Lipid Storage diseases

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Definition:

- Lipidosis are group of inherited metabolic disorders in which harmful amounts of fatty materials (lipids) accumulate in tissues.
- Due to either a deficiency in enzymes that metabolize lipids or to production of dysfunctional enzymes.
- Over time the excess fat causes permanent cellular and tissue damage, particularly in the brain, PNS, liver, spleen, and bone marrow.

- Lipids are important for membranes and myelin sheaths that cover the nerves.
- These lipids are stored naturally in the body's cells, organs, and tissues.
- Lysosomes metabolize the lipids into smaller components to provide energy for the body.

Inheritance

- These disorders are inherited via AR or X-linked way.
- The diagnosis is made via PE, biopsy, genetic testing, molecular analysis of cells or tissue, and enzyme assays.
- In some forms, urinalysis can identify the presence of stored materials.

Classification:

- Gaucher disease
- Niemann-Pick disease
- Fabry disease
- Farber's disease
- Gangliosidoses GM and GM2
- Krabbe disease
- Metachromatic leukodystrophy (MLD)

Gaucher disease (GD)

- The most common form.
- AR
- It affects mostly Ashkenazi Jewish population.

GD (etiology):

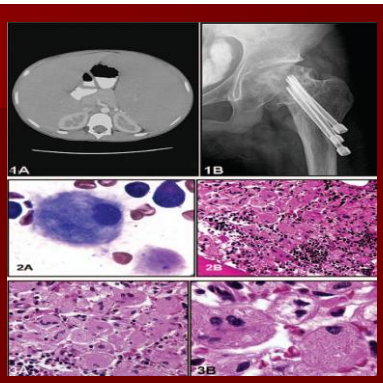
- Caused by deficiency of the enzyme β-glucocerebrosidase.
- Fatty materials accumulate in the spleen, liver, kidneys, lungs, brain, and bone marrow.
- M=F

GD (symptoms):

	Type 1 (nonneuronopathic)	Type 2 (acute neuronopathic)	Type 3 (chronic neuronopathic)
Age of onset	Adults, Ashkenazi Jewish	infancy	juvenile
Incidence	1 in 100 000 general population	1 in 100 000 live births	1 in 50 000 live births
Clinical presentation	HSM, BM suppression, bone abnormalities and pathological fractures	HSM and (early): seizure, dementia, ocular apraxia, myoclonus, and spasticity	HSM, (late, mild) seizure, dementia, ocular apraxia, myoclonus and spasticity.
Enzyme activity	Some activity	Very little activity	Little activity
Prognosis	varies	Death in infancy (<2y/o)	Slowly progressive

GD (diagnosis):

- Diagnosis is made via positive Gaucher cells in a bone marrow aspirate.
- However, enzyme assay to evaluate β-glucocerebrosidase activity in leukocytes in addition to genetic testing is the gold standard for diagnosis.



- The glucocerebrosidase gene (GBA) is located on Chr. 1q21.
- More than 200 mutations have been reported.
- Point mutation is N370S predispose to type 1 disease and precludes neurological involvement.

GD (Rx):

- ERT is the mainstay of treatment Type 1 and 3.
- ERT is given IV q2wks.
- ERT reduces HSM and skeletal abnormalities.
- ERT does not affect neurological abnormalities.

- BMT cures the non-neurological manifestation of the disease.
- Symotpmatic: blood transfusion, splenectomy, joint replacement...
- Future treatments: oral ERT and gene therapy.

Niemann-Pick disease (NP)

- AR.
- Caused by accumulation of fat and cholesterol in the liver, spleen, BM, lung, and brain.
- Neurological symptoms are: ataxia, eye paralysis, brain degeneration, learning problems, and spasticity.
- A cherry-red halo around the retina in 50% of patients.

NP (symptoms):

	NP-A	NP-B	NP-C	NP-D
Severity	Most severe	milder	Varies	Varies
Age of onset	Early infancy	Juvenile onset	Varies	Varies
Symptoms	NL at birth then :HSM, LN enlargement, xanthemas (nodes under the skin), severe brain damage by 6 mos	HSM, ataxia, peripheral neuropathy, abnormal PFT. Brain is unaffected	Mild HSM, severe brain involvement: patients can't look up and down, walking and swallowing difficulties. hearing and visual loss	Same as type C but later onset and slower rate of progression
Prognosis	Progresses rapidly. Death by age 18 mos	Depends on lung functions	Varies	Varies
Etiology	Accumulation of sphingomyelin due to deficinecy of acid sphingomyelinase		Due to lack of the NPC1 protein	Due to lack of the NPC2 protein

NP (Rx):

- Currently there is no cure for NP.
- Only supportive treatment is available.
- Low fat diet for type C and D.

Fabry's disease

- X-linked.
- Caused by deficiency of α-galactosidase A.
- Causes fat accumulation in the autonomic nervous system, eyes, kidneys, and cardiovascular system.

- Incidence is 1:40000 to 1:117000
- Onset usually is at childhood.
- M>F but a milder from is common in females.

