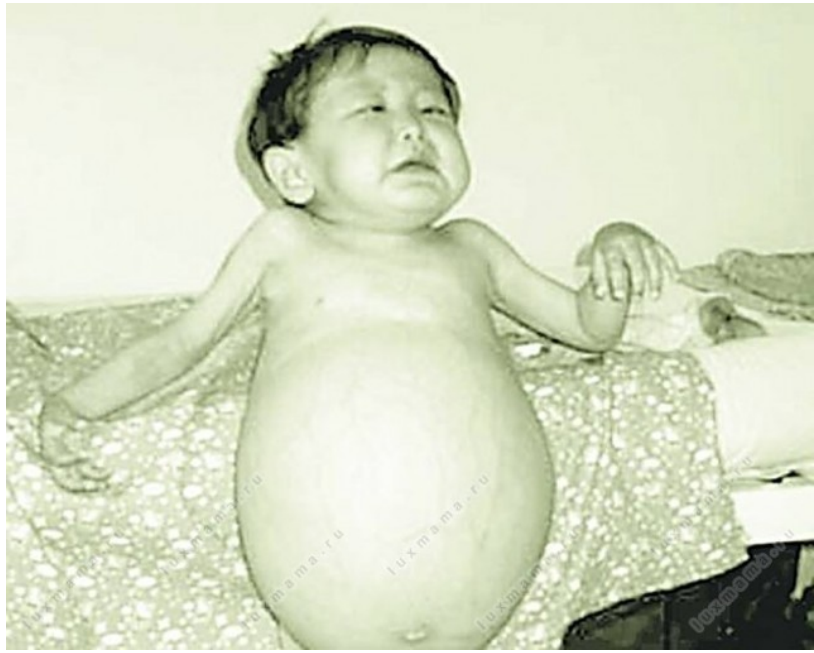
tears and additional damage.

A possible weakness of the bones and severe bone diseases.

There may be lung and kidney disorders.



Gaucher Disease II



The Manifesto of the disease of 3-5 months.

Neurological complications (severe seizures, hypertension, apnea, severe mental retardation) are manifested by 6 months.

Symptoms include hepatosplenomegaly, widespread progressive brain damage, impaired eye motility, spasticity, convulsions, limb rigidity.

Sick children suck and swallow poorly; usually die between the ages of one and two.

Gaucher Disease III

Most have slow progression and moderate neurological symptoms.
The first neurological sign is usually oculomotor apraxia, a disorder of oculomotor functions.
As the disease progresses, join:

- ataxia,
- muscle spasticity and
- dementia.

Splenomegaly is painless and usually detected by accident.
Patients live to adolescence and adulthood.
One of the main causes of disability in type 1 and 3 Gaucher disease is bone tissue damage due to the accumulation of lipids in osteoclasts and the replacement of normal elements of the bone marrow by Gaucher cell infiltrates.
Cases of severe liver failure are rare.
More common relative portal hypertension as a consequence of fibrosis.

Fabry's Disease

301500 Xq22. 1 X-linked disease.

BUT! Heterozygous women with Fabry's disease experience significant life-threatening conditions that require medical treatment and intervention.

Deficiency of α-galactosidase A.

Accumulates-globotriaosylceramide or ceramide trihexoside.

Prevalence from 1/40. 000 to 1/120.000 live newborns.

Symptoms:

generalized autonomic neuropathy, pain and paresthesia in the limbs, chest,

abdomen, due to lesions of the spinal nodes and peripheral nerves;

angioectasia in the form of red-purple nodules in the lower part of the trunk with hyperkeratosis; cardiopathy and nephropathy, dementia, cerebral circulation disorders of ischemic or hemorrhagic type.

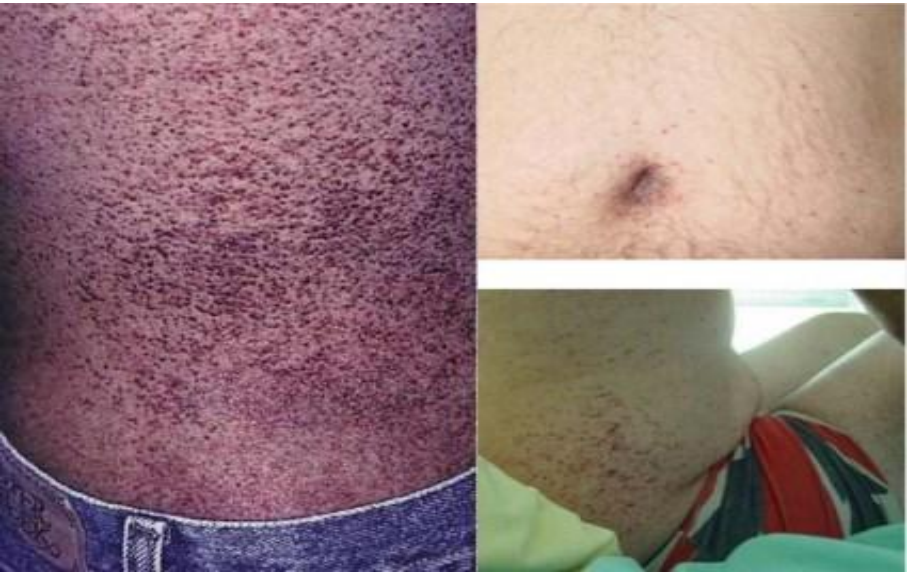
Polysystem manifestation.

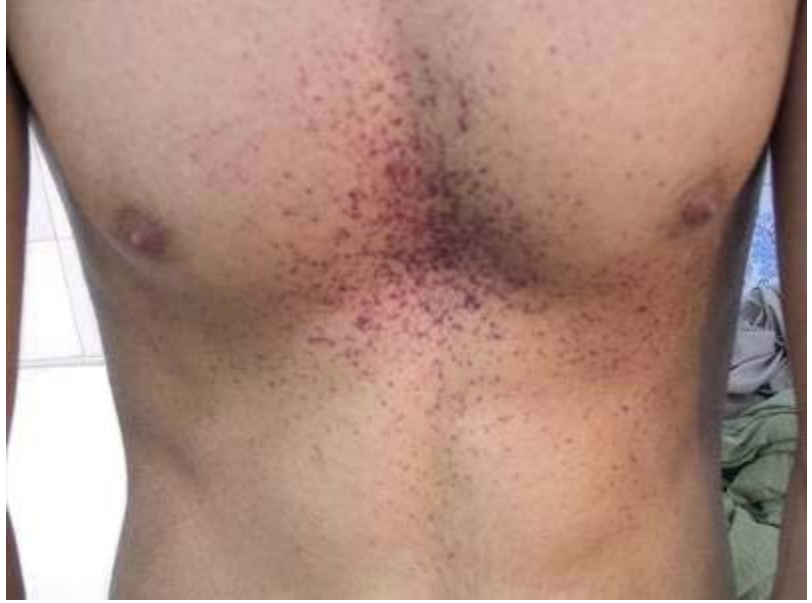
The final stage is due to vascular complications (stroke, myocardial infarction, renal failure).

