Important Doctors slides

Extra Information **Doctors notes**

Biochemistry

SPHINGOLIPIDS AND MYELIN STRUCTURE

ما دمت قررت ذلك
كن قويـًا

Editing file

OBJECTIVES

By the end of this lecture, the students should be able to:

- Recognize the Sphingolipids class of lipids as regard their chemical structure, tissue distribution and functions.
- Be familiar with the biochemical structure and function of myelin.
- Learn the basics of biosynthesis of sphingolipids.
- Be introduced to Sphingolipidosis (lysosomal lipid storage diseases) .

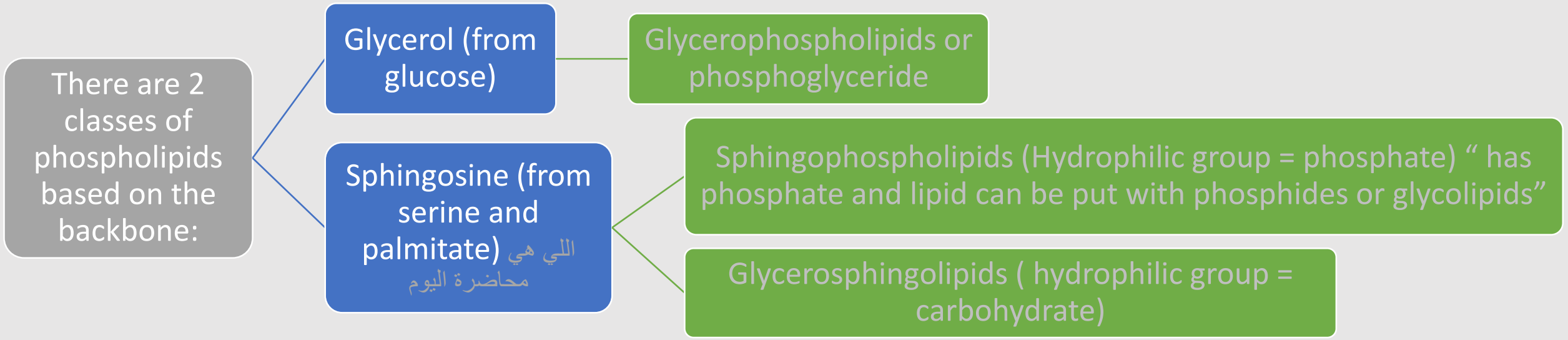
Key principles :

- ✓ Chemical structure of Sphingolipids.
- ✓ Types:

Glycosphingolipids (Glycolipids).
Sphingophospholipids, e.g. Sphingomyelin.

- ✓ Myelin structure and function.
- ✓ Sphingolipidosis.

Background about Phospholipids:



Recall what you studied in foundation!
Phospholipids: Are cell membrane make up
Major structure of it is: Amphipathic
Which is:
Hydrophilic portion = phosphate group
Hydrophobic portion = lipid

Background about Phospholipids:

- Essential component of membranes.
- Abundant in nervous tissue.

The only physiological significant of Sphingophospholipids present in our body is the sphingomyelin
What is the role of it ? It is one of the components of myelin sheath (not the main one)

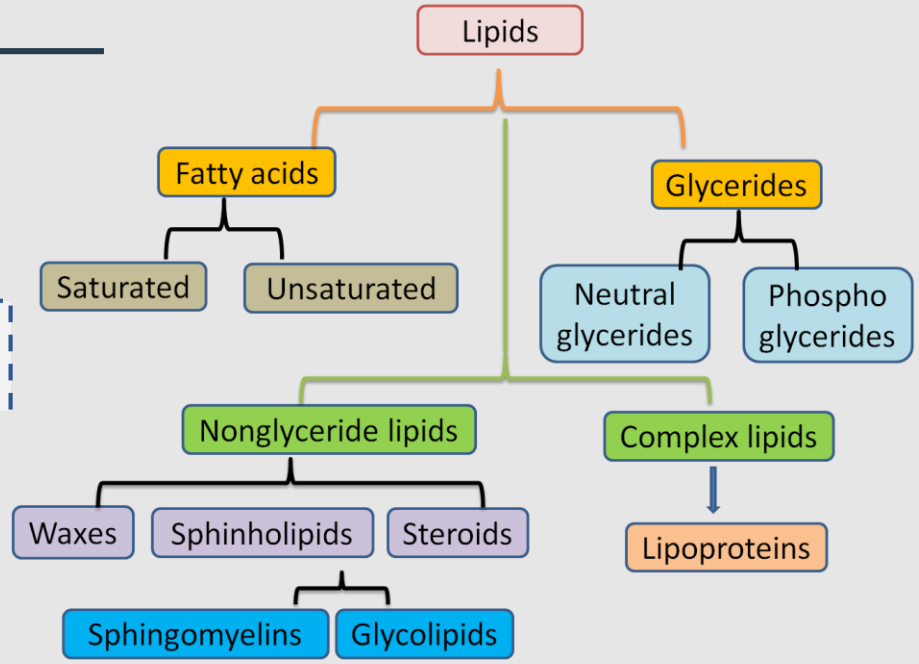
- Plays a role in regulation of growth and development
- Also exist extra-nervous tissue:
  e.g. Receptors (recognition) for :

Cholera toxins, diphtheria toxins & Viruses.

