YU - MEDICINE
PASSION ACADEMIC TEAM

Central Nervous System

Sheet# 2 - Biochemistry

Lec. Title : The Biochemical Basis of Selective Neurological Disorders

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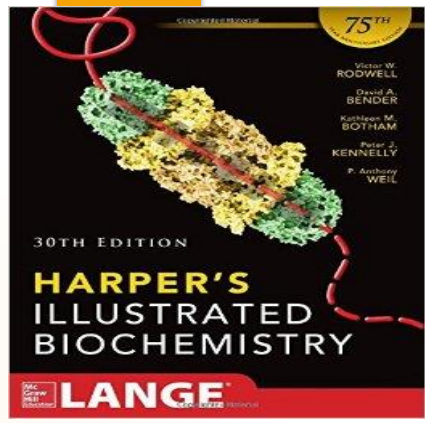
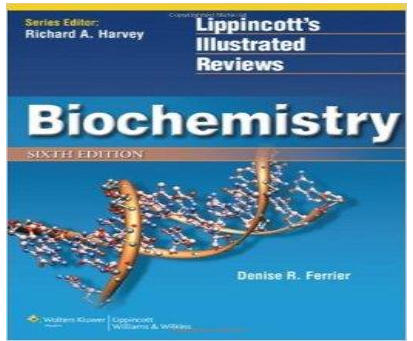
The Biochemical Basis of Selective Neurological Disorders

DR. MAZHAR AL ZOUBI | CNS-BIOCHEMISTRY 2



CHAPTER 24



Outline

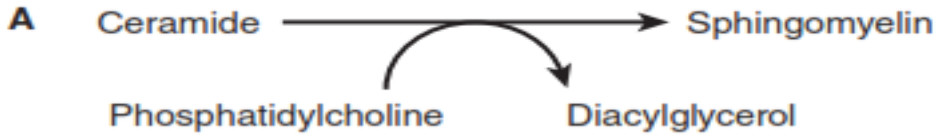
1. Discuss the sphingolipids metabolism and their disorders (sphingolipidoses)
2. Understand the biochemical bases of Huntington disease
3. Understand the biochemical bases of Alzheimer disease
4. Understand the role of biochemical mechanisms in brain damage due to stroke

Sphingolipids metabolism and their disorders (Sphingolipidoses)

ALL SPHINGOLIPIDS ARE FORMED FROM CERAMIDE

What is Ceramide ?

