BIOCHEMISTRY OF MYELIN

Color index:
- Important
- Extra explanation

Recourses:
Slides: Girls' and Boys'
Books: Lippincott

"IT ALWAYS SEEMS IMPOSSIBLE UNTIL ITS DONE"

Check this link before studying to know if there is any corrections in the teamwork

Recall

This slide is Extra ..

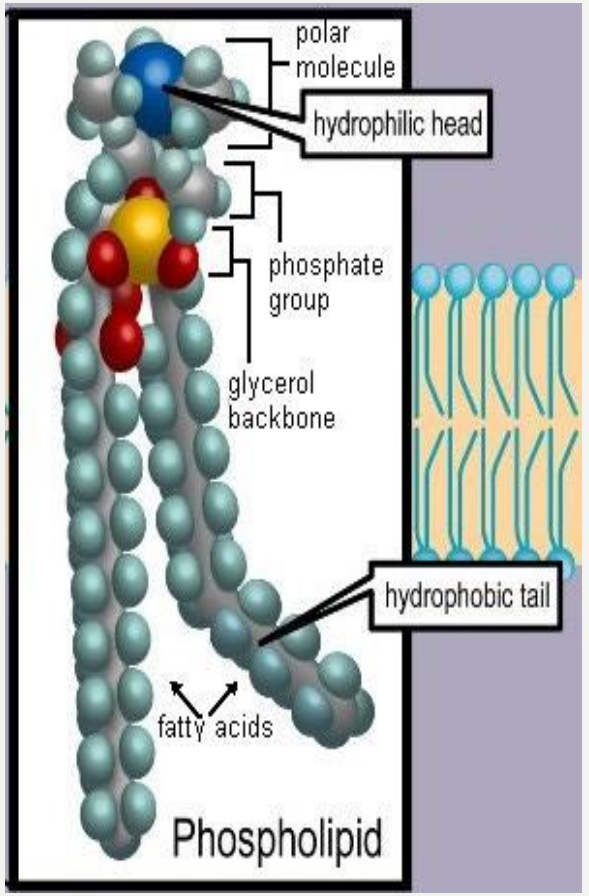
LIPID COMPOUNDS CHARACTERS:

1- Heterogeneous group.
2- water-insoluble except **the ketone bodies**.
3- Soluble in non-polar solvents.

What are phospholipids?

A **phospholipids** are compounds composed of 2 fatty acid chains (tails) attached to 2 carbons of a glycerol molecule, and phosphate group attached to the third carbon of glycerol.

They are divided into : 1- hydrophilic head (glycerol & phosphate).
2-hydrophobic tails (fatty acids chains.)
Thus, it is amphipathic (contain both hydrophobic & hydrophilic characters).



Recall

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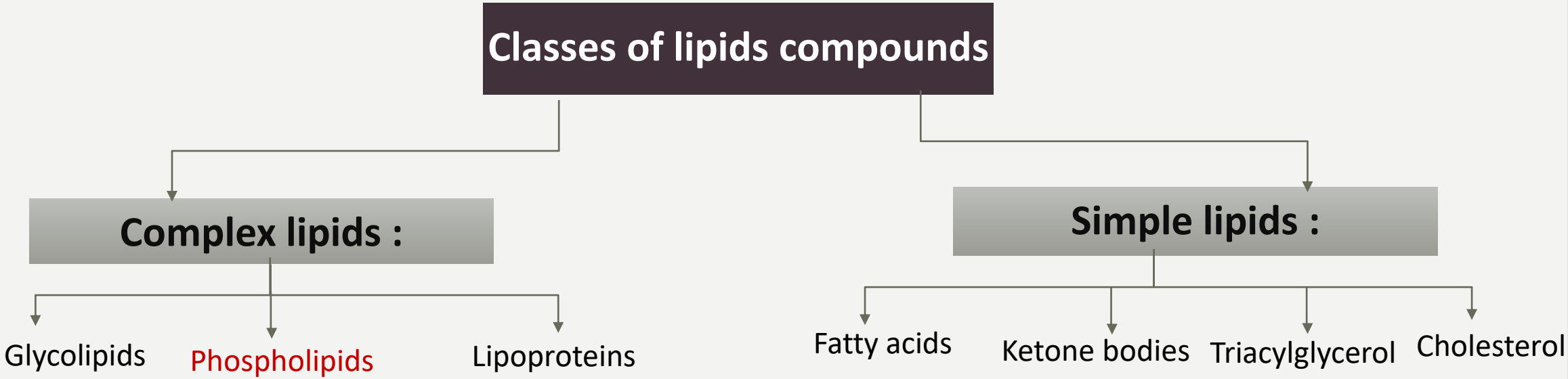


Recall

This slide is Extra ..

CLASSIFICATIONs OF PHOSPHOLIPIDS:

Glycerophospholipids

- They're **Glycerol** (alcohol)-containing phospholipids.
- Parent compound is phosphatidic acid which is made up of phosphate and diacylglycerol.
- Examples:

1- Phosphatidylcholine (Lecithin).

e.g. Surfactant (Dipalmitoylecithin)

2- Phosphatidyl inositol

(Signaling molecule)

- **they're Degraded and remodeled by:** phospholipases.

Degradation and remodeling

Sphingo-phospholipids

- **Sphingosine** (**amino** alcohol)-containing phospholipids.

e.g. sphingomyelin.

- They're Present in myelin sheath.
- **They're Degraded by:** lysosomal phospholipases (sphingomylinases).