- Very antigenic:
  Blood group antigen, embryonic antigen & tumor antigen

Tumor antigens: because carbohydrates that are attached these sphingolipids they keep on changing. So, when the cell is going under transformation, say it becomes cancerous the carbohydrates in the top of the carbohydrate arrangement and the composition of the top layer in cell membrane keeps changing, and that's the marker for cell transformation. That's how they act as tumor antigen

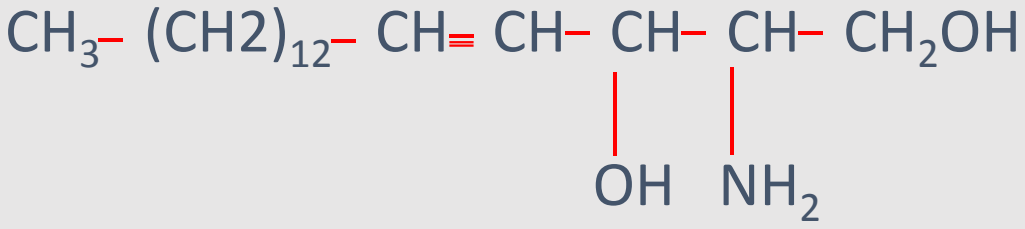
- Plays a role in cell transformation .

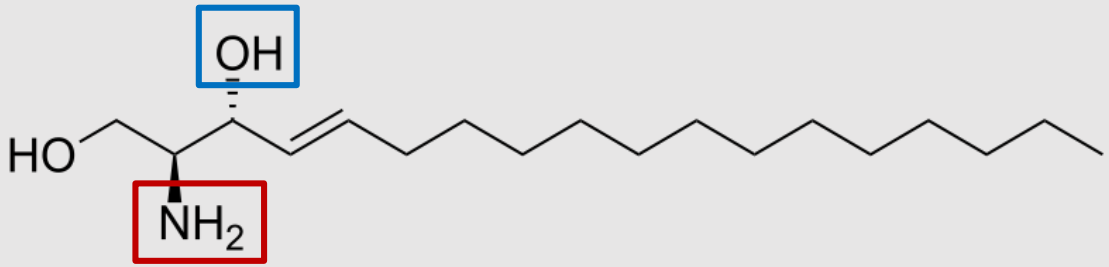


Role other than structural (usually present in extra cellular fluid) : involved in recognition, cellular interaction , adhesion and could serve as antigens (glycosphingolipids)very antigenic

Sphingolipids structure and types:

Sphingosine:





Long chain, unsaturated amino alcohol

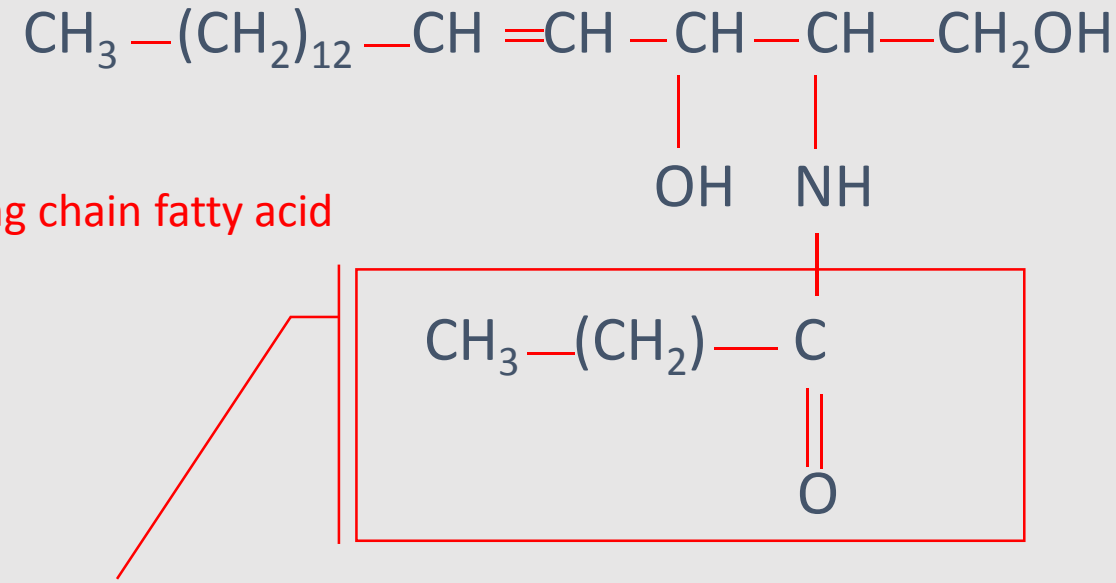
Sphingosine is formed from serine which is an amino acid polar uncharged it has oh2 and palmitoyl acid (fatty acid)

The backbone of sphingolipids

Ceramide:

Parent molecule for all of the sphingolipids

Ceramide = Sphingosine + Fatty acid



- Ceramide play a key role in maintaining the skin's water-permeability barrier. (it's present in some creams and lotions)
- Decreased ceramide levels are associated with a number of skin diseases.