combination of Sphingosine and fatty acid



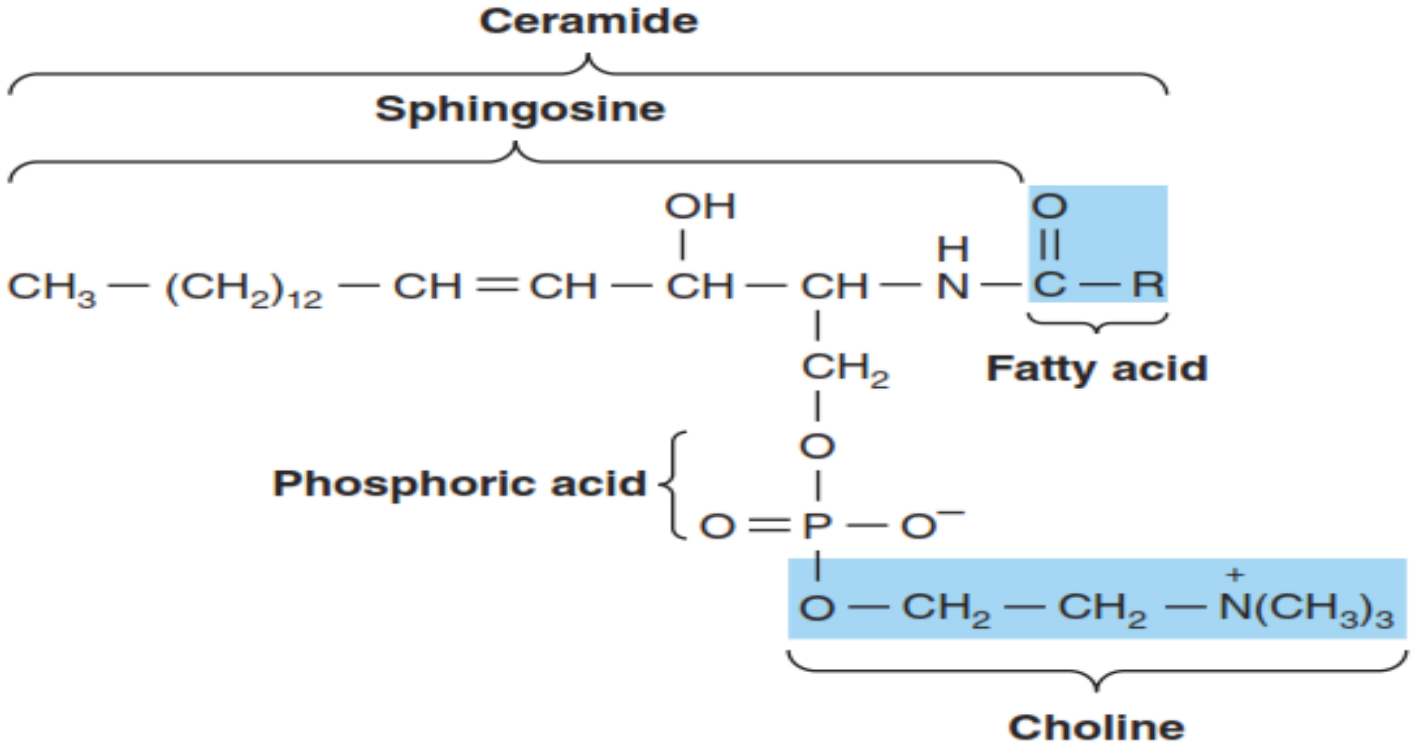


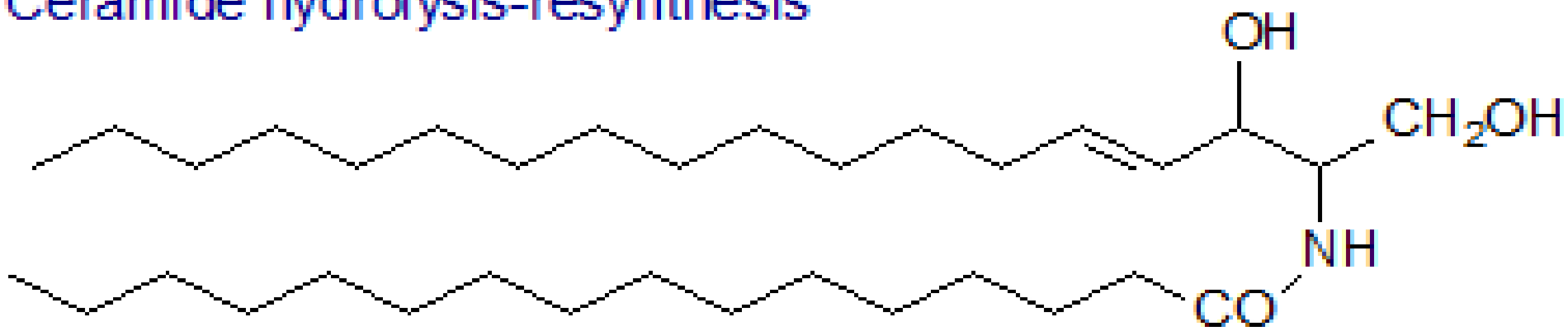
FIGURE 21–11 A sphingomyelin.

the sphingolipids look slide structure that you see .this is called sphingomyelin as lipid and the reason for that is the presence what we called sphingosine structure which contain or consist of the basic structure of base which is called base in this case is choline and the presence of this hydrocarbon chain so this structure which is include these two molecules is called sphingosine .if you add fatty acid to the sphingosine to tell molecule be called ceramide ,so the ceramide is one of the sphingolipid it is that contain sphingosine .and everytime you change the base (choline)you will change the structure of sphingolipid means when you are going to come new sphingolipid .so the disorder of sphingolipid metabolism relate to type of the sphingolipid that we are going to talk about .

so basically it consist of this basic structure which is called sphingosine and sphingosine consist of this hydrocarbon chain as well as choline >fatty acid it will form what is called ceramide (ceramide combination of Sphingosine and fatty acid)and this is prosess how we form sphingomyelin specifically e.g. choline >sphingomyelin >sphingolipid.