Degradation only

OBJECTIVES

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

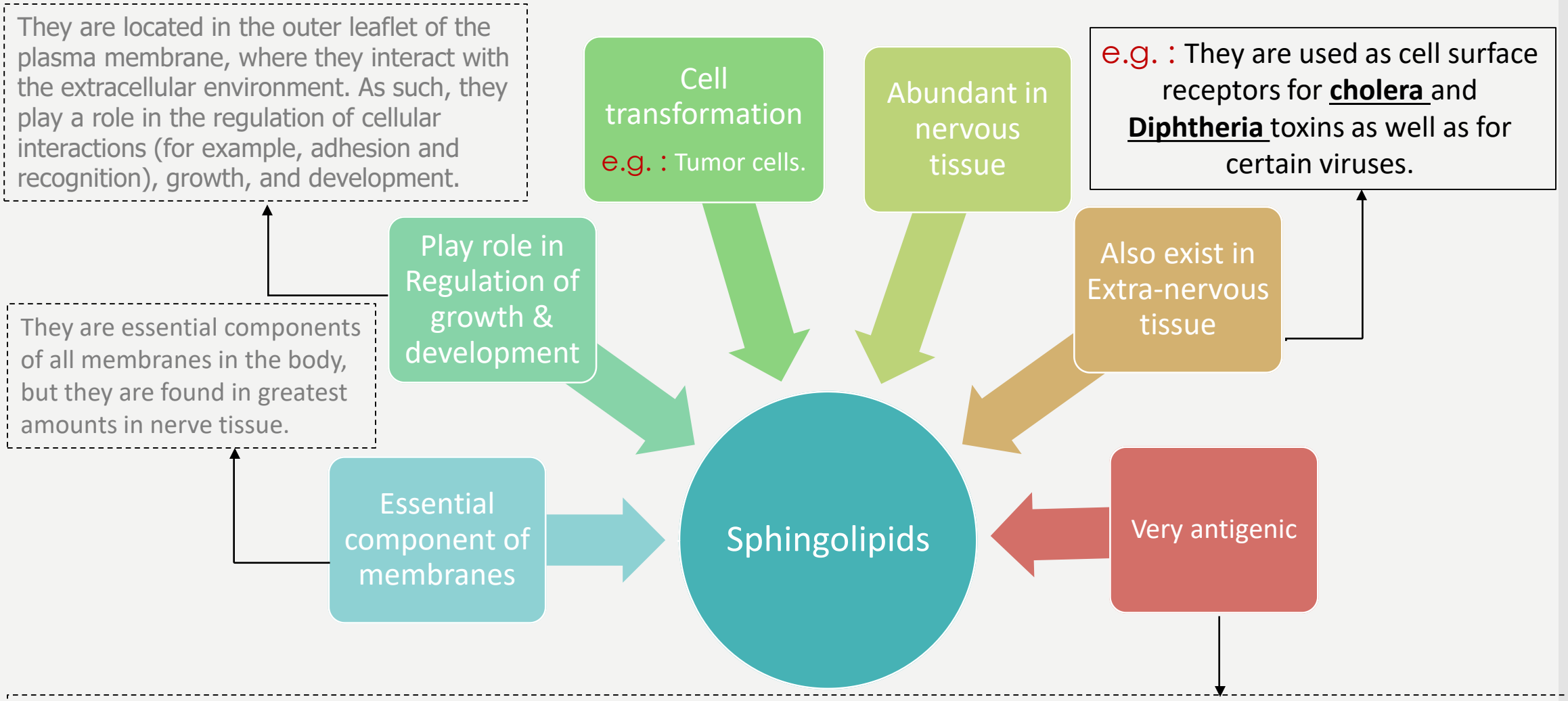
1- recognize the Sphingolipids class of lipids as regard their:
- Chemical structure.
- Tissue distribution and functions.

2- be familiar with the biochemical structure of myelin.

3- learn the basics of biosynthesis of sphingolipids.

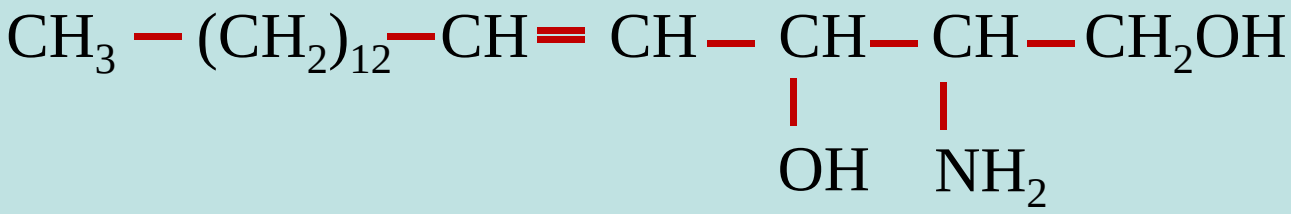
4-be introduced to Sphingolipidosis.

Sphingolipids properties

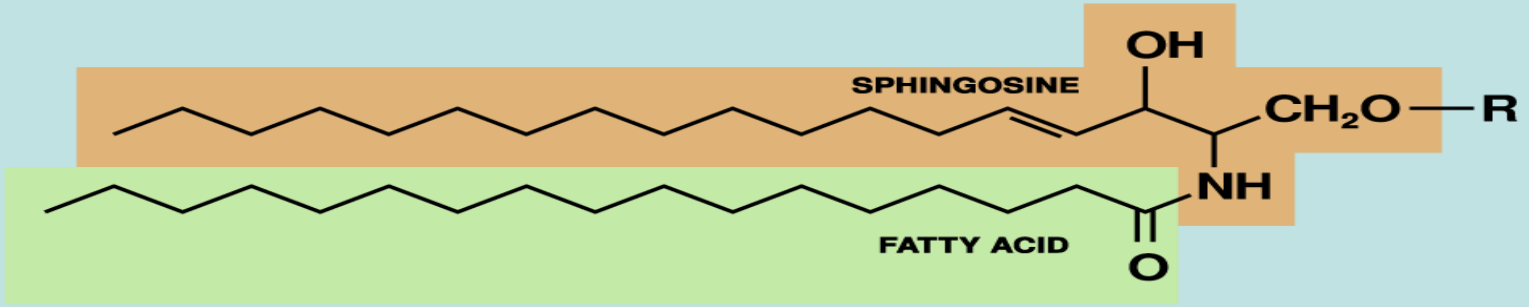


Sphingolipids

- First of all, you should know that sphingolipids - as the name reveals - are based on the unsaturated long chain amino alcohol called **sphingosine** (see its structure below).



- When a long fatty acid chain is attached to the amino group of sphingosine, it will produce Ceramide, which is the parent compound of the most of sphingolipids.



Sphingosine is an aminoalcohol (has an amino group and alcohol group).

Note: if the structures confused you, just skip them. We don't have to memorize them. ☺

Sphingolipids

This slide is Extra ..

sphingolipids

1-sphingophospholipids

Sphingophospholipids are both sphingolipids and phospholipids

2-glycosphingolipids

Examples (both of the following DON'T have phosphate):

1- cerebrosides: monosaccharide (glucose or galactose or fructose) forms the polar head of cerebroside.

while ceramide forms the hydrophobic tail

2-gangliosides(most complex)

- the backbone of phospholipids is an alcohol called glycerol.
What is the difference between sphingophospholipids and glycosphingolipids?
Both have ceramide as their parent compound and both are lipids but sphingophospholipids is a phospholipid(has po4) while glycosphingolipid is not.