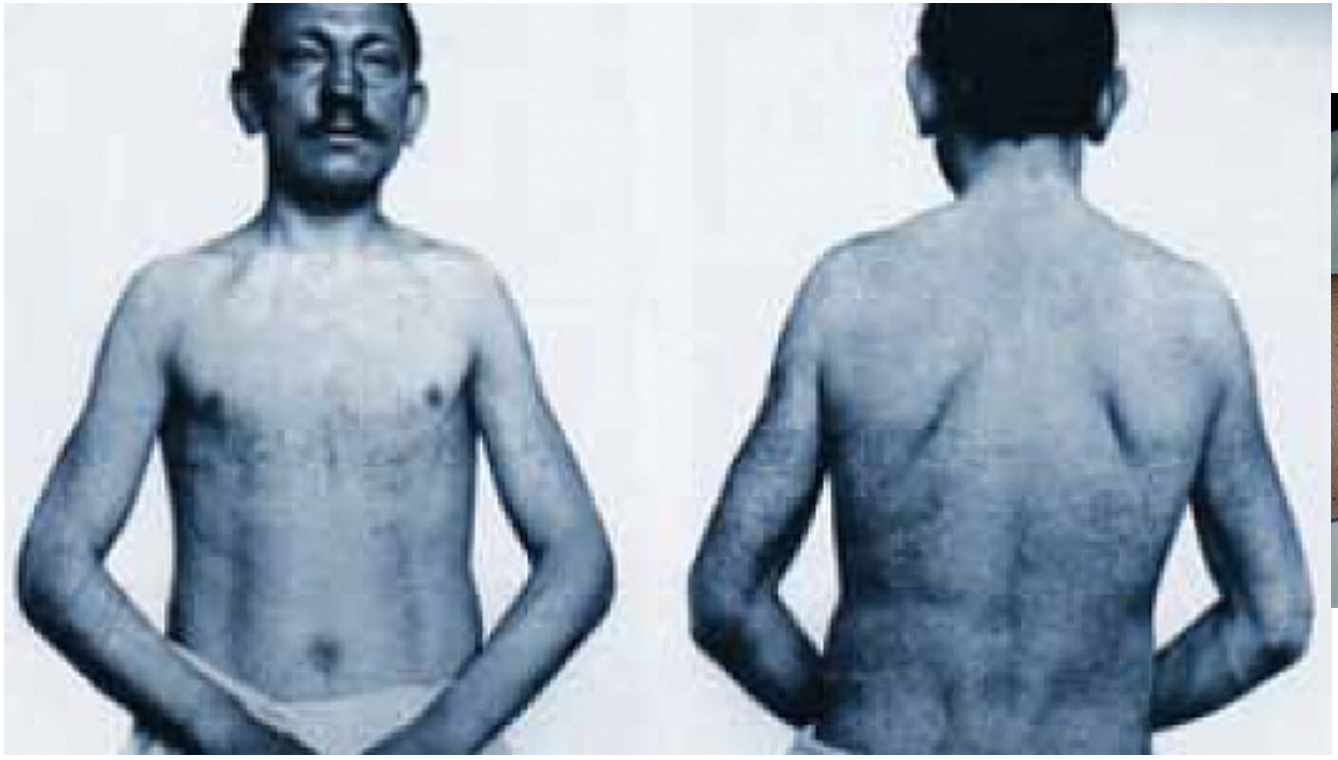
Polysystem manifestations

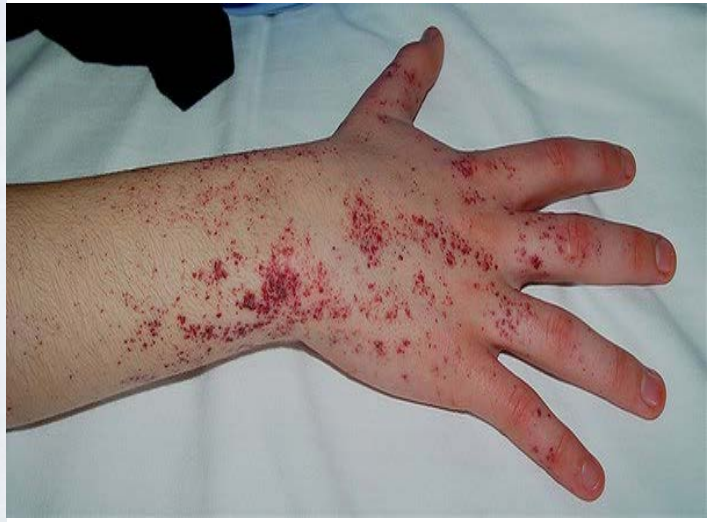
Progressive accumulation of GL-3 associated with progressive involvement of multiple organs and systems:

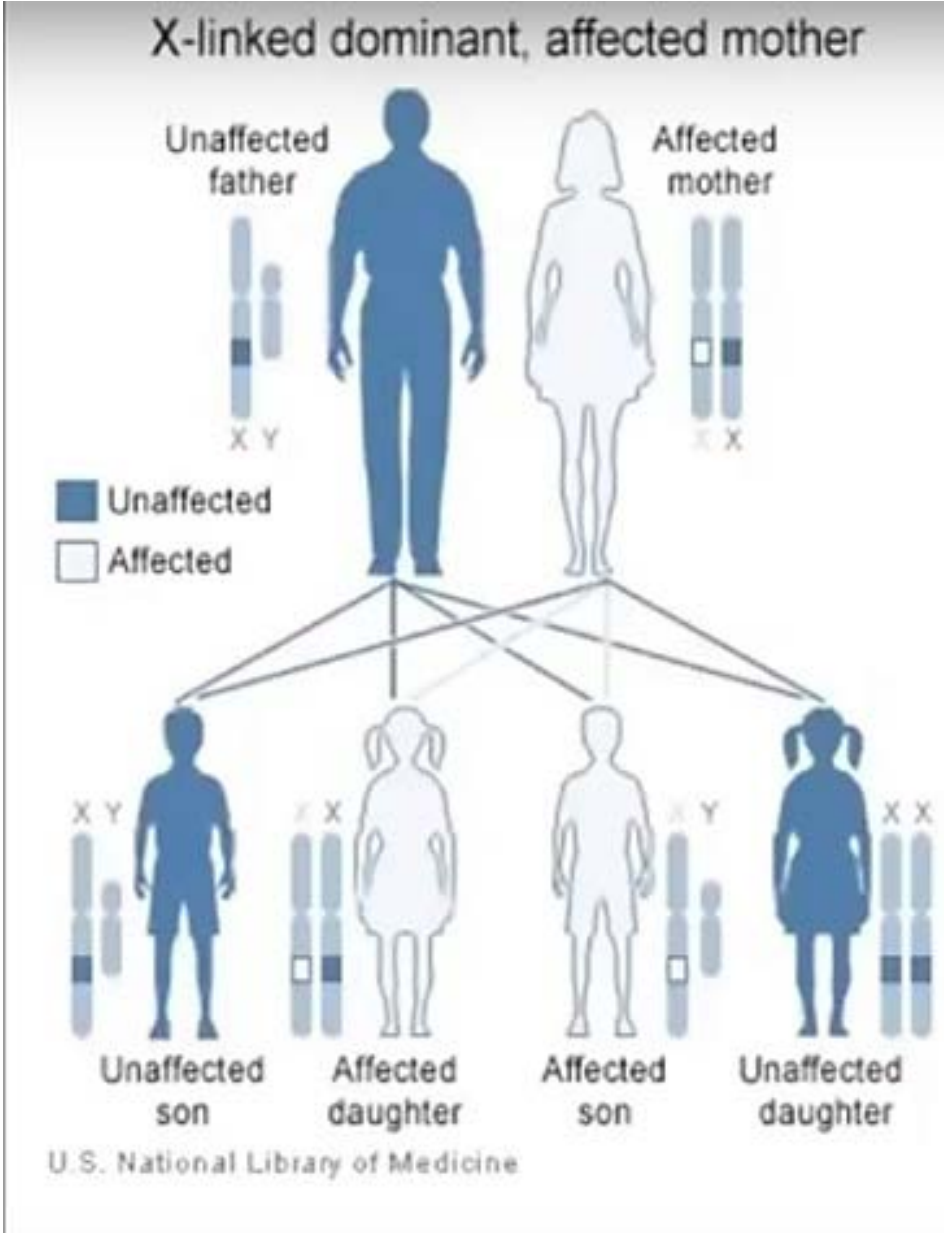
- Neurological
- Dermatological
- Ocular
- Gastrointestinal
- Renal
- Cardiological
- Cerebrovascular