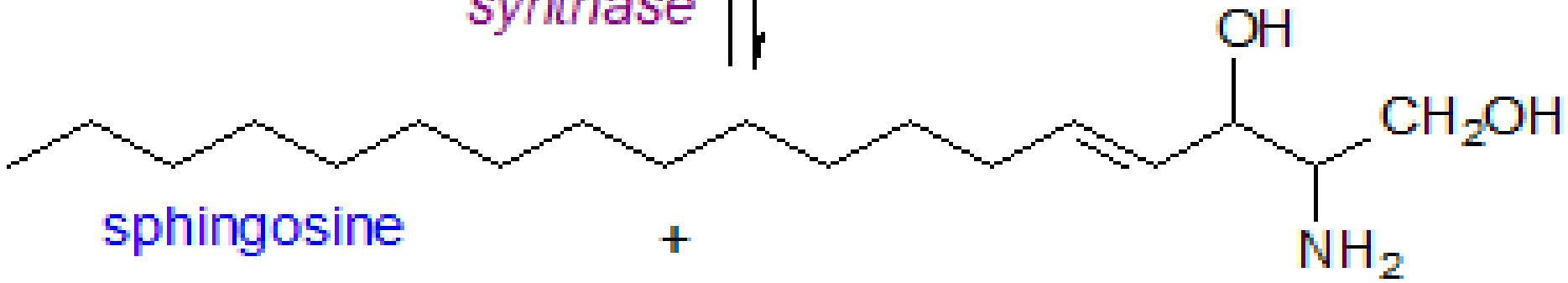
ceramide is conjugated to phosphatidylcholine in order to form sphingomyelin structure by transferase activity (transferring group from one molecule to another).

Ceramide hydrolysis-resynthesis



ceramide

ceramide synthase ⇌ *ceramidase*



sphingosine

+

fatty acid

The sphingolipid and ceramide as one of the sphingolipid are subjected to metabolism of either synthesis or degradation ,so ceramidase is responsible for degradation of ceramide to form sphingosine and fatty acid
otherwise ceramide molecule synthase is responsible for formation of the ceramide molecule and depend on the need of that molecule .

Ceramide

Signaling molecule (second messenger):

1. **Apoptosis.**
2. **Cell cycle.**
3. **Cell differentiation**
4. **Senescence.**

This molecule is working as signaling molecule very important signaling pathway in:

1)apoptosis : which is organised or regulated death(عمليةdeath مبرمج)
2)cell cycle : how going to be proceed or not
3)cell differentiation
4)senescence :aging of cells.

اذا بدنا نذكر second messenger نتذكر cAMP

ceramide (second messenger in this case)has cascade reaction (down sphingo cascade reaction)>> بمعنى آخر بأثر على moleculeمثل kinesis and will start to do what we called cascade continuous reaction

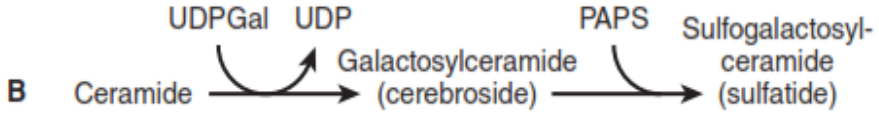
نفس الشي بالنسبة للceramide >>will ....or it will regulate function of other proteins (down step enzyme)

بمعنى اخر انه pathway ماشيين من فوق لتحت.

Glycosphingolipids Are a Combination of Ceramide With One or More Sugar Residues

❖ **Glycosphingolipids (cerebrosides) :** The major glycolipids found in animal tissues.

❑ **Galactosylceramide (GalCer):** is a major glycosphingolipid of brain and other nervous tissue.