Sphingolipids

- Ceramide
- Sphingomyelin
- Cerebrosides
- Gangliosides

What is it?

- It's the precursor of sphingomyelin – and the other sphingolipids -.

بمعنى أنه هو "الأب الروحي" لباقي السفينجوليبدز ، بحيث أنه يعتبر أساسي في تكوينها.

*Ceramide is important in the skin.

How is it produced?

- By attaching of a long fatty acid chain to the amino group of sphingosine.

Ceramide = Sphingosine + fatty acid.

What is it?

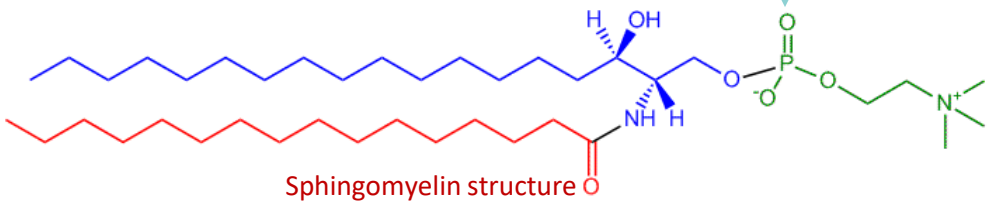
- It's the major structural lipid in the membranes of nerve tissue.

Sphingomyelin = Ceramide + Phosphorylcholine.

* it's the only significant sphingophospholipid in humans.

How is it produced?

- By reaction of ceramide and phosphat**idyl**choline. It'll result in separation of phosphatidylcholine to diacylglycerol and phospho**ryl**choline (phosphate + choline) . Phospho**ryl**choline will then bind to ceramide to make sphingomyelin.



Sphingomyelin structure

Sphingolipids

- Ceramide
- Sphingomyelin
- Cerebrosides
- Gangliosides

What are they?

- another group of sphingolipids, which are more complicated than sphingomyelin, **Why?** because they contain carbohydrates in their structures. you can find them in nervous tissue.
- As their name implies, cerebrosides are found predominantly in the brain and peripheral nervous tissue, with high concentrations in the myelin sheath.

-They're the simplest neutral (uncharged) glycosphingolipids.

Cerebrosides = Ceramide + Monosaccharides ← galactose , or maybe glucose or even more complex monosaccharide

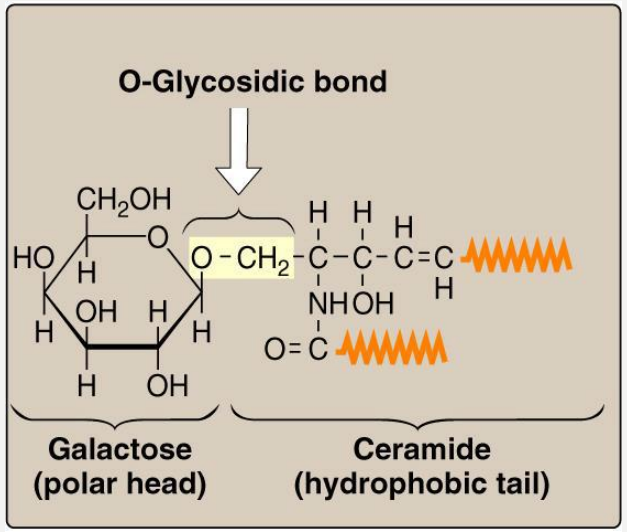
How is it produced?

By reaction of ceramide with UDP-Galactose or UDP-Glucose (UDP is a carrier for sugar), then UDP will leave the sugar with ceramide resulting in Gluco/Glactocerebroside.

Glactocerebroside may react with **PAPS** (which is a sulfate carrier) and take Sulfate from it to make **Sulfatide**, which is an important lipid compenent in the brain (can be found also in the kidneys.

This is Glactocerebroside
(Galactose + ceramide)

UDP stands for : uridine diphosphate



Sphingolipids

- Ceramide
- Sphingomyelin
- Cerebrosides
- Gangliosides

What are they?

- These are the most complex glycosphingolipids. They are found in the ganglion cells of the CNS, particularly at the nerve endings. They contain more than one group of carbohydrates.

Gangliosides = Ceramide oligosaccharides + NANA

- Recall: oligosaccharide: is a saccharide polymer containing a small number of monosaccharides (from 3 to 10)

How is it produced?

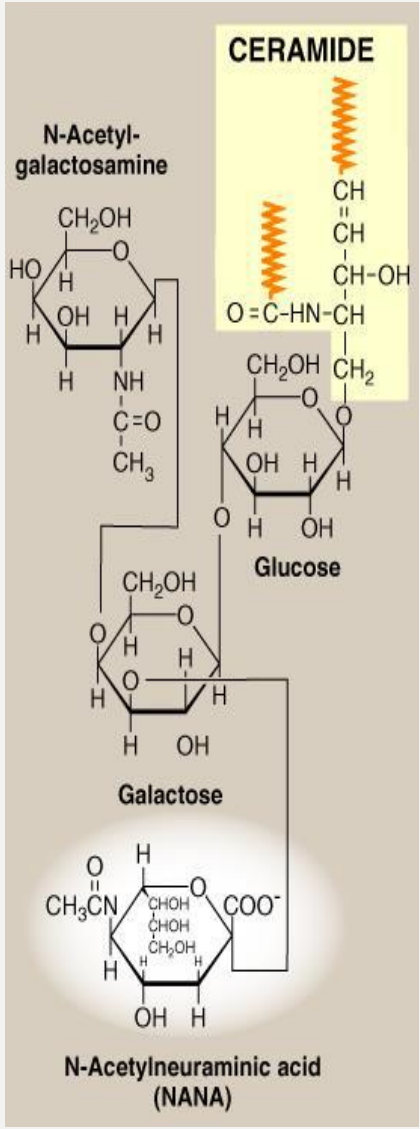
By reaction of ceramide with two or more UDP-sugars to produce Globoside, which will react with CMP-NANA (CMP is a carrier for NANA) and CMP will leave resulting in the synthesis of a ganglioside.

NANA: stands for N-Acetylneuroaminic acid (it's a type of sialic acids).