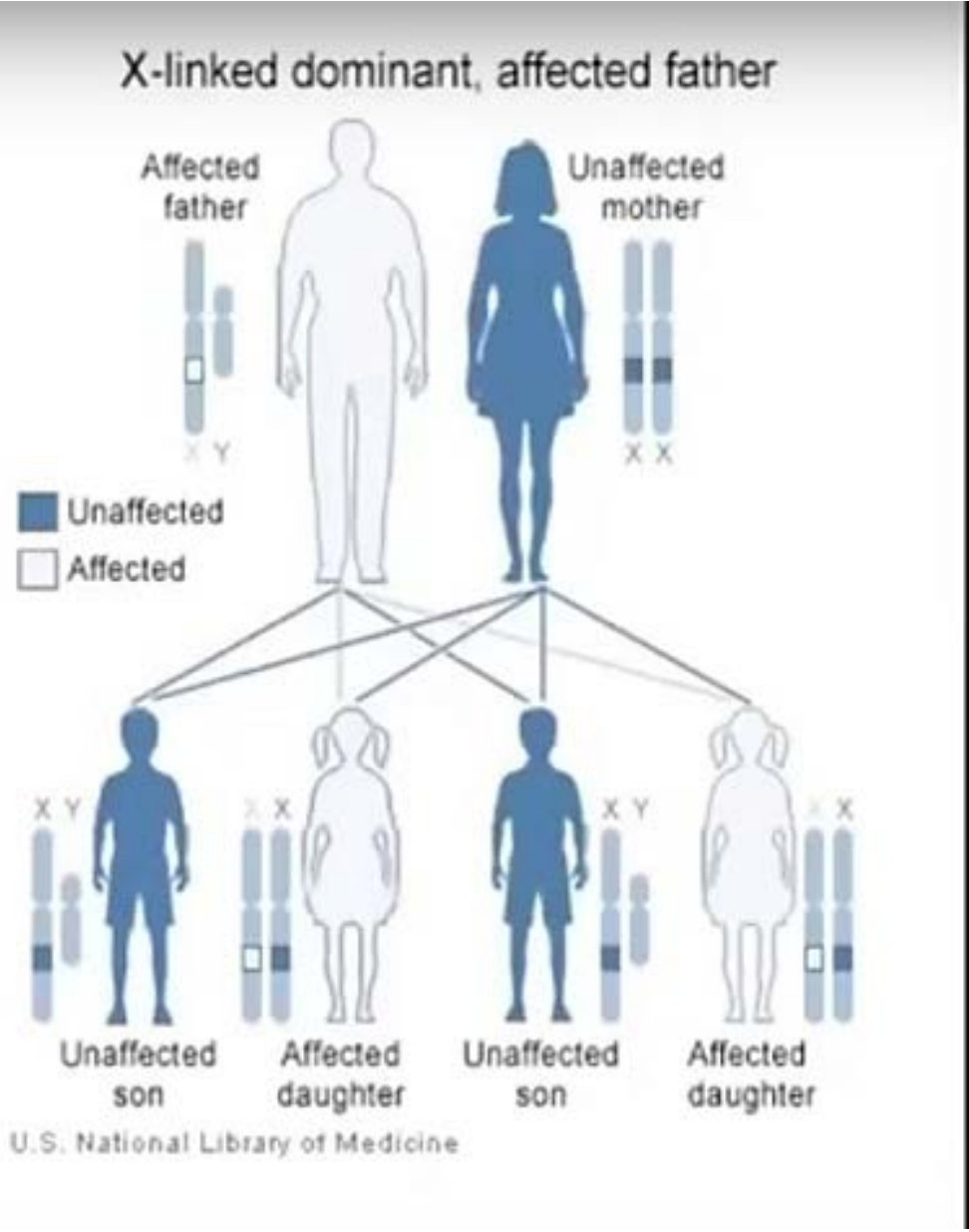




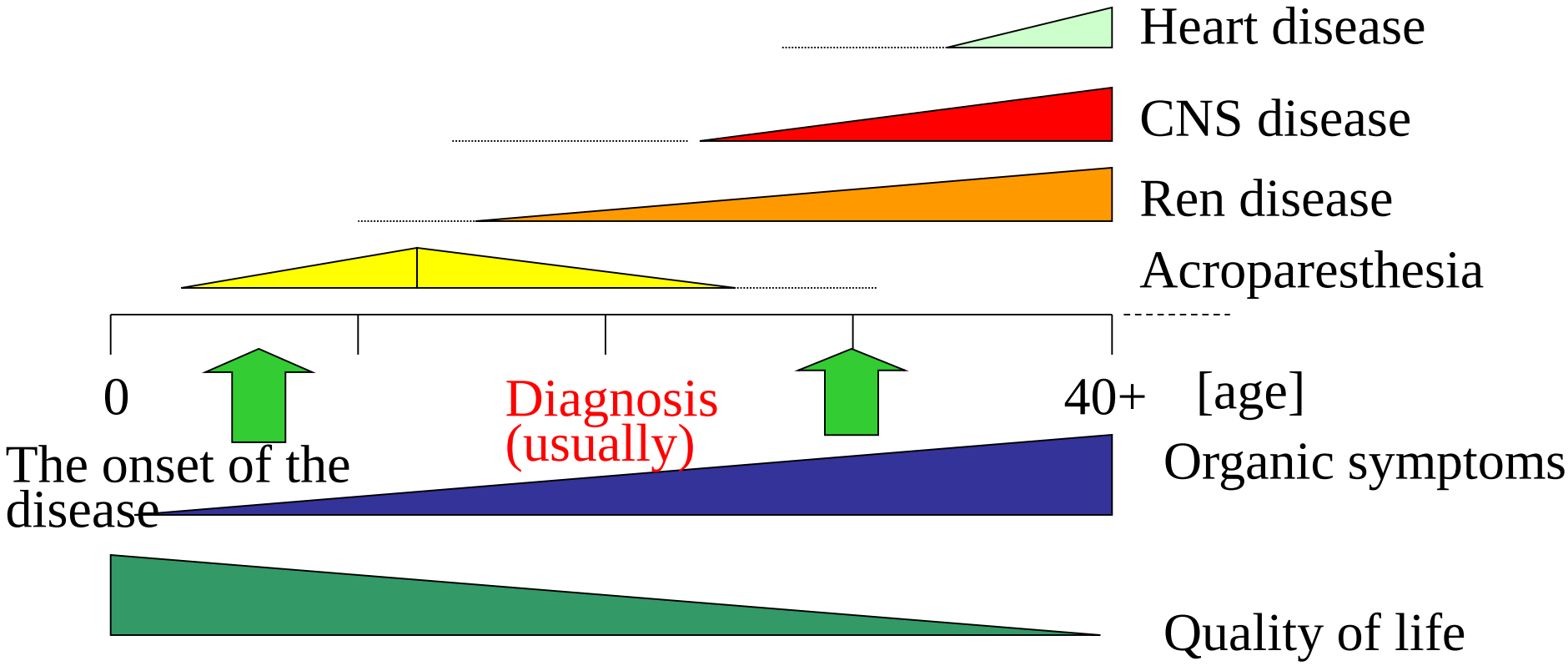


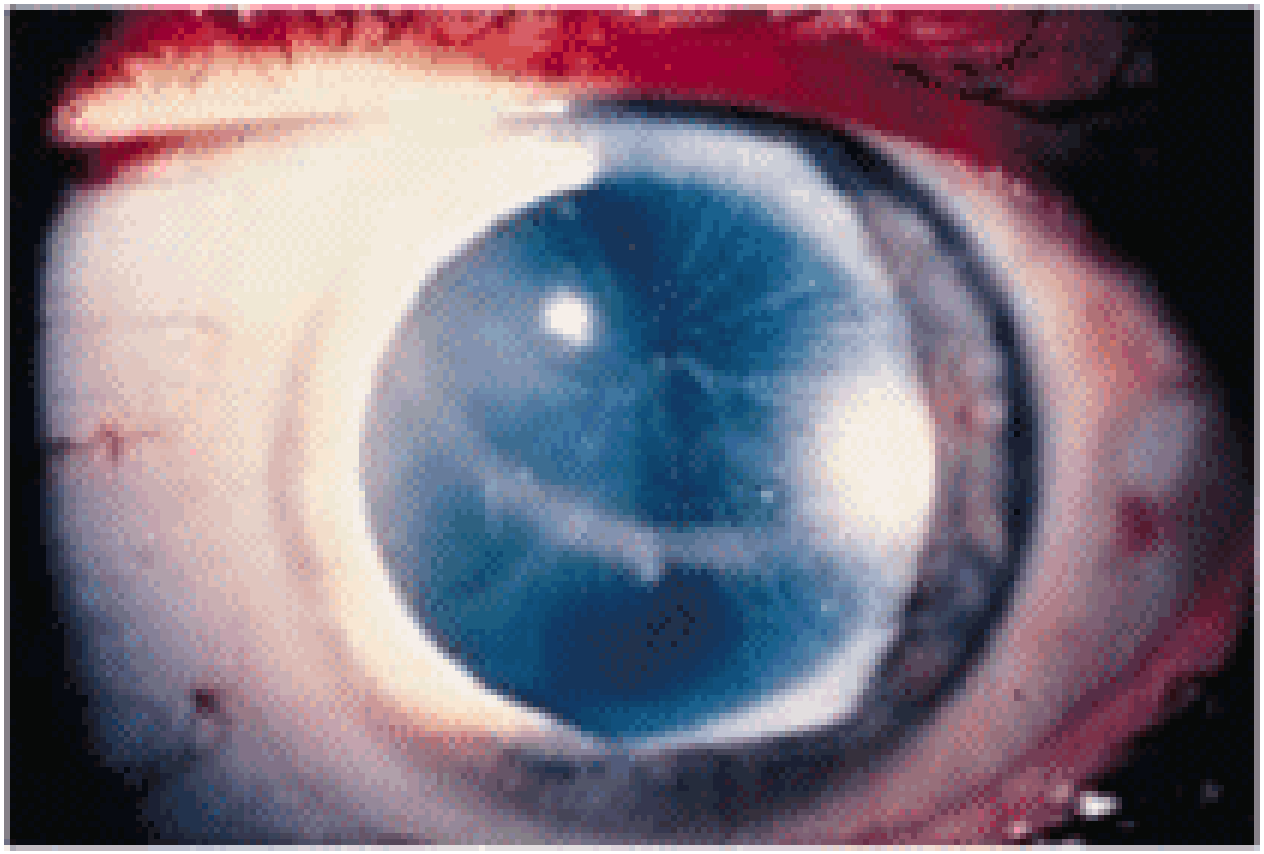



X-linked dominant, affected mother
Unaffected father
Affected mother
X Y
X X
Unaffected
Affected
X Y
X X
X Y
X X
Unaffected son
Affected daughter
Affected son
Unaffected daughter
U.S. National Library of Medicine


