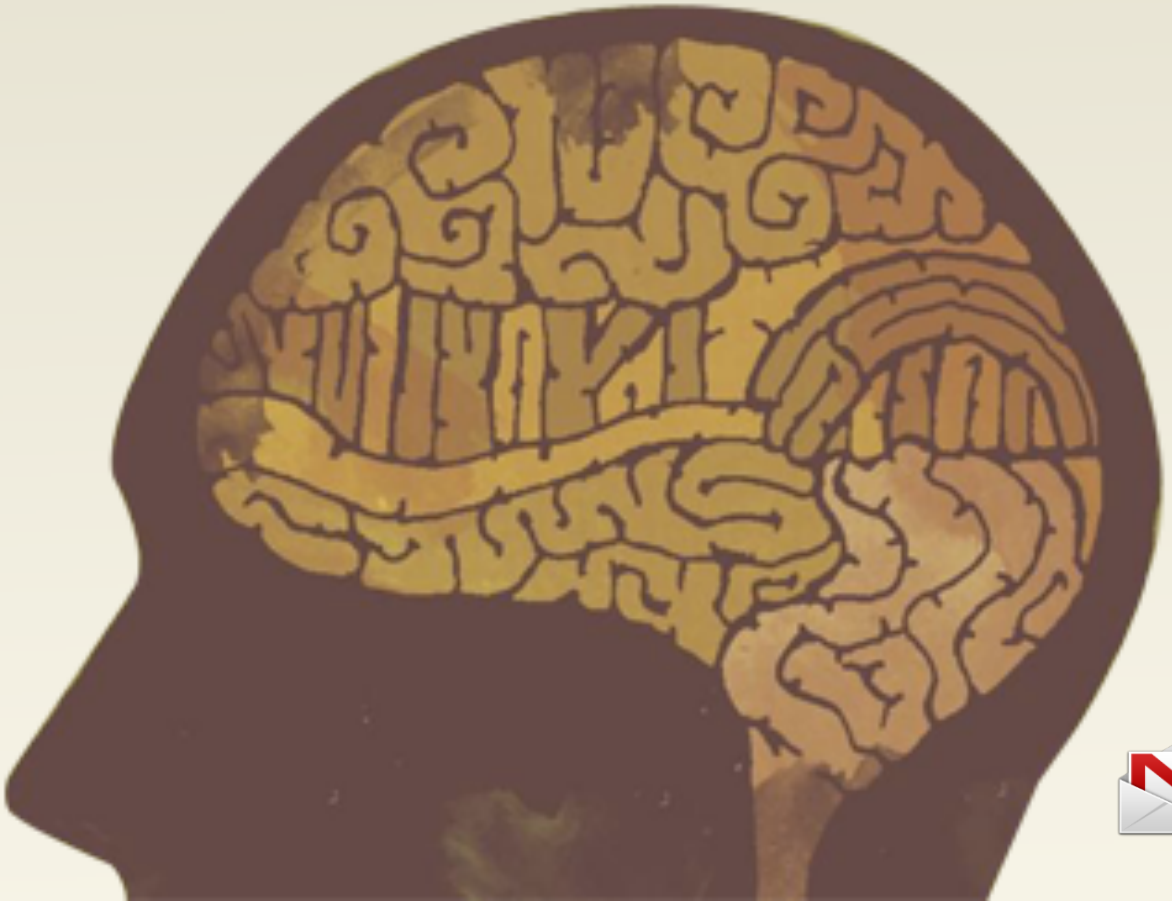
Sphingolipids and Myelin Structure



OBJECTIVES:

- Sphingolipids:
  - Chemical structure
  - Tissue distribution and functions
- Biochemical structure of myelin
- Biosynthesis of sphingolipids
- Sphingolipidosis

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Sphingolipids

Sphingophospholipids e.g., Sphingomyelin
-They have a **phosphate** group

Glycosphingolipids (Glycolipids)
- They have a **carbohydrate** group.

types

Structures and types

CERAMIDE = Sphingosine + fatty acid

Sphingomyelin = CERAMIDE + Phosphorylcholine

Cerebrosides = CERAMIDE + Monosaccharides

Gangliosides* = CERAMIDE oligosaccharides + N-acetyl Neuraminic Acid (NANA)

*The difference between Gangliosides and Cerebrosides is that a Monosaccharides is added to the ceramide in Cerebrosides, while in Gangliosides, ceramide polysaccharides are added to NANA

Background

- Essential component of membranes
- Abundant in nervous tissue
- Available in Extra-nervous tissue: e.g., Receptors for Cholera toxins, Diphtheria toxins, Viruses (they use these receptors to access cells).
- Regulation of growth & development
- Very antigenic (stimulate the production of antibodies) : they have been identified as a source of:
  - Blood group antigen
  - Embryonic antigen
  - Tumor antigen
- Involved in cell transformation to malignant cells.
- Myelin structure and function

Myelin

Multiple sclerosis (MS)

Neuro-degenerative, auto-immune disease, in which there is breakdown of myelin sheath (demyelination) of the nerves which causes defective transmission of their impulses.