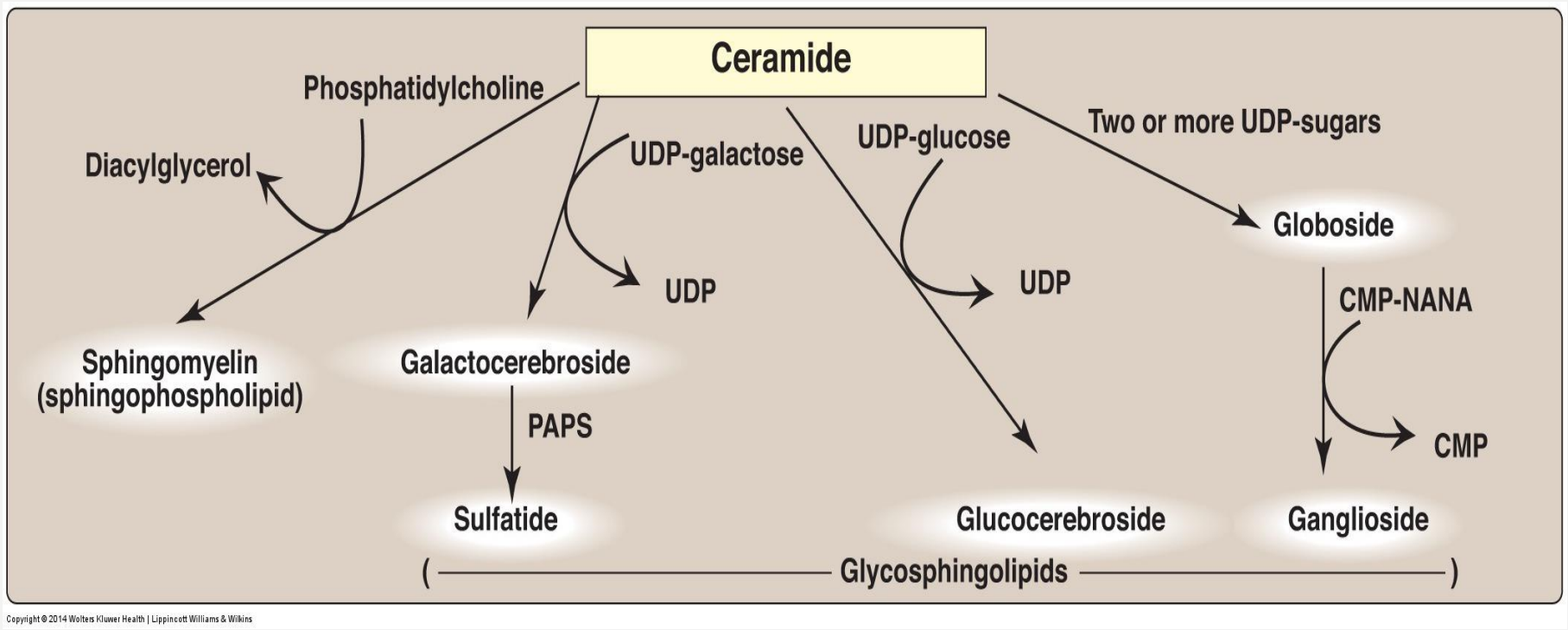
This structure is called GM2

G: refers to ganglioside
M: one (mono) molecule of NANA
2:designate the monomeric sequence of the carbohydrate attached to the ceramide.

Note that sphingomyeline is a sphingophospholipid and a sphingolipid, while cerebrosides and gangliosides are sphingolipids ONLY.



Sphingolipids' Synthesis Summary



*Note that phosphatadylcholine =phosphorylcholine + diacylglycerol

*Acidic glycosphingolipids: are negatively charged at physiologic pH. The negative charge is provided by NANA in gangliosides, or by sulfate groups in sulfatides.

Myelin Structure & Function

What is it?

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

It's function:

Myelin sheath insulates the nerve axon to:

1- avoid signal leakage.

2- greatly speeds up the transmission of impulses along axons.

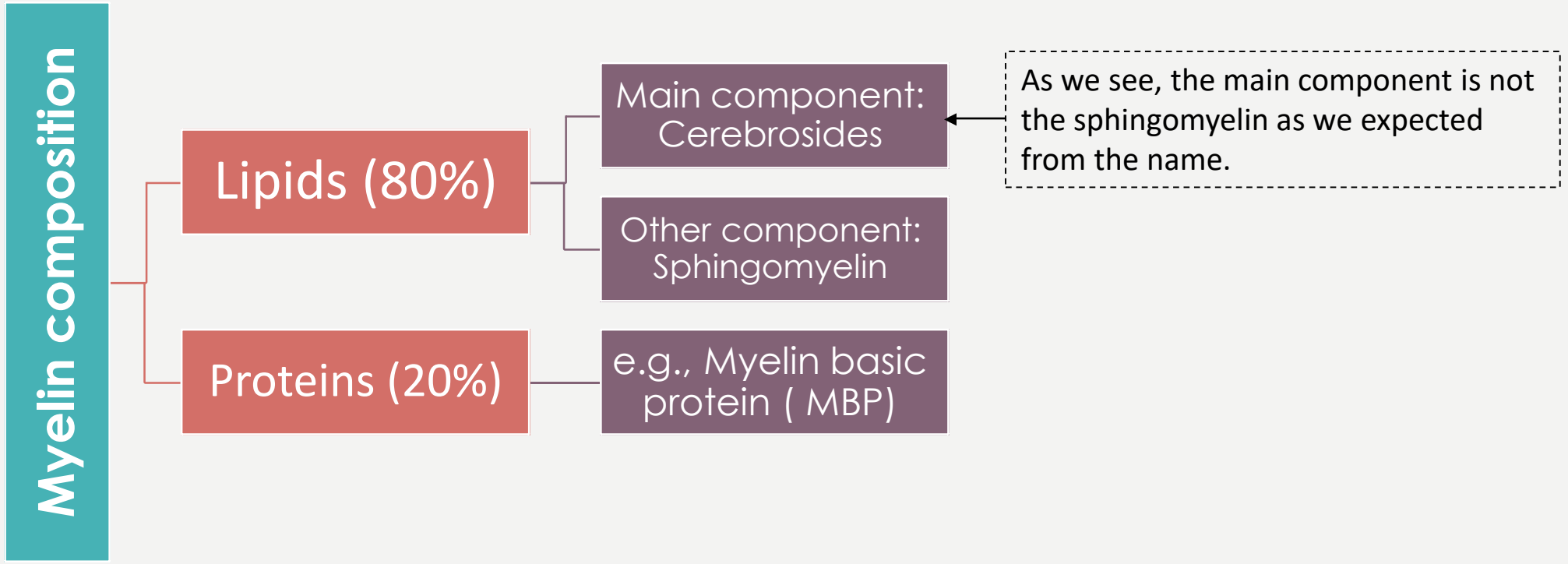
Myelin is produced by

- Schwann cells → Exist in Peripheral nerves
  - Each schwann cell forms the axon of only one neuron (discontinuously due to the presence of Ranvier nodes), while each oligodendrocyte forms the axon of maximally 40 neurons.
- Oligodendrocytes → Exist in CNS

Fatty acid of myelin sheath: Very long chain fatty acids, it's either [Lignoceric 24:0] or [Nervonic 24:1 (15)].