FD (symptoms):

- Burning pain in arms and legs, worse with hot water or following exercise.
- Corneal clouding.
- Stroke or heart attack due to fatty storage in blood vessel walls.
- Other: cardiac and renal failure, reduced sweating and GI motility d/o.
- Angiokeratomas: small, reddish-purple skin rash.

FD (Rx):

- Early death due to cardiac, renal complications, or stroke.
- Management is supportive only.
- AEDs for neuropathic pain.
- Reglan for GI motility d/o.

FD (Rx):

- Renal transplant or HD.
- ERT can reduce storage, ease pain, and improve organ function in patients with FD.

Farber's disease

- AR
- Fatty materials accumulate in the joints, heart, kidneys, and CNS.
- M=F
- It starts at early age but sometimes later.

- Affected children develop neurological symptoms within the first few weeks of life.
- These symptoms include: impaired mental ability and swallowing problems.
- Other organs: liver, heart, lungs, and kidneys.

- Arthritis and joint effusion is common.
- Also contactures, xanthemas around the joints as the disease progresses.
- Death occurs by age 2 due to pulmonary disease.

- There is no treatment for this disease.
- Steroids may relief pain.
- BMT in patients with no lung or CNS involvement.

The gangliosidosis GM1

- AR
- M=F
- Due to deficiency of beta-galactosidase.
- Leads to deposits in CNS and PNS.

	Early infantile	Late infantile	Adult
Age of onset	Since birth	Age 1-3 ys	3-30 ys
Severity	Most severe	Less severe	Least severe
Symptoms	Neurodegeneration, sz, HSM, coarsening of facial features, skeletal abnormalities, hyperstimulation to noise, and gait problems Cherry-red spots in 50% of cases. Children became deaf and blind by age 1	Ataxia ,sz, dementia and speech difficulties	Muscle atrophy, dystonia, angiokeratomas in the lower part of the trunk. No HSM
Prognosis	Death by age 3 due to pulmonary or cardiac complications		Slowly progressive, less severe.

The gangliosidosis GM2

- Results from deficiency of beta-hexosaminidase.
- 2 types: Tay-Sachs disease and Sandhoff disease

	Tay-Sachs disease (variant B)	Sandhoff disease (variant AB)
Enzyme deficient	Beta-hexoaminidase A	Beta-hexoaminidase A and B
Age of onset	<6 months old	At 6 months of age
Neurological symptoms	Affected children are born healthy. Progressive loss of mental ability, dementia, decreased eye contact, increased startle reflex to noise, progressive hearing loss, blindness, macrocephaly ,dysphagia, cherry-red spots, Seizures in the 2nd year of age	Progressive deterioration of CNS, weakness, increased startle reflex to noise, hearing loss (progressive), spasticity, myoclonus, seizures, macrocephaly, and cherry-red spots,
Other organ involvement	none	Heart murmur, URT infections, HSM
prognosis	Death by age 4 due to recurrent infections	More severe than Tay-Sachs. Death by age 3 due to URT infections
Rx	Non specific	Non specific

Krabbe disease

- Globoid cell leukodystrophy.
- AR.
- Deficiency of the enzyme galactosyl-ceramide beta galactosidase.
- Onset: infancy (less than 6 months old)

- It may start later (teenage, adults).
- Fatty materials accumulate in the myelinated sheath of the nerves causing severe degeneration of mental and motor skills.
- CNS: hypertonia, myoclonic seizures, spasticity, deafness, optic nerve atrophy, dysphagia.

- PNS: muscle weakness, areflexia, slow CV on NCS.
- Infancy form: death by age 2.
- Adult onset: milder form.
- No treatment.

Metachromatic leukodystrophy (MLD)

- AR.
- Storage in the white matter of the CNS and PNS.
- Also in the kidney sometimes.
- Storage occurs in the myelin sheath.

- Due to deficiency of arylsulfatase A.
- M=F
- 3 phenotypes: late infantile, juvenile, and adult.

	Late infantile form	Juvenile	Adult form
Age of onset	12-20 months	3-10 years	>16 y/o
Symptoms:	Normal at birth. Later: difficulty walking, frequent falls, pain in the arms and legs (PN), progressive visual loss, dysphagia, seizures, and dementia.	Reduced school performance, neuropsych regression, ataxia, seizures, and dementia	Poor concentration, depression, ataxia, seizures, tremors, dementia
Prognosis	Death by age 5	Death by age 10-20 ys	Death within 6-14 years of onset

- Lab: high CSF protein.
- Imaging: diffuse demyelination, spared subcortical U fibers.
- Path: demyelination, metachromatic bodies.

- There is no treatment for MLD.
- BMT may delay progression in some cases

Some highlights for the board exam

- Name of the enzymes for these d/os.
- Which one affects PNS vs CNS vs both.
- Fabry disease, inheritance and clinical history.
- Tay-sach clinical history.
- MRI for MLD.
- NP: ocular symptoms.