And for the following each time we'll add a group that changes the name of the compound

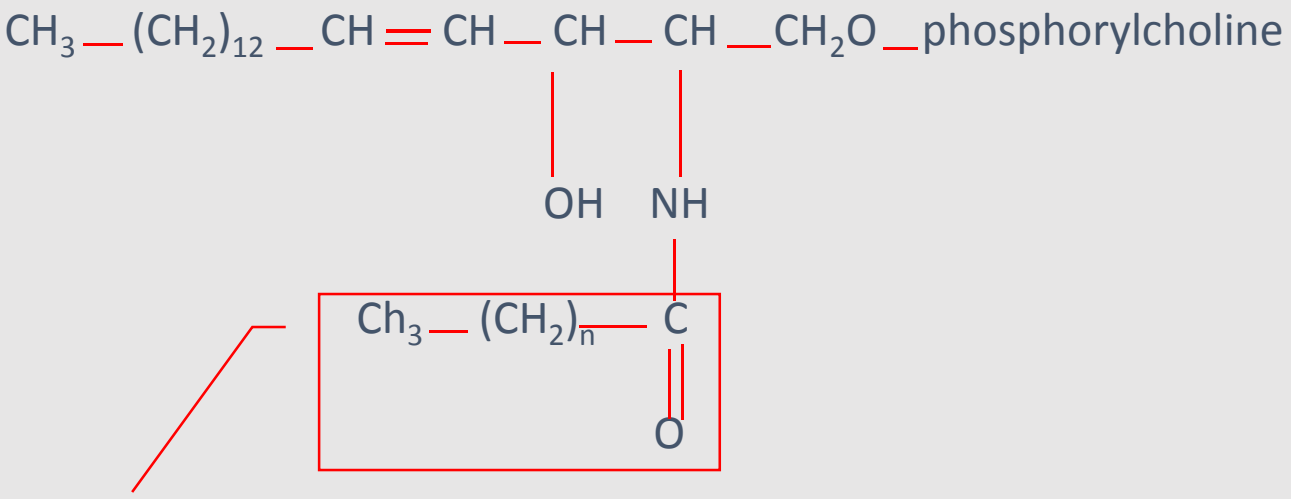
Sphingolipids structure and types:

Two types of glycosphingolipids:
1) Neutral (like these in the slide)
2) acidic

Sphingomyelin:

Sphingomyelin = Ceramide + phosphorylcholine

Or Sphingosine + Fatty acid + Phosphorylcholine, choline is an amino acid alcohol



Long chain fatty acid

- Sphingomyelin is the only significant sphingolipid in humans

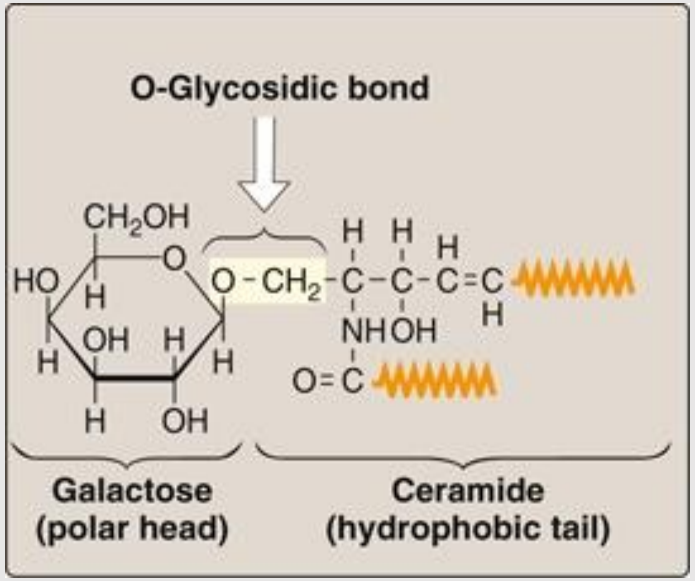
Cerebrosides:

Cerebrosides = ceramide + monosaccharides

eg. Galactocerebroside

is the most abundant in nervous tissue ..

What brings this galactose or glucose? By the carrier UDP (uridine diphosphate) Uridine is nitrogenous base ..