- The numbers between brackets : the left number refers to the number of the carbons, and the right number refers to the number of the double bonds in the structure, and "15" refers to the site of double bond – on carbon no.15). 0 = saturated , 1=unsaturated.
- Lignoceric is a SATURATED fatty acid due to the absence of double or triple bonds.
- Nervonic is unsaturated due to the presence of double bond in carbon 15.

Myelin Structure & Function



Multiple sclerosis

What is it?

A Neuro-degenerative, auto-immune disease.

How does it happen?

By the breakdown of myelin sheath (demyelination), which leads to a defective transmission of nerve impulses.

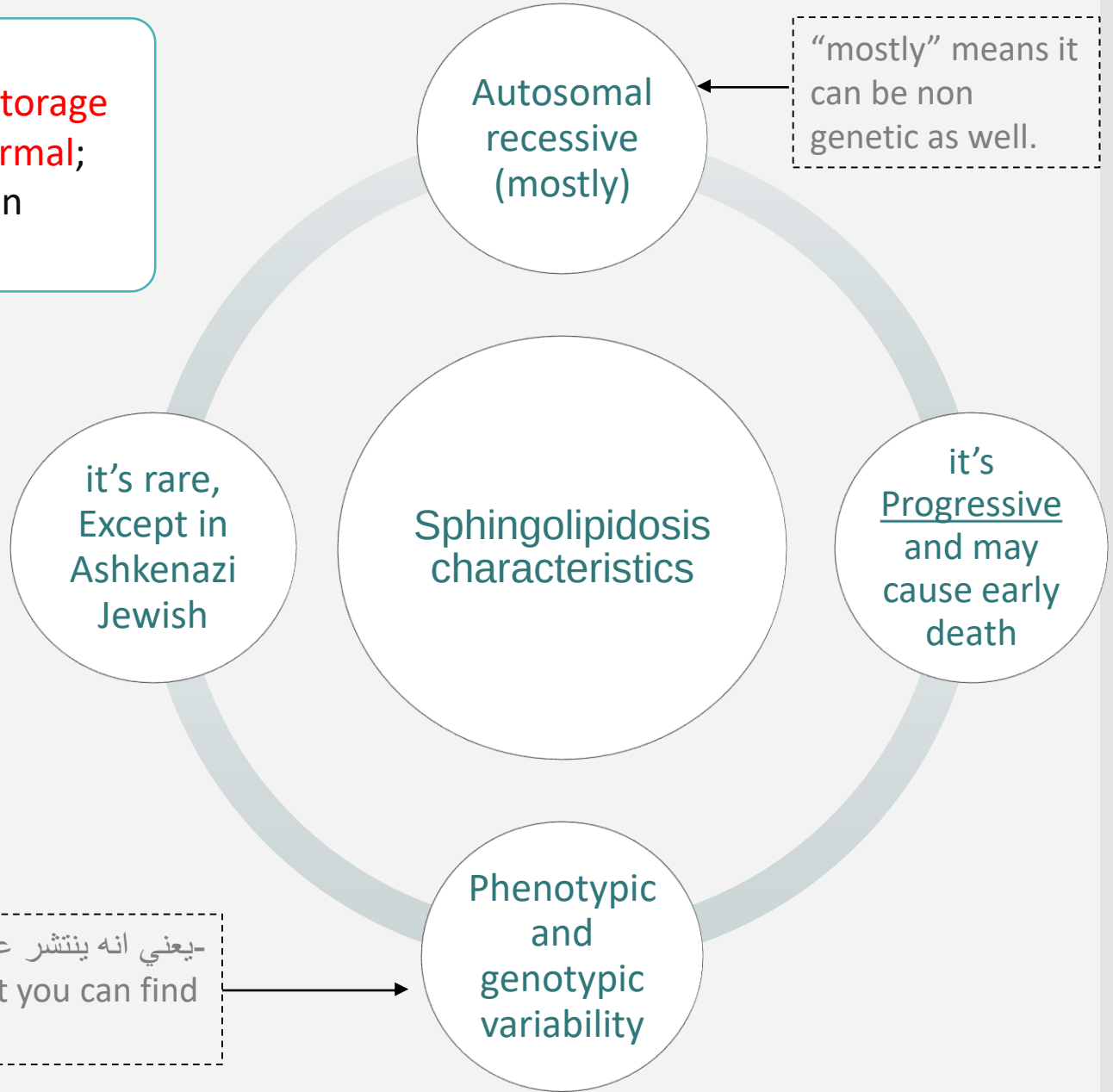
Sphingolipidosis

What is it?
An abnormal condition (known as lysosomal lipid storage disease) where the Synthesis of sphingolipids is normal; but the Degradation is defective, which will result in **Substrate accumulates in organs.**

Why is it called lysosomal lipid storage disease?
because the defected enzymes are in the lysosome, so the substrates will accumulate in the lysosomes.

Do not get confused between multiple sclerosis & sphingolipidosis!
Multiple sclerosis → demyelination.
(break down of myelin sheath).
sphingolipidosis → accumulation of sphingolipids.

-يعني انه ينتشر عند العائلات الي فيها افراد حاملين للمرض، مثل هذي الطائفة من اليهود.
-Genotypic variability means there's no specific gene that you can find the mutation on.



Sphingolipidosis

Diagnosis

ليه نقيس الـenzyme activity ؟
لأن الأنزيمات في هذه الحالة ما تكسر السفينجوليبدز، فنتأكد هي تعمل ولا لا.

Measure enzyme activity

By:

1-Culturing fibroblasts or peripheral leukocytes.