X-linked dominant, affected father
Affected father
Unaffected mother
X Y
X X
Unaffected
Affected
X Y
X X
X Y
X X
Unaffected son
Affected daughter
Unaffected son
Affected daughter
U.S. National Library of Medicine

Progression of Fabry's disease





Spicelike corneal opacity in Fabry's disease

Diagnostics - inspection on the slit lamp

Due to the accumulation of GL-3 in the walls of corneal vessels

Does not lead to vision loss

Diagnostics:

A decrease in the activity α-galactosidase

- plasma
- leukocytes
- skin graft

Increase of GL - 3 level in plasma or urine

The sad reality

- 9 specialists before diagnosis
- 15 years of symptoms before diagnosis
- Often a wrong diagnosis

Why so? - lack of awareness of doctors!

Specific therapy

- Enzyme replacement therapy substitution α-GAL
  - Fabrazyme® (agalsidase beta)
  - Replagal ® (agalsidase alfa)
- Gene therapy
  - replacement of the gene responsible for function α-GAL
- Substrate suppressing therapy
  - Blocking or inhibition of the synthesis of the substrate

Fabrazyme® (agalsidase beta) for the treatment of Fabry's disease

Recommended dose and mode of administration:

1 mg/kg patient body weight

Every 2 weeks

Infusion time-at least 2 hours

The results of the therapy

- Stabilization of kidney function
- Long lasting supportive effect
- Reducing the risk of cardiocerebral complications
- No additional risks associated with long-term therapy were identified.

Niemann-Pick Disease

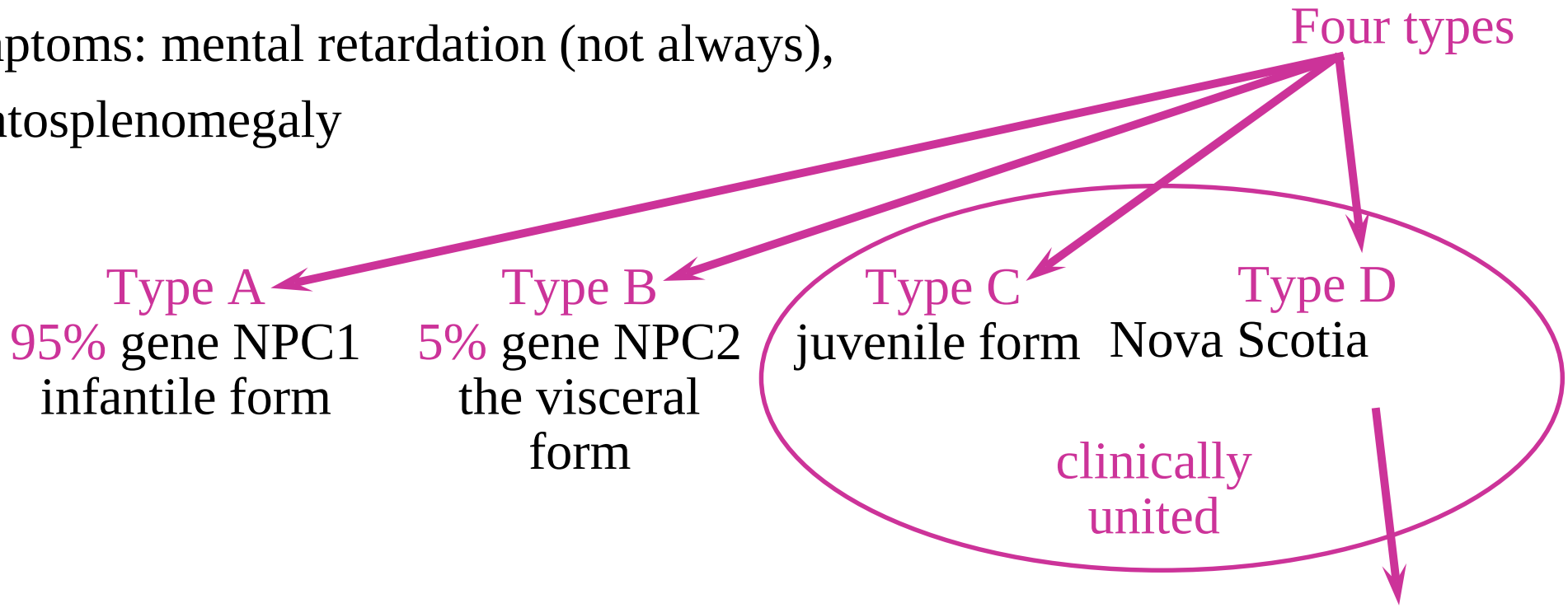
257220 18q11.2 Autosomal recessive inheritance

Deficiency of sphingomyelinase

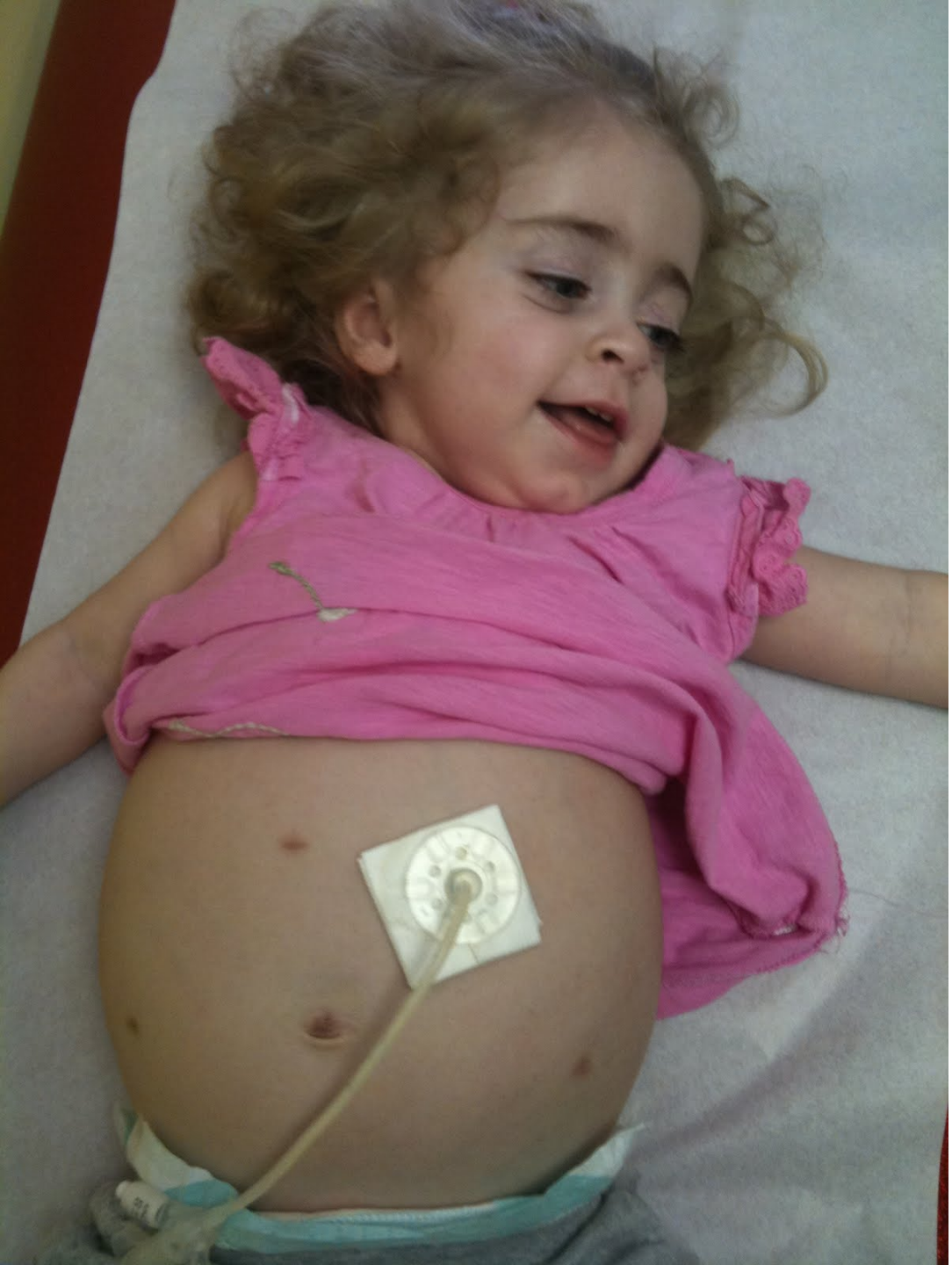
Accumulates-sphingomyelin primarily in the liver, spleen, lungs, bone marrow and brain.