Sphingolipids structure and types:

Gangliosides

Gangliosides = Ceramide + Oligosaccharides

Oligo = 3 or more

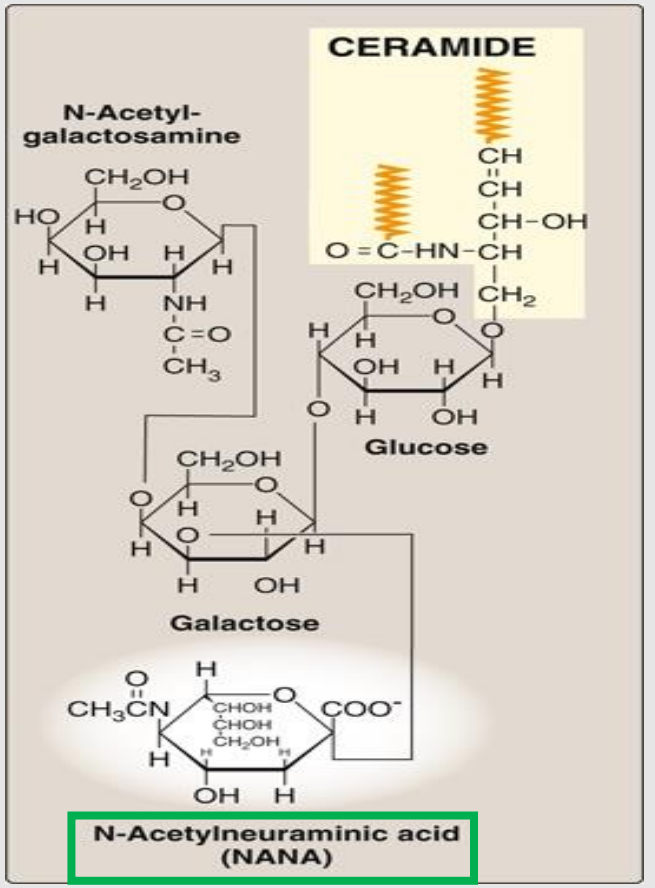
+

NANA

example : G_{m2}

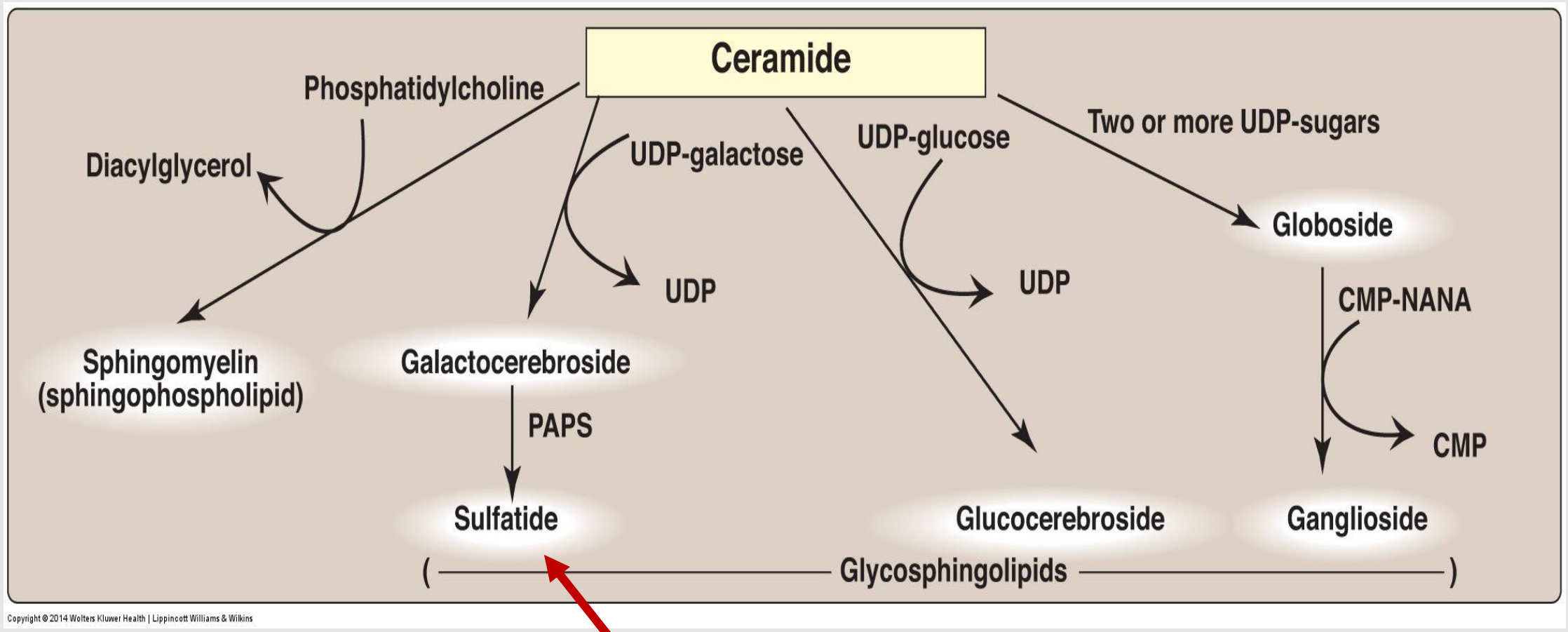
- For Gm2: G=ganglioside; M=mono molecule of NANA; 2=the monomeric sequence of the carbohydrate attached to the ceramide

N-Acetylneuraminic acid "NANA" is the predominant sialic acid found in mammalian cells.