2-Culturing amniocytes (prenatal)

- ليه نسوي culture للفايبروبلاست او الليوكوسايت؟
لأن الجينات والكروموسومات هي نفسها بكل خلايا جسمنا فما فيه داعي اننا نبحث عن الطفرة في الخلايا العصبية، يكفي ان نأخذ من الجلد مثلا او خلايا الدم البيضاء أو غيرها عشان فيها جينات (إلا الـRBCs لكونها لا تحتوي على نواة وجينات)
- متى نسوي culture للـamniocytes ؟
اذا كنا شاكين بأن الأم حاملة للمرض وهي حامل نقدر نأخذ عينة من الـ amionic fluid ونسوي كلتشر ونشوف فعالية الانزيمات للسيفنجوليبدز عشان نتأكد

Histologic examination

يتم صبغ الخلية تحت المايكروسكوب، إن كان فيه المرض راح تكون الخلية فيها كثير lipids & lysosomes

DNA analysis

We do this when we know the exact gene that have the mutation

Sphingolipidosis

Treatment

Replacement Therapy

Recombinant human enzyme.

(like patients with hypothyroidism, we give them the thyroid hormone because they don't have it, likewise here we give the patient the protein (enzyme) that he doesn't have).

Bone marrow transplantation

For Gaucher disease.

(by taking stem cells form a normal person and give them to the patient with Gaucher disease).

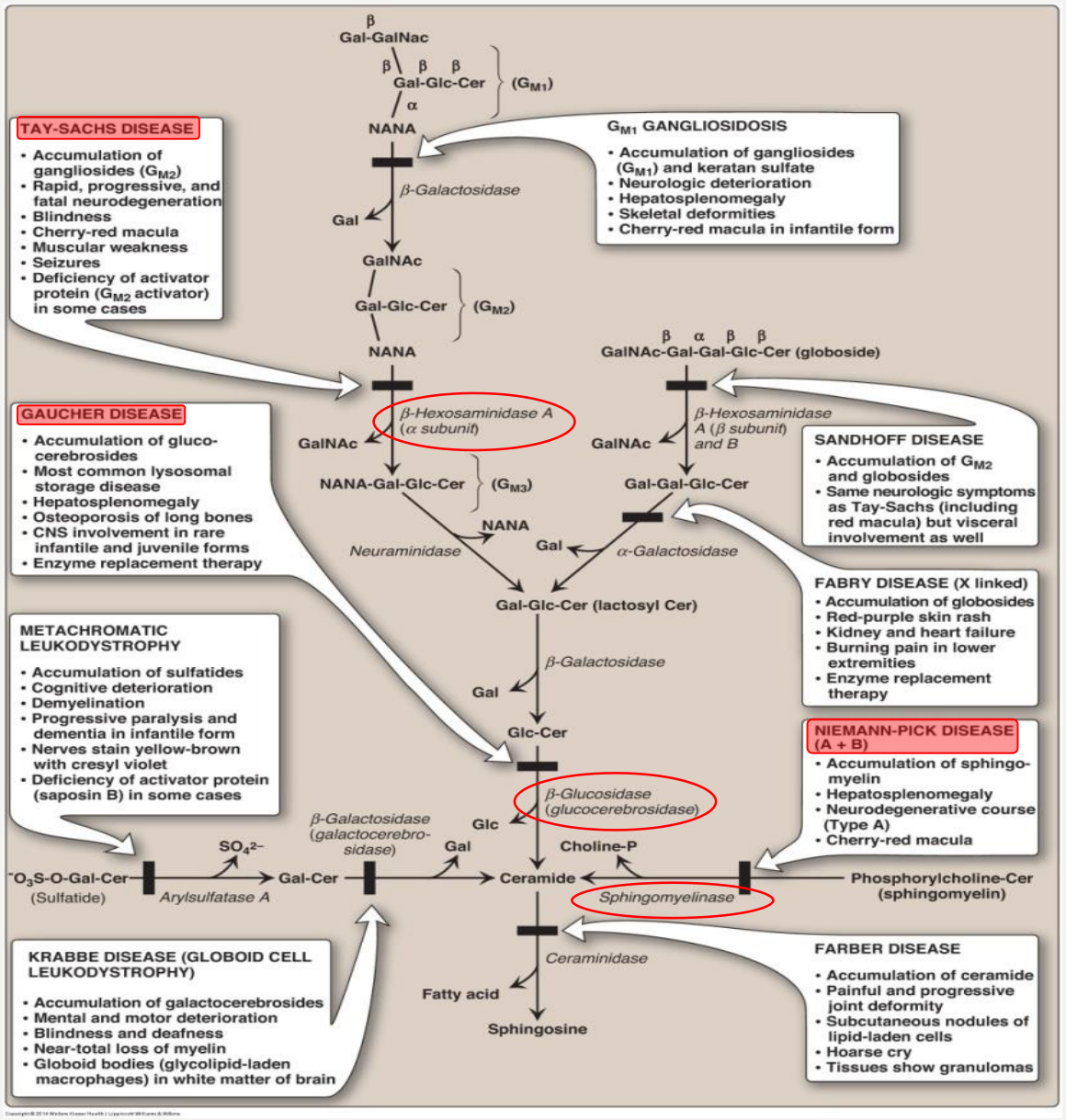
-it's effective because macrophages are derived from hematopoietic stem cells

Sphingolipidosis

Gaucher disease : it's a disease in which macrophages become engorged with glucocerebrosides and take the "crumpled tissue paper" appearance.

Why hepatosplenomegaly?
Because the enzymes are high in the spleen and liver, so when the enzymes defect the liver and spleen are the primary sites of lipid deposits and are, therefore, greatly enlarged.

Summarized in the next slide



نحن مطالبين فقط بالأمراض المحددة ، أسماؤها و خصائصها والانزيمات المتضررة فيها.

د. أحمد ركز على gaucher و niemann-pick وقال أن الثالث غير مهم، وقال أن أهم شيء هو أن نعرف الإنزيم المتضرر والمادة المترسبة في كل مرض.