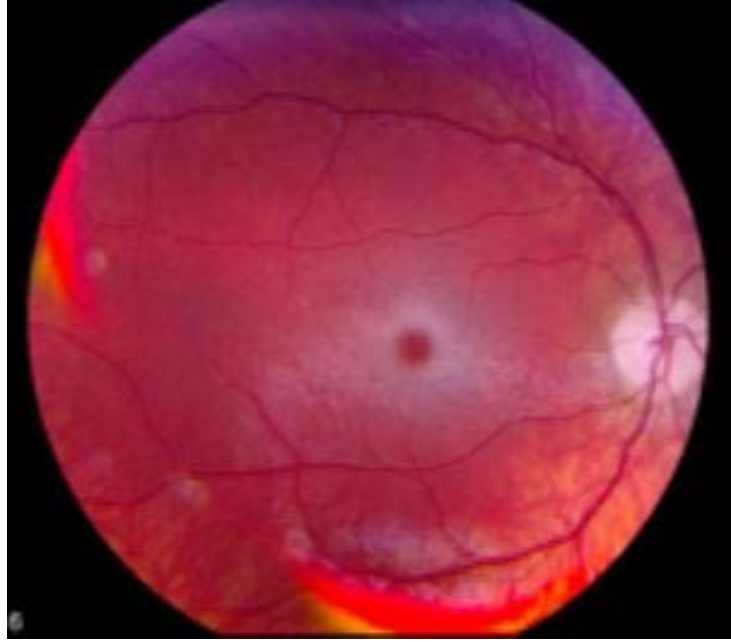
Symptoms: mental retardation (not always),

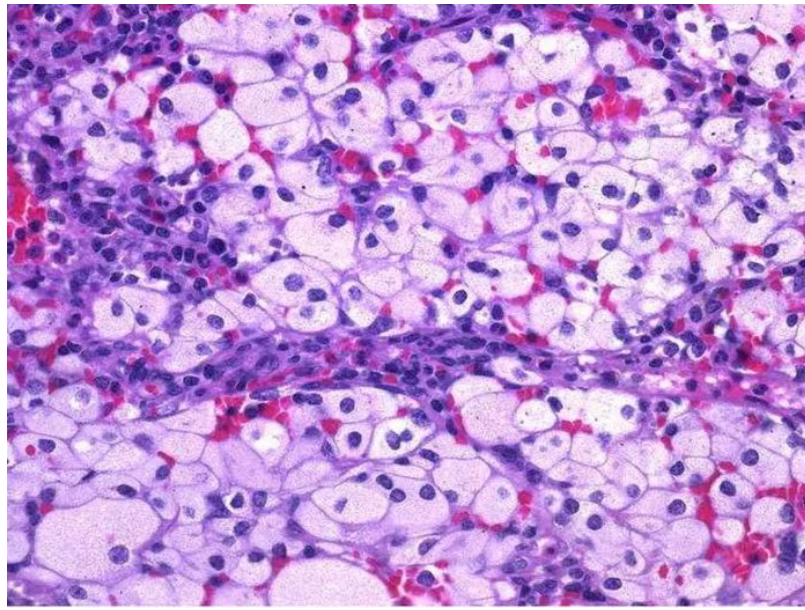
hepatosplenomegaly



Nova Scotia
The Arcadian origin
A province in southeastern Canada







Frothy cells

http://niemannpick.blogspot.com/2011/05/

Manifesto in infancy, mainly in the first half of the year.

Initial symptom:

- refusal of the child from food,
- periodic vomiting,
- sharp weight loss with the development of hypotrophy, a delay of psychophysical development,
- gradual enlargement of the liver and spleen, when palpated they are dense, with a smooth surface, painless, later, ascites develops.

The skin has a waxy hue with areas of increased pigmentation. There is a lesion of the nervous system. Further develops hypotonia of the muscles, expressed sharp backlog of the child in mental development, idiocy, deafness, in many patients, there comes an atrophy of the optic nerve. The disease can occur with a predominant lesion of the nervous system, liver, spleen.

Specific treatment is not developed!

The prognosis is unfavorable. The disease quickly leads to exhaustion and death. Survival beyond the age of five is extremely rare.

Farber's Lipogranulomatosis

228000 8p22 Autosomal recessive inheritance
Acid ceramidase deficiency
Accumulates – ceramide

Genodermatosis. Manifest in the newborn period-nodular erythematous foci of compaction of the skin of a testy consistency, localized in the joints (initially wrist), as well as in the places of skin injury. Histologically, the skin seals are lipogranulomas.
Symptoms: hepatosplenomegaly, arthralgia, convulsive syndrome, pyramidal and extrapyramidal disorders, mental and motor development delay.
In the nervous system, both neurons and glial cells are filled with non-sulfated glycosaminoglycans.
Patients die at the age of 2-4 years from pulmonary complications.
Symptomatic treatment: vitamins, lipotropic agents.

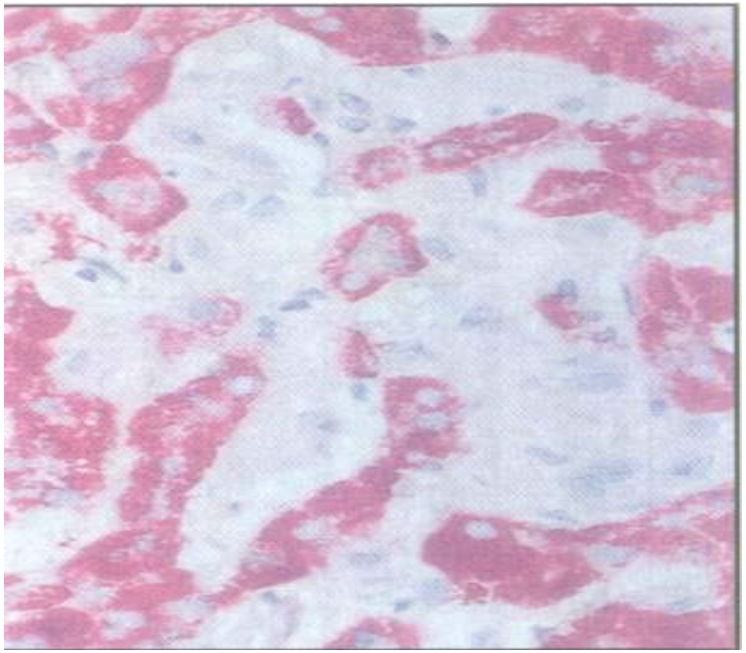
The mucopolysaccharidoses (glycogenoses) VIII типов