Golgi apparatus

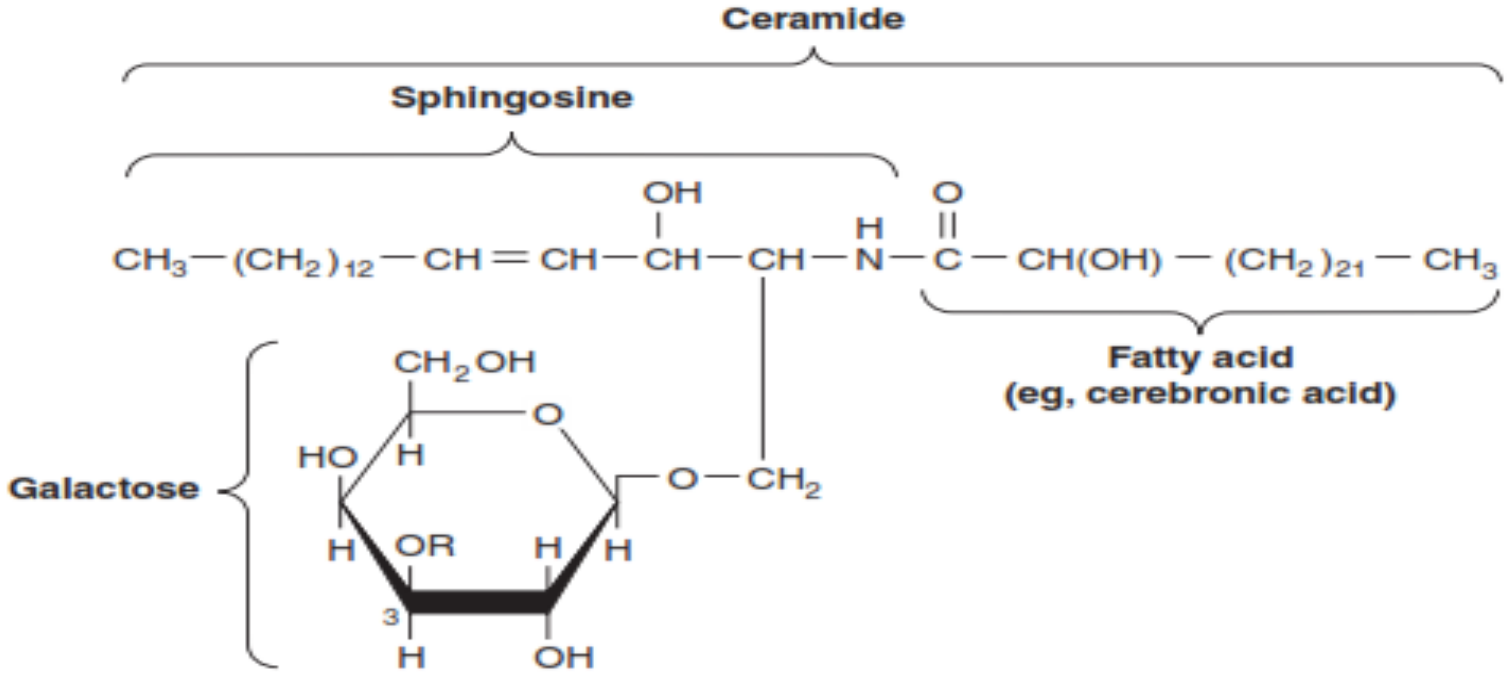


FIGURE 21–15 Structure of galactosylceramide.

This is another example of sphingolipid and here we can see change in structure of sphingolipid and this sphingolipid is conjugated with carbohydrate that's why this kind of sphingolipid is called glycosphingolipid .
عند اضافة carbohydrate على sphingolipid بتزيد التعقيد وبتزيد ال posability لل function بالنسبة لهذول sphingolipid.

مثال: اذا اضفنا glycosphingolipid بوجود الجلوكوز(glyco usually mentioned the presence of glucose)

if you add glucose to previous molecule (ceramide molecule)basically instead of choline it will be called glycosphingolipid (cerebrosides)

if you add galactose it will be called Galactosylceramide (GalCer).>> galactosyl means that we have covalent bond in the galactose and ceramide molecules

B)we have enzyme and other form of galactose for example in order to conjugated with ceramide so we have transferase enzyme that is responsible to formation of cerebroside molecule and by action of another molecule sulfer containing molecule it will form another molecule(sulfo galactosylceramide).

Glycosphinogolipids

GalCer is a major lipid of **myelin**

GlcCer is the major glycosphingolipid of **extraneural tissues** and a **precursor** of most of the more complex glycosphingolipids.

