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.

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.

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.
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 $\beta$-glucocerebrosidase.
- Fatty materials accumulate in the spleen, liver, kidneys, lungs, brain, and bone marrow.
- M=F

GD (symptoms):

<table>
<thead>
<tr>
<th></th>
<th>Type 1 (non-neuronopathic)</th>
<th>Type 2 (acute neuronopathic)</th>
<th>Type 3 (chronic neuronopathic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Adults, Ashkenazi Jewish infant</td>
<td>infancy</td>
<td>juvenile</td>
</tr>
<tr>
<td>Incidence</td>
<td>1 in 100,000 general population</td>
<td>1 in 100,000 live births</td>
<td>1 in 30,000 live births</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>HSM, BM suppression, bone abnormalities and pathological fractures</td>
<td>HSM (early), seizures, dementia, ocular apraxia, myoclonus, and spasticity</td>
<td>HSM (late), mild seizures, dementia, ocular apraxia, myoclonus and spasticity</td>
</tr>
<tr>
<td>Enzyme activity</td>
<td>Some activity</td>
<td>Vary little activity</td>
<td>Little activity</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Varies</td>
<td>Death in infancy (&lt;2y/o)</td>
<td>Slowly progressive</td>
</tr>
</tbody>
</table>
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.

Symptomatic: 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):

<table>
<thead>
<tr>
<th></th>
<th>NP-A</th>
<th>NP-B</th>
<th>NP-C</th>
<th>NP-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td>Most severe</td>
<td>mild</td>
<td>Varies</td>
<td>Varies</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Early infancy</td>
<td>Neonatal</td>
<td>Varies</td>
<td>Varies</td>
</tr>
<tr>
<td>Symptoms</td>
<td>NL at birth, HSM, LN enlargement, xanthomas</td>
<td>HSM, ataxia, peripheral neuropathy, abdominal PFT</td>
<td>Mild HSM, severe brain involvement, patients can't look up and down, swallowing and feeding difficulties, hearing and vision loss</td>
<td>Same as type C but later onset and slower rate of progression</td>
</tr>
<tr>
<td>Progress</td>
<td>Progresses rapidly, death by age 18 months</td>
<td>Depends on lung functions</td>
<td>Varies</td>
<td>Varies</td>
</tr>
<tr>
<td>Etiology</td>
<td>Accumulation of sphingomyelins due to deficiency of acid sphingomyelinase</td>
<td>Due to lack of the NPC1 protein</td>
<td>Due to lack of the NPC2 protein</td>
<td></td>
</tr>
</tbody>
</table>
Fabry’s disease

- X-linked.
- Caused by deficiency of \( \alpha \)-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 form 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 relieve 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.

The gangliosidosis GM2

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

<table>
<thead>
<tr>
<th>Age of onset</th>
<th>Early infantile</th>
<th>Late infantile</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Since birth</td>
<td></td>
<td>Age 1-3 yrs</td>
<td>3-30 ys</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity</th>
<th>Most severe</th>
<th>Less severe</th>
<th>Least severe</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Neurodegeneration, seizures, HSM, cardiovascular, skeletal abnormalities, cherry-red spots in 50% of cases, children become deaf and blind by age 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Axonia, ataxia, and speech difficulties</td>
</tr>
<tr>
<td></td>
<td>Muscle atrophy, dystonia, angiokeratomas in the lower part of the trunk, no HSM</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Death by age 3 due to pulmonary or cardiac complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slowly progressive, less severe.</td>
</tr>
</tbody>
</table>
Krabbe disease

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

<table>
<thead>
<tr>
<th>Enzyme deficient</th>
<th>Tay-Sachs disease (variant B)</th>
<th>Sandhoff disease (variant AB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>&lt;6 months old</td>
<td>At 6 months of age</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>Affected children are born healthy. Progressive loss of mental ability, dementia, increased head size, increased startle reflex to noise, progressive hearing loss, dysphagia, cherry red spots, seizures in the 2nd year of age</td>
<td>Progresses characterized of CNS: weakness, increased startle reflex to noise, hearing loss (progressive), spasticity, tetany, maculopapular eruptions, and cherry red spots</td>
</tr>
<tr>
<td>Other organ involvement</td>
<td>None</td>
<td>Heart murmur, URI infections, CNS</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Death by age 4 due to recurrent infections</td>
<td>More severe than Tay-Sachs. Death by age 2. Due to URI or URI infections</td>
</tr>
<tr>
<td>Rx</td>
<td>Non specific</td>
<td>Non specific</td>
</tr>
</tbody>
</table>

- 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.

<table>
<thead>
<tr>
<th>Age of onset</th>
<th>Late infantile form</th>
<th>Juvenile</th>
<th>Adult form</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-20 months</td>
<td>Normal at birth;</td>
<td>3-10 years</td>
<td>&gt;16 yrs</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Later difficulty walking, frequent falls, pain in the arms and legs (PN), progressive visual loss, dysphagia, seizures, and dementia</td>
<td>Reduced school performance, depression, apathy, astasia, ataxia, and dementia</td>
<td>Poor concentration, depression, ataxia, tremors, seizures, dementia</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Death by age 5</td>
<td>Death by age 10-20 yrs</td>
<td>Death within 3-4 years of onset</td>
</tr>
</tbody>
</table>

- 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.