Sphingolipidosis

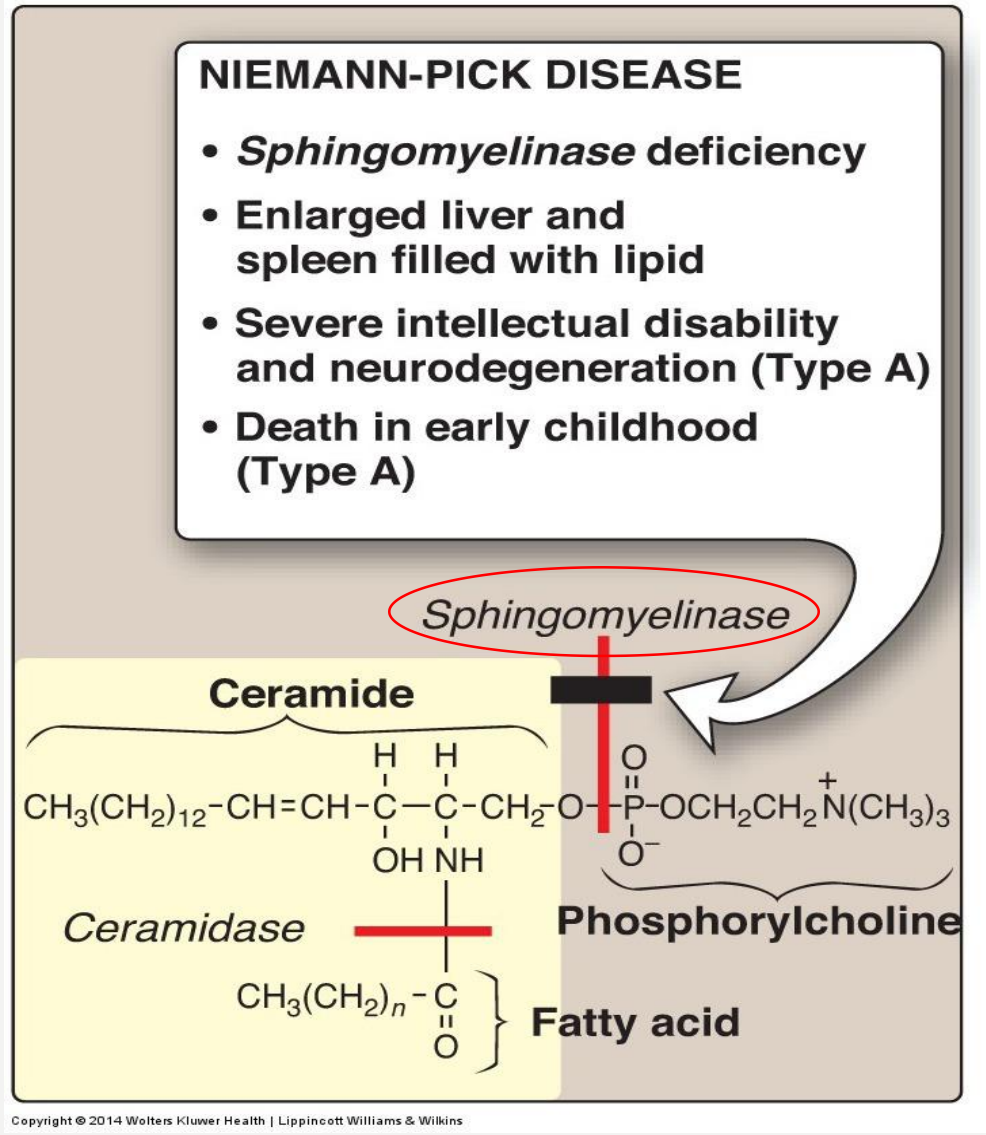
Biochemistry Team

Disease	Tay-sachs	Gaucher	Niemann-pick (A+B)	
Deficient Enzyme	β-Hexosaminidase A (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.	**Type A:** -Enzyme Activity is reduced to 1% and less than normal. -Fatal Disease -More severe. -Death in early childhood. - Hepatosplenomegaly -Neurodegenerative course. -*Cherry red macula	**Type B:** - Little enzyme act - Chronic Disease. -Less severe form type A -Later onset - Little enzyme act -Hepatosplenomegaly -*Cherry red macula

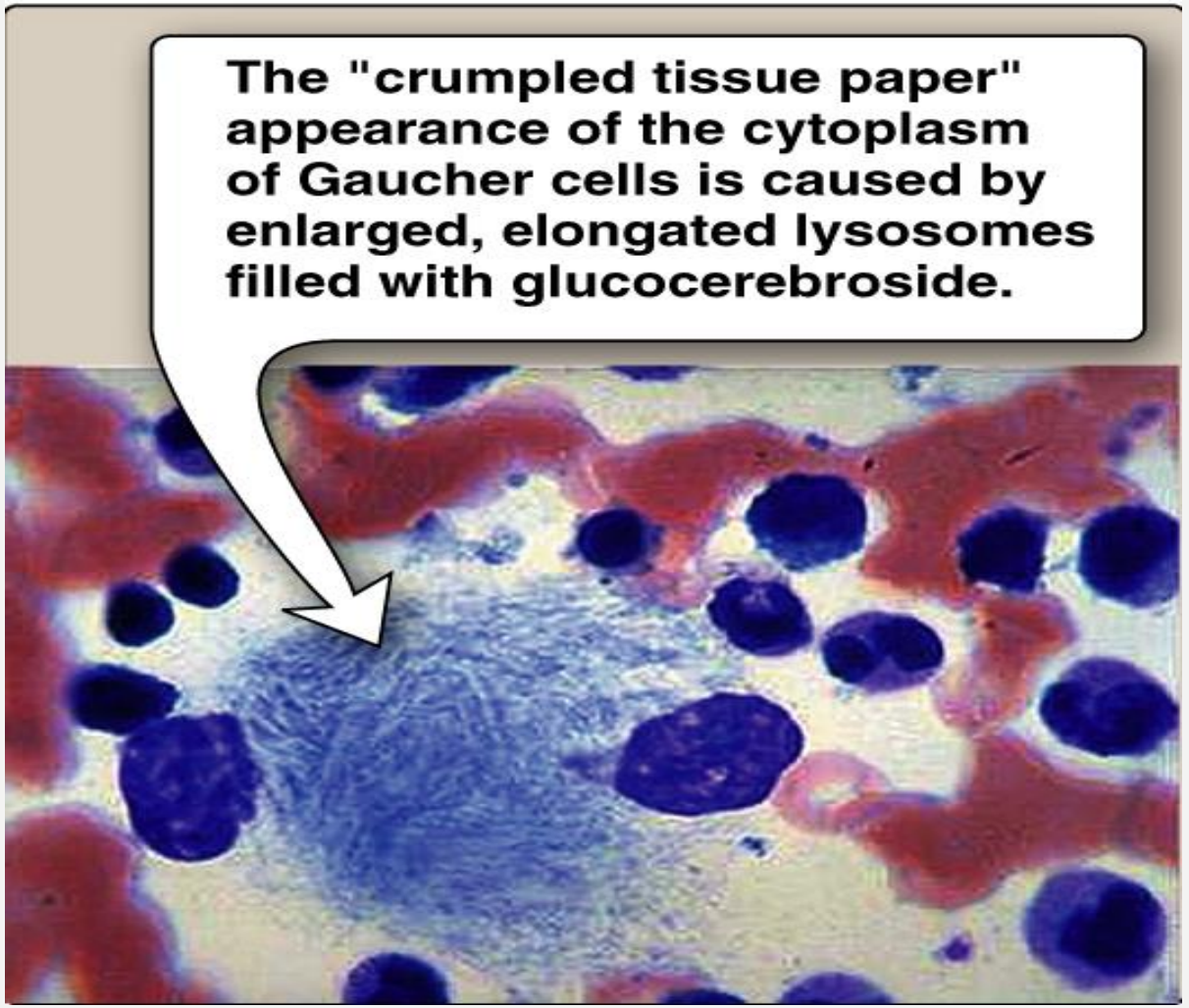
*Cherry-red macula is: There is an area in the retina that is called macula, it acts as a natural sun-block (it blocks ultraviolet rays that enter and harm the eye), usually it's yellow in color but when it's affected it becomes red under the light.