Myelin sheath contains some very long chain fatty acids that include Lignoceric / Nervonic fatty acids

- Myelin is a specialized cell membrane that ensheathes an axon to form a myelinated nerve fiber

- Myelin is produced by:

Schwann cells → Peripheral nervous system

Oligodendrocytes → Central nervous system

- Myelin composition:

Lipids (80%):

Main component: Cerebrosides

Other component: Sphingomyelin

Proteins (20%): e.g., Myelin basic protein

- Function

- Insulates the nerve axon to avoid signal leakage
- Greatly speeds up the transmission of impulses along axons

Sphingolipidosis

Treatment

- Replacement Therapy: Recombinant human enzyme
- Bone marrow transplantation: Gaucher disease*

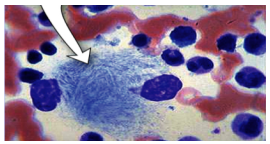
* Bone marrow transplantation was successfully tried in treatment of this disease.

Diagnosis

- Measure enzyme activity
  - ✓Cultured fibroblasts (because they are easly reached) or peripheral leukocytes
  - ✓Cultured amniocytes (prenatal)
- Histologic examination
- DNA analysis

- A group of diseases (9) in which Myelin Synthesis is Normal; but its Degradation is Defective.
- Substrate accumulates in organs
- Progressive, early death
- Phenotypic and genotypic variability(which means that each individual's genetic info and clinical presentation differs from one to another)
- Autosomal recessive (mostly)
- Rare, Except in Ashkenazi Jewish

Disease	Deficient enzyme	Substrate accumulated	Manifestation
TAY-SACHS DISEASE	Beta hexoaminidase A	GM2 (Gangliosides)	❖ Rapid and progressive neurodegeneration ❖ Blindness ❖ Cherry-red macula ❖ Muscular weakness ❖ Seizures
GAUCHER DISEASE (see picture below)	Beta-glucosidase	Gluco-cerebrosides	❖ Most common lysosomal storage disease ❖ Hepatosplenomegaly ❖ Osteoperosis of long bones ❖ CNS involvement in rare infantile and juvenile forms
NIEMANN PICK DISEASE	sphingomyelinase	Sphingo-myelin	❖ Hepatosplenomegaly (filled with lipids) ❖ Neurodegeneration course (seen in type A) and sever mental retardation ❖ Early childhood death



In gaucher disease: Crumpled tissue paper appearance of the affected cells are due to the enlarged and elongated lysosomes filled with glucocerebrosides

1) The main lipid component in the structure of myelin is?
A- Cerebroside
B- Ganglioside
C- Glycophospholipids
D- Glycosphingo

2) Which ONE of the following statements is correct about sphingolipidosis:
A- It is a common disease.
B- The synthetic pathways are usually spared.
C- Most of the time they are autosomal dominant.
D- It has a good prognosis.

3) The precursor of all sphingolipids is:
A- Phosphorycholine
B- Ceramide
C- Phospholipids
D- Sphingosine

4) Which ONE of the following will attach to ceramide in order to form Cerebroside
A- Monosaccharides
B- Oligosaccharides
C- Phosphorycholine
D- NANA

5) The main source of Myelin in the peripheral nervous system is:
A- Oligodendrocyte
B- Schwan cells
C- Astrocytes
D- Microglia

6) Which ONE of the following is NOT a diagnostic procedure for Sphingolipidosis:
A- PCR
B- Measurement of enzyme activity
C- Histologic examination
D- DNA analysis

7) Patient with beta-Glucosidase enzyme deficiency is most likely to develop
A- Gaucher disease
B- Niemann-pick disease
C- Tay-Sachs disease
D- Farber disease

8) a 1-year old baby presented with physical disabilities due to muscle weakness.Physical examination was done by the general practitioner reveals Cherry-red macula of the eyes.The most-likely accumulated substrate in such conditionis:
A- Glucocerebrosides
B- Sphingomylin
C- Sulfatides
D- Gangliosides

9) Hepatosplenomegaly is a main manifestation of all the following diseases except:
A- Gaicher disease
B- Tay-sachs disease
C- Niemann-pick disease
D- Hepatitis

10) Patient suffering from osteoporosis of long bones accompanied by hepatosplenomegaly.Liver biopsy was performed and showed crumpled tissue paper appearance of the cytoplasm.The most-likely diagnosis is:
A- Gaucher disease
B- Niemann-pick disease
C- Tay-Sachs disease
D- Farber disease

1) A 2) B 3)B 4)A 5)B 6)A 7)A 8)D 9)B 10)A

Thank You!

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