OMIM	Localization	Deficit	Glycogen storage disease, type:
# 232200	17q21. 31 gene G6PC	Glucose-6-phosphatase	Ia (von Gierke disease)
# 232300	17q25. 3 gene GAA	Acid maltase (alpha-1,4-glucosidase)	II (Pompe disease)
# 232400	1p21. 2 gene AGL	Amyli-1,6-glucosidase	IIIa; IIIb (Forbes-Cori disease)
# 232500	3p12. 2 gene GBE1	D-1,4-glucano-α-glucosyltransferase	IV, Andersen's disease
#232600	11q13. 1 gene PYGM	muscle glycogen phosphorylase	V; McArdle's disease
# 232700	14q22. 1 gene PYGL	liver glycogen phosphorylase	VI; Gers disease
# 232800	12q13. 11 gene PFKM	muscle isoform of phosphofructokinase	VII; Tarui disease
# 306000	Xp22.13 gene PHKA2	hepatic phosphorylase kinase	VIII; IXa1, X-linked liver glycogen storage disease

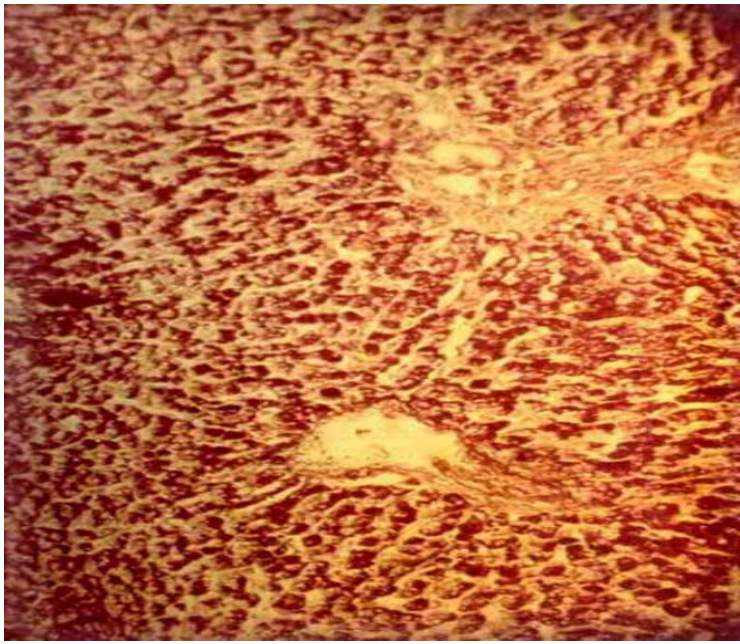
Glycogen storage disease I
(nepropagande glycogen storage disease,
or illness Gierke)

1 : 2000 **AR** ♂=♀

Manifest during the first year of life with severe hypoglycemia and hepatomegaly caused by the accumulation of glycogen in the liver and kidneys. Growth retardation, puberty, lactic acidemia, hyperlipidemia, hyperuricemia, in adults-high incidence of liver adenomas. The body meets its energy needs by enhancing fat metabolism → hyperlipidemia, fatty degeneration of the liver, kidneys, xanthomatosis.



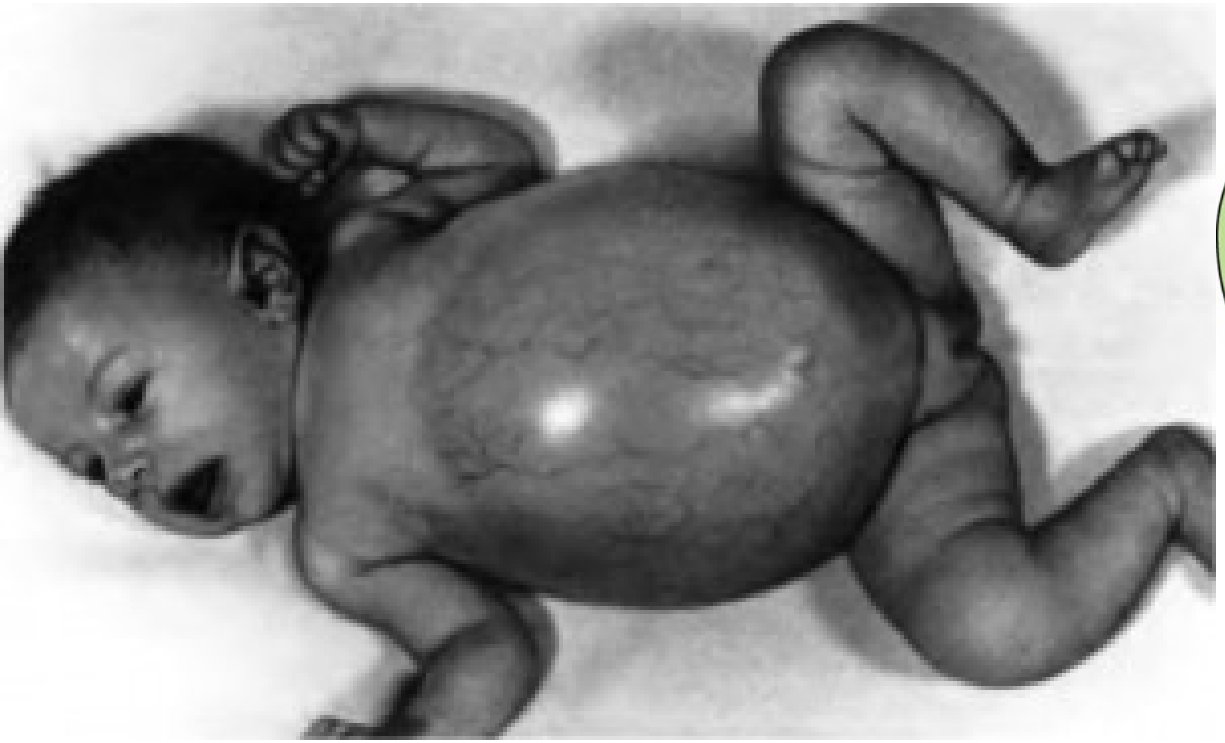
the liver in illness Gierke

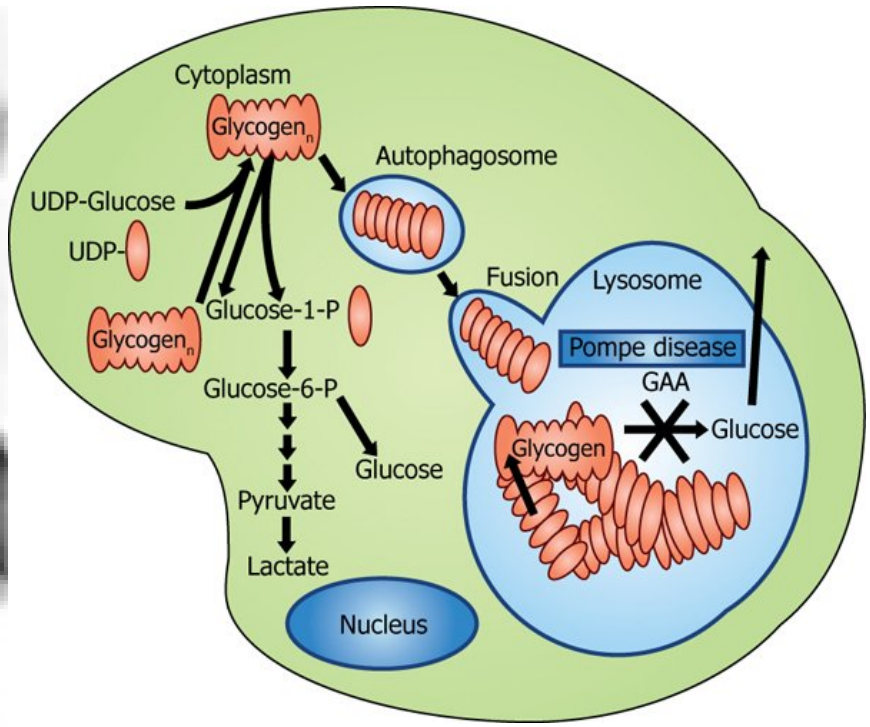


Normal liver

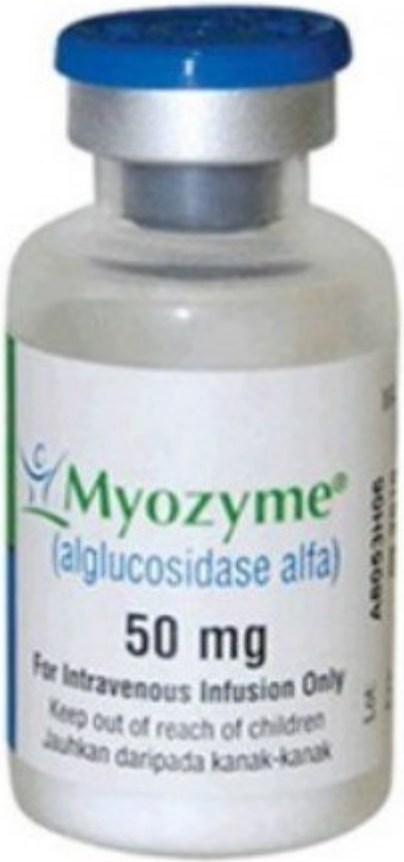
Glycogen storage disease II
(Pompe disease, glycogen storage disease idiopathic generalized)

Characterized by glycogen retention in lysosomes; glycogen is not cleaved due to the lack of acid maltase. Symptoms of the Disease appear after birth or after a few weeks. Children are apathetic, eat poorly, there is frequent vomiting. Hepatomegaly develops early.