It is important to memorize the name of each compound and to know that the origin of each compound is sphingosine

Sphingolipids synthesis:



Galactocerebroside + sulfate = Sulfatide (which is a negatively charged cerebroside).
By the carrier phosphoadenosine phosphosulfate (PAPS).

Myelin structure:

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

Each Schwann cell serve a single axon
While oligodendrocyte serve multiple axons at once

Fatty acid that is present in brain grey matter: stearic acid.

Myelin is produced by:

Schwann cells: Peripheral nerves.
Oligodendrocytes: CNS.

✓ Fatty acid of Sphingomyelin:

Myelin sheath: Very long chain fatty acids

Lignoceric 24:0
Nervonic 24:1(15)

Myelin composition:

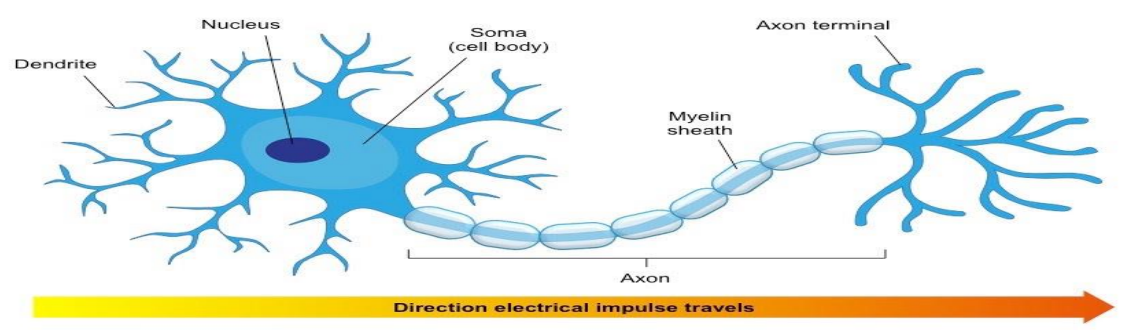
Lipids (80%): Main component: Cerebrosides
Other component: Sphingomyelin

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

Myelin structure and function:

Myelin sheath insulates the nerve axon to avoid signal leakage and greatly speeds up the transmission of impulses along axons.

Direction of nerve impulse



Multiple sclerosis “MS” :

Neuro-degenerative, auto-immune disease.

Breakdown of myelin sheath (demyelination).

Defective transmission of nerve impulses.

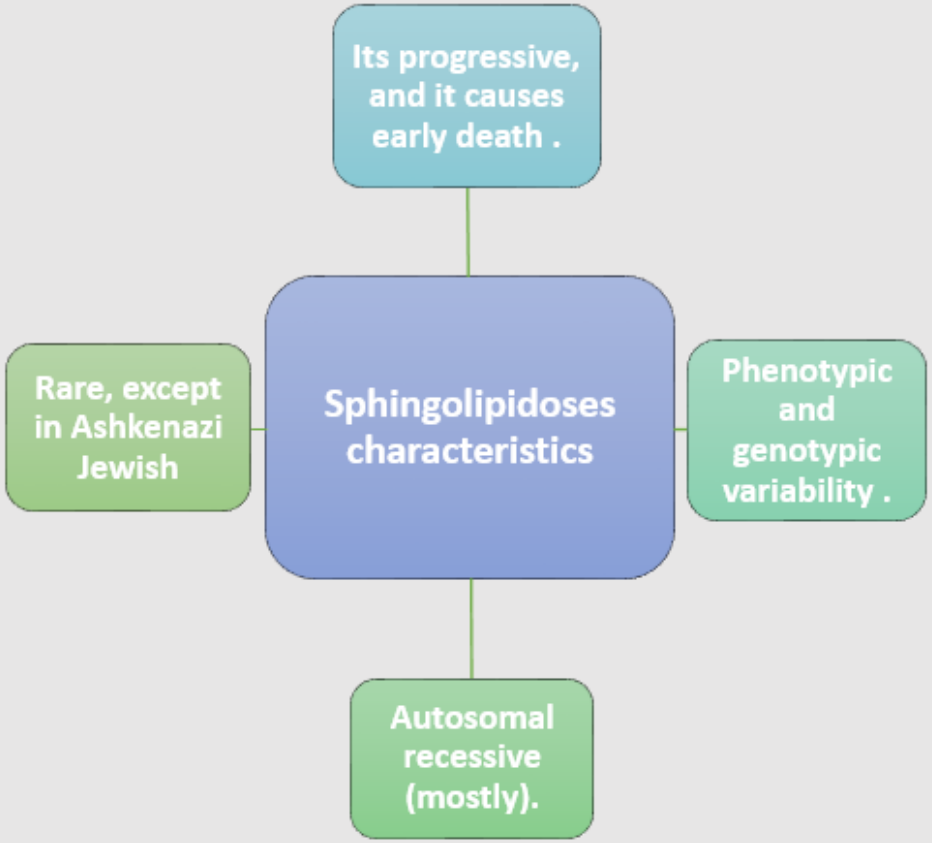
Sphingolipidoses (lysosomal lipid storage diseases).. أغلب أنواعه وراثية وهي اللي بنركز عليها

What is it ?