Examples of Sphingolipidosis

NIEMANN-PICK DISAESE



Gaucher Disease



MCQs

1-Sphingomyelin is made up of ceramide and:

A. Phosphorylcholine.
B. Monosaccharides.
C. Sphingosine.
D. fatty acid.

2-Which one of the following DOES NOT produce Myelin?

A. Oligodendrocytes.
B. Schwaan cells.
C. Microglia.

- **3-Which one of the following is the precursor of sphingolipids?**

A. Phosphorylcholine.
B. Monosaccharides.
C. Sphingosine.
D. Ceramide.

4-Which one of the following is considered the main component of myelin composition?

A. Cerebrosides.
B. Sphingomyelin.
C. Sphingosine.
D. fatty acid.

5-In sphingolipidosis synthesis is _____ and degradation is _____

A. Defective, normal.
B. Normal, normal.
C. Normal, defective.
D. Defective, defective.

1-A
2-C
3-D
4-A
5-C

MCQs

- **6-Patient with sphingomyelinase deficiency will most likely develop..**

A. Gaucher disease.

B. Farbry disease.

C. Tay-sachs disease.

D. Niemann-pick disease.

7-Which one of the following diseases involves osteoporosis of long bones?

A. Gaucher disease.

B. Farbry disease.

C. Tay-sachs disease.

D. Niemann-pick disease.

8-Which one of the following diseases DOES NOT involve hepatosplenomegaly?

A. Gaucher disease.

B. Tay-sachs disease.

C. Niemann-pick disease.

9-A Neuro-degenerative, auto-immune disease that involves the breakdown of myelin sheath

A. Multiple sclerosis.

B. Tay-sachs disease.

C. Niemann-pick disease.

D. Fabry disease .

10-In which of the following diseases would you see a crumpled tissue paper appearance?

A. Gaucher disease.

B. Tay-sachs disease.

C. Niemann-pick disease.

6-D
7-A
8-B
9-A
10-A

SAQs

❖ **Q1:A mother of a 7 months old infant came to the pediatric clinic ,complaining that her child has noticeably decreased his daily movement (sitting, turning, crawling).The mother also noted a decreased response to visual stimuli. After further investigation, the physician identified the presence of a red cherry macula of the infant's retina.(note : that the infant is of Jewish decent).**

1-What is the most likely diagnosis?

Tay-Sachs disease.

2-What is the cause of this disease?

Beta-hexoseaminidase A deficiency or defect /may also be due to deficiency of activator protein(GM2 ACTIVATOR).

3-What is the accumulating substance in this disease?

gangliosides (GM2).

4-What are other symptoms the infant may present with as the disease progresses?

Blindness, muscular weakness, seizures.

5-What is the prognosis?

Bad prognosis due to its ultimate fatality.

SAQs

❖ **Q2:How are sphingolipidosis diseases diagnosed prenatally and postnatally?**

Prenatally By: PRENATAL DNA analysis or by culture of amniocytes.

Postnatally By: POSTNATAL DNA analysis ,histological examination, culture fibroblasts and peripheral leukocytes to check for enzyme deficiencies in said cells.

Q3:A mother of a three month old infant came to the ER when she noticed that her infant has a noticeably enlarged abdomen. Upon physical and radiological examination, hepatosplenomegaly and cherry red macula were found present in the infant. Blood testing confirmed deficiency of sphingomyelinase enzyme. What is the most likely diagnosis?

Niemann-pick disease (type A)

we specifically stated that it was type A because the disease had an early manifestation ,with increased severity.

-EXTRA: diagnosis of Niemann-Pick is made by checking the levels of sphingomyelinase in WBCs of blood or bone marrow.

SAQs

❖ **Q4:A 25 year old woman with a history that included hepatosplenomegaly with eventual removal of spleen, with bone and joint pain with several fractures of the femur, and a liver autopsy showed wrinkled looking cells with accumulation of glucosylceramides.**

What is the likely diagnosis ?

The adult form of Gaucher disease.

Explanation: because adult Gaucher disease presents with hepatosplenomegaly, osteoporosis of long bones with a characteristic appearance of wrinkled cytosol cells.

What is the cause of this disease?

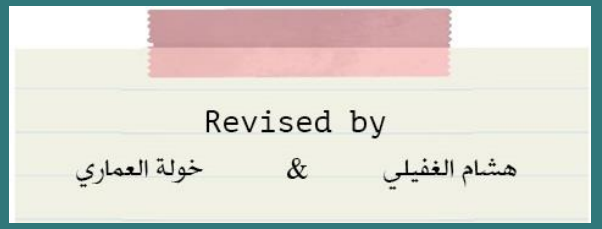
Deficiency in beta-glucosidase enzyme A (alpha subunit).

Team Members:

- لينا اسماعيل.
- سارة الخليفة.
- ربى السليمي.
- ملاك الشريف.
- مروج الحربي.
- نوف الرشيد.
- رفان هاشم.
- ثاني معافى .
- خالد النعيم.
- فارس المطيري.
- أحمد الرويلي.
- إبراهيم الشايع.
- فراس المؤمن.
- محمد الصهيل.
- عبدالله الشنيفي.

Team Leaders:

- عبدالله الغزي.
- نوف العبدالكريم.



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