The heart is enlarged, shortness of breath and intermittent cyanosis.
On ECG sinus tachycardia, ↑ prong P, negative prong T, high voltage.
Frequent repeated bronchitis, atelectasis, pneumonia. Muscle tone dramatically reduced → myopathy.
In the serum – ↑glutamicoxaloacetic transaminase and aldolase and uric acid.
In muscles and liver deficiency of alpha-1,4-glycosidase.
The glucagon and epinephrine samples are unchanged.
This type of glycogenosis is prognostically most unfavorable.
Death occurs at the 1st year of life from heart or respiratory failure, often with the addition of aspiration pneumonia.
Currently established drug Miosis (the "Genzyme") for the enzyme-replacement therapy.

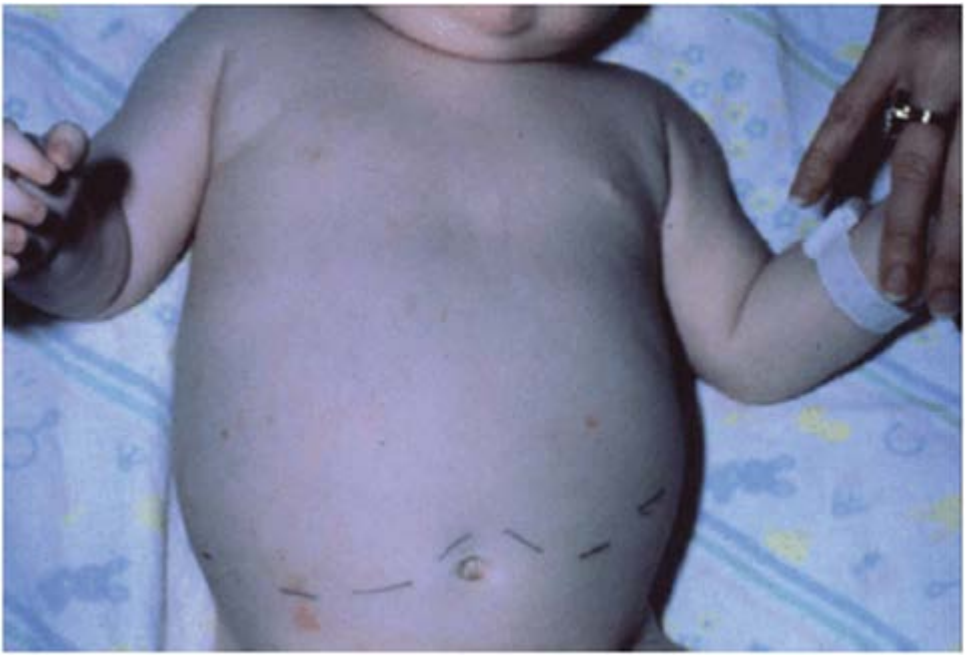


Myozyme®
(alglucosidase alfa)

$300,000 a year

Glycogen storage disease III (limitrequestline) Disease Forbes-Cori

In the population of Sephardic Jews, the disease occurs with a frequency of 1: 5400 newborns.



https://doctorlib.info/genetics/medical-genetics/8.html

Theresa and Carl Cory together won the Nobel prize in physiology or medicine in 1947 "for their discovery of the catalytic conversion of glycogen."

The treatment of the disease Forbes-Cori

The purpose of treatment is to prevent hypoglycemia of fasting and compensate for amino acid deficiency.

It is carried out as follows:

- taking the necessary amount of glucose in the form of raw corn starch in combination with a diet containing sufficient protein and other nutrients eliminates metabolic disorders and growth retardation;
- patients with severe growth retardation and severe myopathy are shown continuous night probe feeding with a mixture containing glucose, oligosaccharides and amino acids, and frequent intake of protein-rich foods in the daytime.

Glycogenosis IV (Andersen's disease, amylopectinosis, diffuse glycogenosis with cirrhosis of the liver)

AR

Disease manifests itself only hepatosplenomegaly, delay development → cirrhosis liver progresses → portal hypertension, ascites, enlargement veins esophagus.

Some patients develop hepatocellular carcinoma.

Life expectancy is significantly reduced-without liver transplantation, death occurs at 4-5 years of life.

Atypical forms are described with a slowly progressive liver disease or with a primary lesion of cardiac muscle.

The neurological variant of the disease in adults (disease with polyglucosan bodies) is similar in clinical manifestations to amyotrophic lateral sclerosis.

Glycogenosis V (Macardle's disease)

AR

Manifestations of the disease in children become apparent after minor physical activity:

- muscle pain,
- spasms,
- fatigue,
- weakness.

Sometimes the tonic contraction of the muscles become generalized and lead to total stiffness.

Later develop muscular dystrophy, heart failure.

At rest, children seem healthy.

The treatment is not developed.

Glycogen storage disease VI (Gers disease)

AR

It is one of the mild forms to moderate hypoglycemia, weak ketosis, growth retardation and prominent hepatomegaly.

The heart and skeletal muscles are not affected.

The prognosis is favorable.

According to Gers, glycogenosis type VI is any glycogenosis in which there is normal activity of amyl-1,6-glucosidase and glucose-6-phosphatase.

The activity of phosphorylases is sharply reduced, sometimes it is normal, but never show its complete absence.

Glycogen storage disease VII (Tarui disease)

AR

Glycogen storage disease type VII is characterized by muscle weakness, fatigability.

These children walk on their fingers, which is associated with shortening of the muscle fibers of the calf muscles.

Hepatomegaly is characteristic.

Treatment is aimed at combating metabolic disorders, including acidosis.

In some cases, the use of glucagon, anabolic hormones and glucocorticoids is effective.

Frequent meals with a high content of digestible carbohydrates are necessary for hypoglycemia.

With muscle forms of glycogenosis, improvement is noted with a diet high in protein, the appointment of fructose (inside 50-100 g per day).

Glycogen storage disease VIII
(X-linked liver glycogen storage disease)

X-linked recessive.

One of the easiest of glycogen storage human.

Clinical symptoms include hepatomegaly, growth retardation, increased glutamate pyruvate transaminase and glutamate oxaloacetate transaminase, hypercholesterolemia, hypertriglyceridemia, and fasting hyperketosis these clinical and biochemical disorders gradually disappear with age, and most adult patients are asymptomatic.