Lysosomal lipid storage diseases caused by these deficiencies are called sphingolipidoses, A partial or total missing of a specific lysosomal acid hydrolase leads to accumulation of a sphingolipid.
When the **synthesis is normal** and **degradation is defective** Substrate accumulates in organs .

- Usually only a single sphingolipid accumulates in the involved organs in each disease

*Mainly liver and spleen responsible for that



في الإنسان الطبيعي عملية التصنيع والهدم للـ glycosphingolipids متزنة الهدم = البناء فكمياتها بالميمبرينز ثابتة لكن لما يكون أنزيم acid hydrolase الموجود باللايسوسومز مفقود بتكون عندنا مشكلة في عملية الهدم وتتراكم المواد

The breakdown of the sphingolipid is defected not the synthesis

Hepatosplenomegaly, because liver is involved in lipid's storage

Fabry & Tay-Sachs are examples for lysosomal lipid storage diseases but they are rare

Sphingolipidoses are autosomal recessive diseases, except for fabry disease which is X linked

Sphingolipidoses

Diagnosis :

✓ By measuring the enzyme activity :

A. Cultured fibroblasts or peripheral leukocytes.
B. Cultured aminocytes with chronic villi (Prenatal)

✓ Histological examination

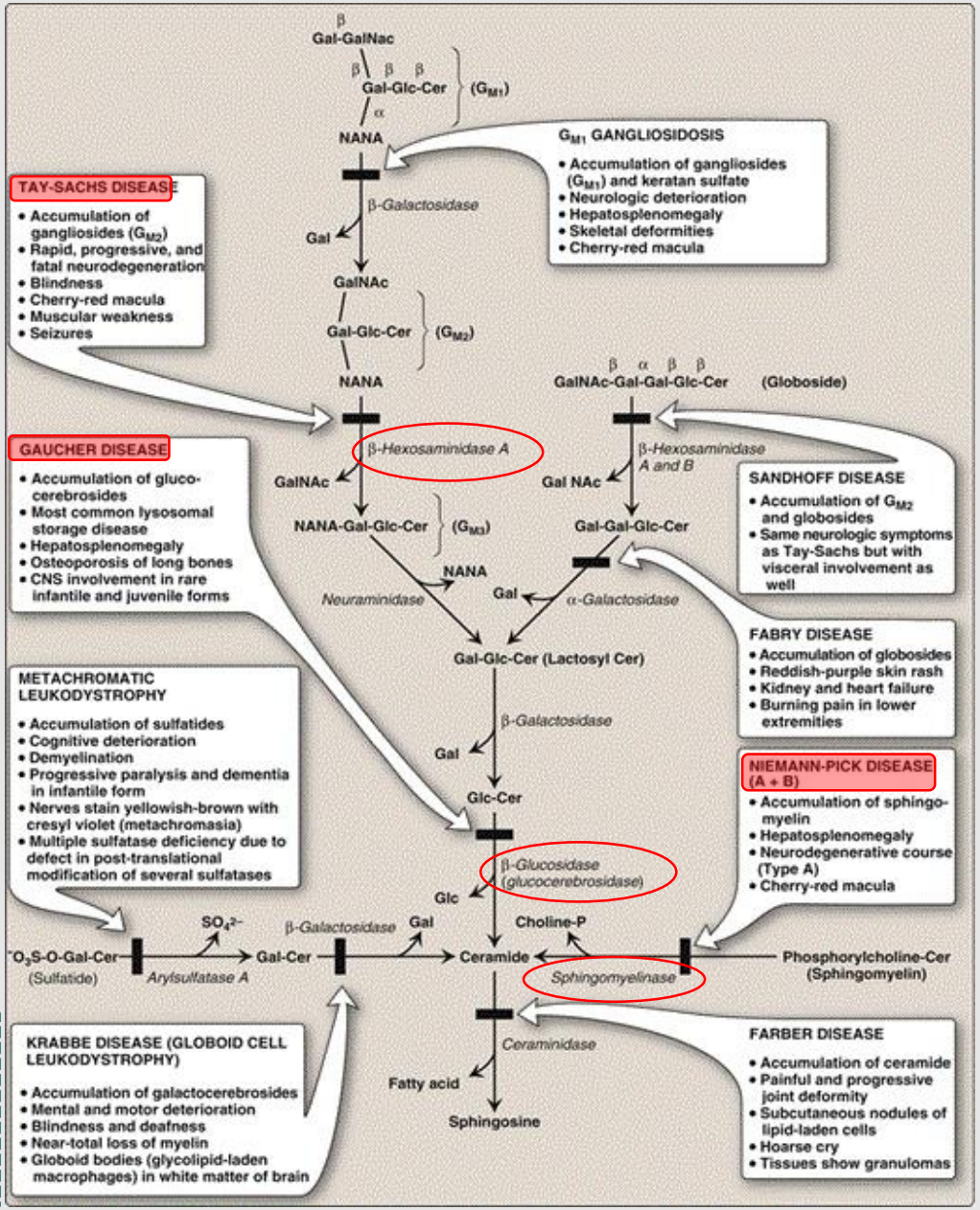
✓ DNA analysis

Treatment e.g. Gaucher disease

1. Replacement therapy
   e.g. Recombinant human enzyme.
2. Bone marrow transplantation

In DNA analysis first you must know which mutation is specific for which disease

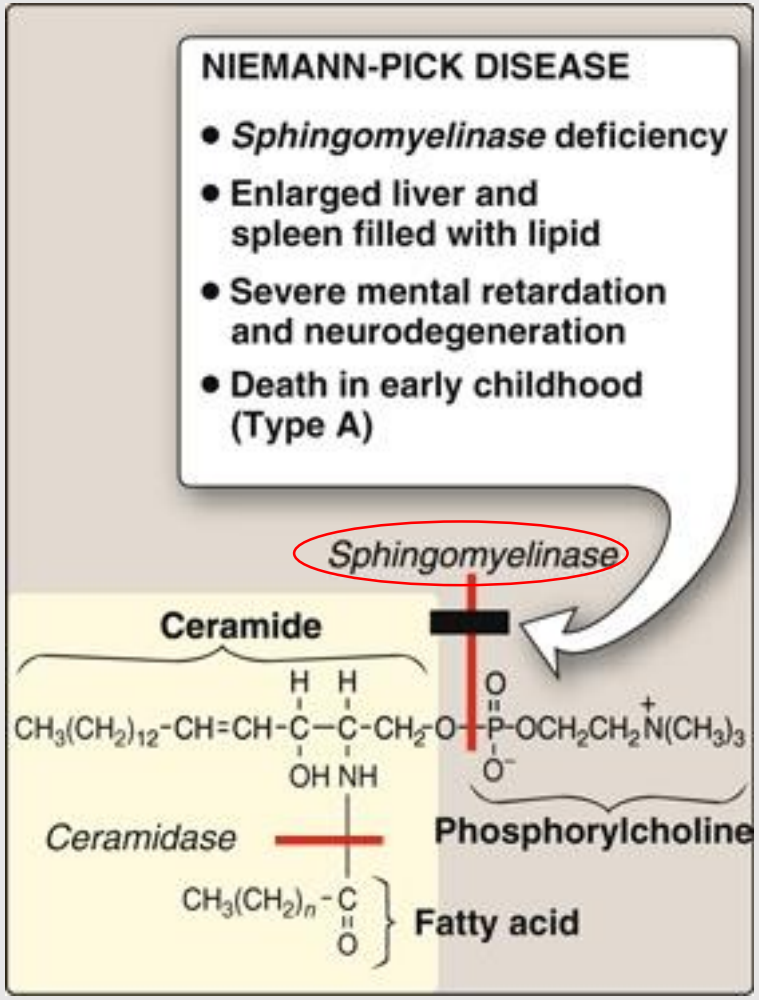
Recombinant human enzyme is not broadly used because its expensive ..