Peroxisomal diseases

Zellweger syndrome

Infantile Refsum disease

Neonatal adrenoleukodystrophy

Rhizomelic point chondrodysplasia

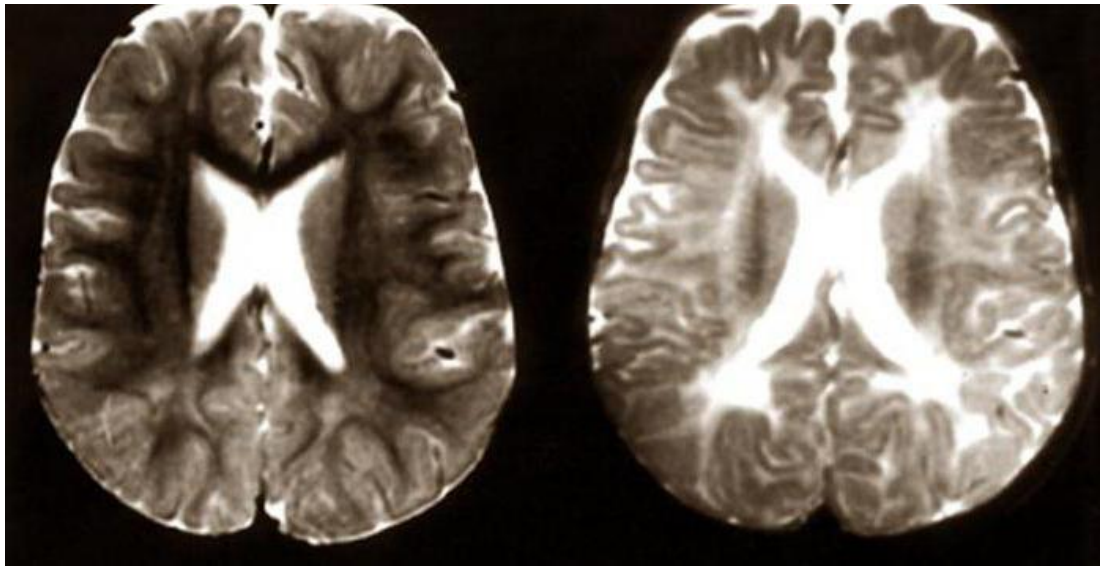
Zellweger Syndrome

214100 AR 7q21.2 gene PEX1

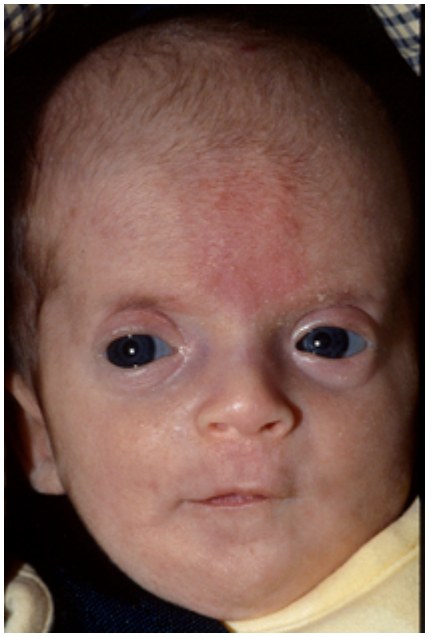
Severe neurological dysfunction, craniofacial abnormalities and liver dysfunction.

Biochemical – lack of piroxicam.

The most severely affected people with the classic Zellweger syndrome phenotype die within the first year of life.



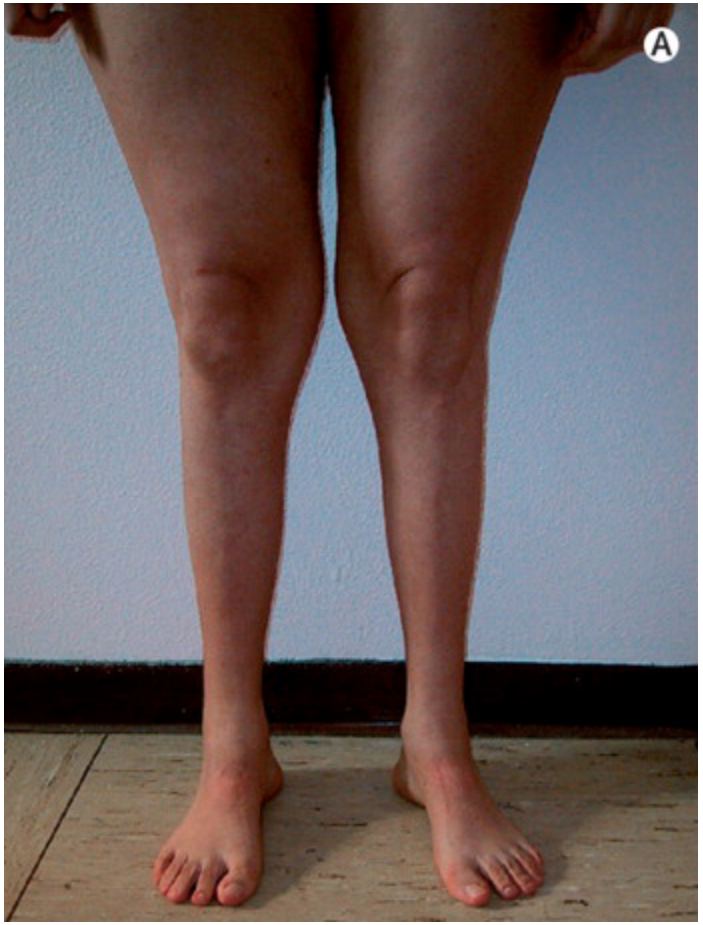
https://fb.ru/article/281640/sindrom-tselvegera-opisanie-prichinyi-simptomyi-i-osobennosti-lecheniya



http://symptomsofpravi.blogspot.com/2015/07/symptoms-of-zellweger-syndrome.html

Infantile Refsum disease

266500 AR 10p13 gene PHYH. Phytanoyl-COA hydroxylase deficiency/ The accumulation of phytic acid in the tissues of the body: neurological disorders, deterioration of vision, hearing, smell, ichthyous skin changes, disorders of the heart. It is diagnosed by the level of phytic acid in the blood and urine. Additionally, the study of the nervous system, visual function, hearing and smell, heart activity. The basis of treatment is a diet with restriction of nutrients containing phytanic acid. In severe patients, plasmapheresis is indicated.



http://zdravua.org.ua/index.php/lechebnye-ucherezhdeniya/2-uncategorised?start=104

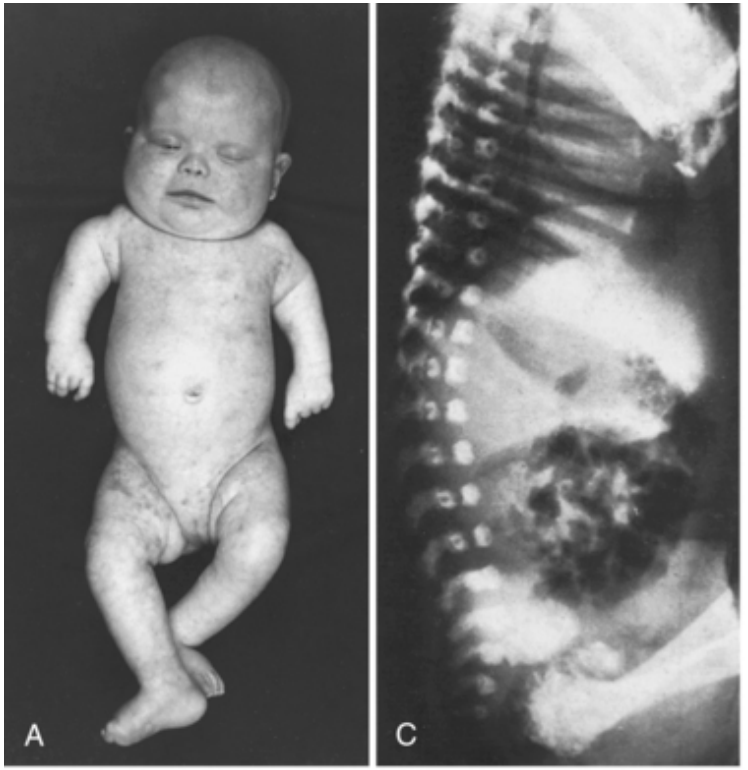
Neonatal adrenoleucodystrophy (violation of peroxisomal biogenesis 1B)

601539 AP 7q21.2 gene PEX1. 1 : 50.000 ♂=♀
Debut in the first three months of life, often represented by craniofacial dysmorphia, psychomotor retardation of varying severity, hepatomegaly, decreased hearing and vision, which in most cases, have a slowly progressive course. In some cases, liver damage can be the leading symptom of the disease, which often leads to the development of vitamin K-dependent coagulopathy, and in some cases, the disease can be complicated by the development of intracranial hemorrhages. In these syndromes, there is no chondrodysplasia and cysts in the kidneys.

https://raduga-omsk.ru/news/188337/

Rhizomelic point chondrodysplasia

215100 AP 6q23.3 gene PEX7. Violation of the peroxisomal signal receptor targeting type 2.
Growth retardation, disproportionate shortening of limbs with primary proximal lesions (point mineralization), multiple joint contractures (60 %), microcephaly.
The face of the patients is flat, with a sunken bridge of the nose, an anti-Mongoloid cut of the eyes.
In 80% of cases of bilateral cataracts was observed in 28 % of cases ichtiozoformnye dysplasia of the skin, alopecia.
Radiologically revealed ossification of the ventral or dorsal vertebrae, symmetrical shortening and deformation of the metaphyses of the humerus and femur.
Severe mental retardation is noted.
The majority of patients die in the 1st year of life.



Rhizomelic point chondrodysplasia

https://neupsykey.com/peroxisomal-disorders/