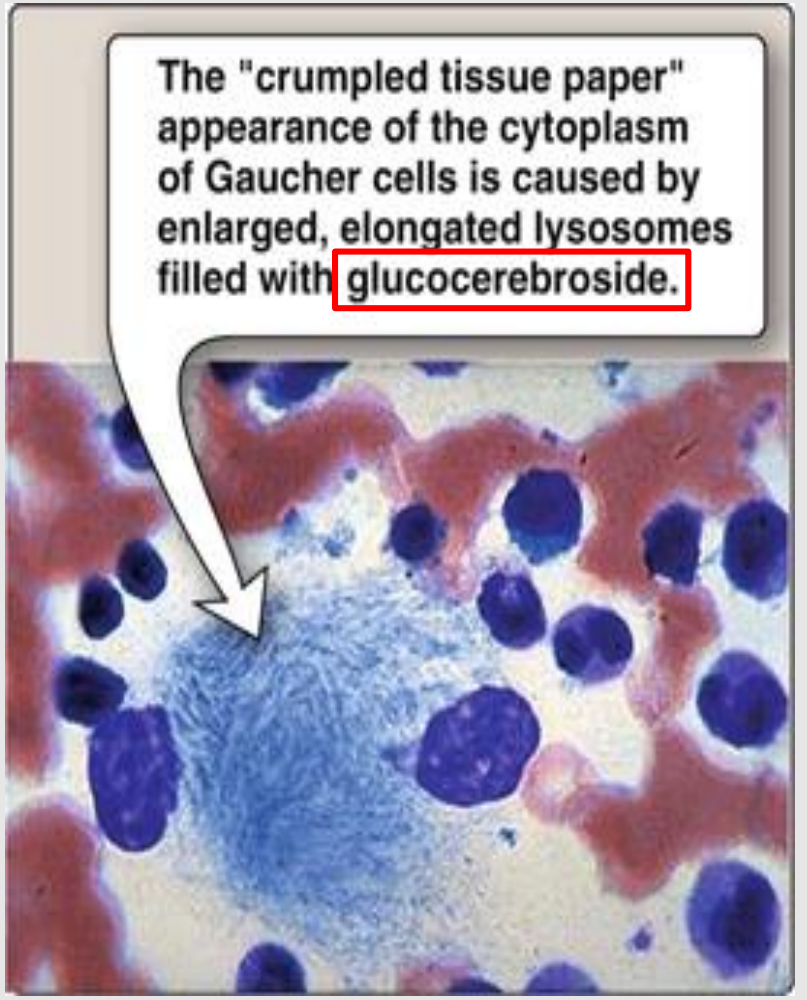
Sphingolipidoses

Niemann-pick disease

sphingomyelinase deficiency



Gaucher disease



From 435 team

Disease	Tay-sachs	Gaucher	Niemann-pick (A+B)	
Deficient Enzyme	β-Hexosaminidase (α subunit)	β-glucosidase (glucocerebrosidase)	Sphingomyelinase	
Lipid accumulated	Gangliosides (Gm2)	glucocerebrosides	Sphingomyelin	
Clinical Features	Blindness. -Cherry-red macula.* -muscular weakness and seizures. -Deficiency of activator protein (Gm2 Activator)	The most common one. - Hepatosplenomegaly - Osteoporosis of long bones. - CNS involvement in rare infantile (in infants) and juvenile (in children) forms. - Enzyme Replacement therapy is usually successful for this disease. Cytoplasm looks like crumbled tissue paper due to accumulation of Galactocerebrosides	Type A : -Enzyme Activity is reduced to 1% and less than normal. -Fatal Disease	Type B : - Little enzyme act - Chronic Disease.
			-More severe. -Death in early childhood. - Hepatosplenomegaly -Neurodegenerative course. -*Cherry red macula	-Less severe form type A -Later onset - Little enzyme act -Hepatosplenomegaly -*Cherry red macula

*Cherry-red macula is: There is an area in the retina that is called macula, it acts as a natural sun-block (it blocks ultraviolet rays that enter and harm the eye), usually it's yellow in color but when it's affected it becomes red under the light. Examples of Sphingolipidoses

Summary

Types and Structures of Sphingolipids					
Type	1. Sphingosine	2. Ceramide	3. Sphingomyelin	4. Cerebrosides	5. Gangliosides
Structure	Long chain, unsaturated amino alcohol	= Sphingosine + Fatty acid	= Ceramide + phosphorylcholine	= ceramide + monosaccharides	= Ceramide + Oligosaccharides + NANA
Example	-	-	-	Galactocerebroside	Gm2

Myelin Structure and Function	
Structure	1. It is the membrane around the axon that forms a myelinated nerve fiber. 2. Myelin is produced by Schwann cells and Oligodendrocytes. 3. It is composed of 80% lipids and 20% proteins.
Function	Nerve insulation: to avoid signal leakage, and to increase velocity of impulse transmission.

Sphingolipidoses: Lysosomal Lipid Storage Diseases				
How?	The substrate is synthetized normally but there's a defect in its degradation, so it accumulates in the organs.			
Facts	Autosomal recessive disease.	Progressive disease.	Rare, except in Ashkenazi Jewish.	
Diagnosis	1. Measuring enzyme activity	2. Histological examination	3. DNA Analysis	
Treatment	1. Replacement therapy		2. Bone marrow transplantation	
Examples	1. Tay Sachs disease	2. Fabry disease	3. Gaucher disease	4. Niemann Pick disease

Take home messages

- ✓ Sphingolipids are complex lipids that includes sphingo-phospholipids and glycolipids.
- ✓ Ceramide is the precursor of all sphingolipids.
- ✓ Sphingolipids are present mainly in nerve tissue, but they are also found extra-neural.
- ✓ Myelin sheath insulates the nerve axon to avoid signal leakage and speed up impulse transmission.
- ✓ Sphingolipidoses are rare genetic diseases due to defective degeneration of sphingolipids.

Good luck

Quiz

1) **Which of the following consist of " ceramide + phosphorylcholine " ?**

a) Sphingomyelin
b) Cerebrosides
c) Gangliosides
d) None of them

2) **In peripheral nerves myelin is produced by .....**

a) Astrocytes
b) Oligodendrocytes
c) Schwann cells
d) None of them

3) **Replacement Therapy is a way to treat multiple sclerosis .**

a) True
b) False

4) **Myelin is composed of high amount of proteins and low amount of lipids .**

a) True
b) False

Q : Discribe the characterstics of Niemann-pick disease ?

Q : What is the reason behind the crumpled tissue paper appearance in gaucher disease ?

4-B
3-B
2-C
1-A

Suggestions and recommendations

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THANK YOU

FOR CHECKING OUR WORK

PLEASE CONTACT US IF YOU HAVE ANY ISSUE

- Lippincott's Illusrated Reviews Biochemistry 6th E

https://www.youtube.com/watch?v=7udUG8KkN_E

Don’t forget to review the notes

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