Gangliosides are synthesized from **ceramide** by the stepwise addition of **activated sugars** (eg, UDPGlc and UDPGal) and a
Sialic acid, usually N-acetylneuraminic acid

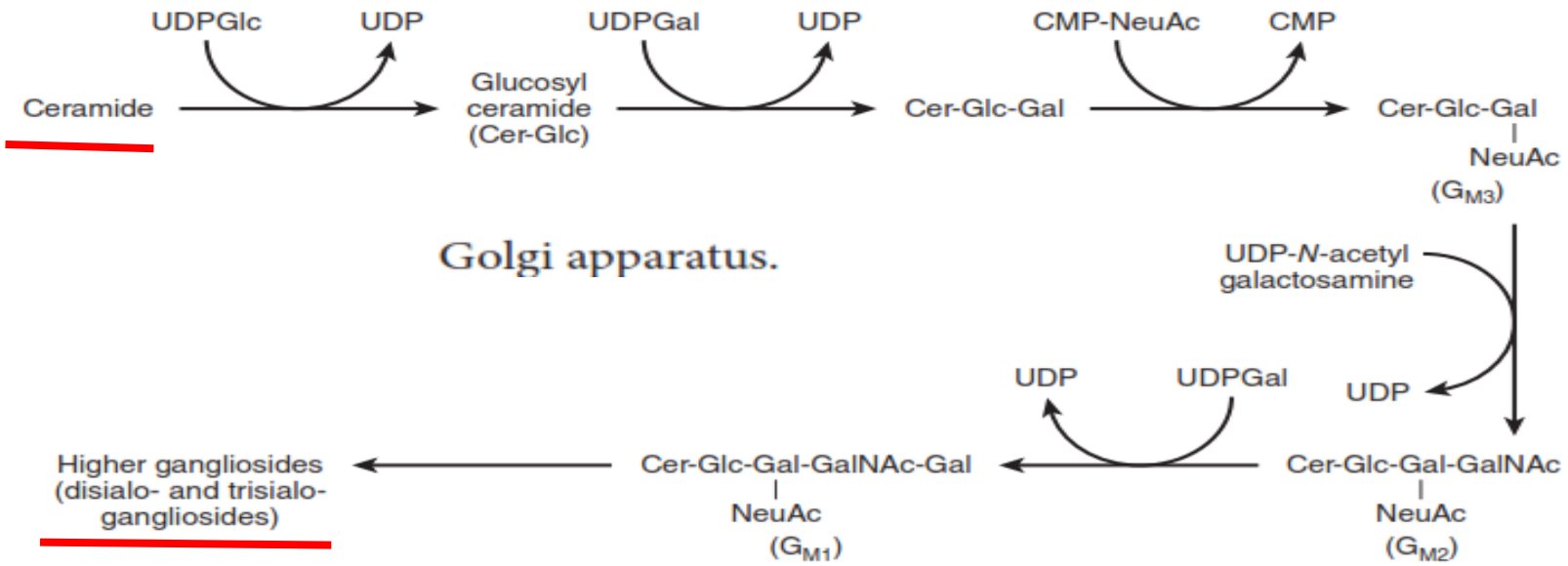


FIGURE 24–9 **Biosynthesis of gangliosides.** (NeuAc, *N*-acetylneuraminic acid.)

We can imagine the complexity of the glycosphingolipid due to impossibility of glycosylation or due to possibility of add different type of carbohydrate.
in general modification to proteins almost perform in golgi apparatus
we have enzyme that are responsible for addition and removing of carbohydrate
GlcCer >>>starting with ceramide >>>>>>glucosylceramide >>> we can modified in order to make different type of glycosphingolipid

(cer-gle contain glucose +galactose)>>>>and so on we add another type of carbohydrate to modify.

Role of Glycosphinogolipids

- **Glycosphingolipids** are constituents of the outer leaflet of plasma membranes and are important in **cell adhesion and cell recognition.**

- **Some are antigens, for example, ABO blood** group substances.

- Certain gangliosides function **as receptors for bacterial toxins** (eg, for **cholera toxin, which subsequently** activates adenylyl cyclase).

CLINICAL ASPECTS

Phospholipids & Sphingolipids are Involved in Multiple Sclerosis and Lipidoses

Classified into two groups:

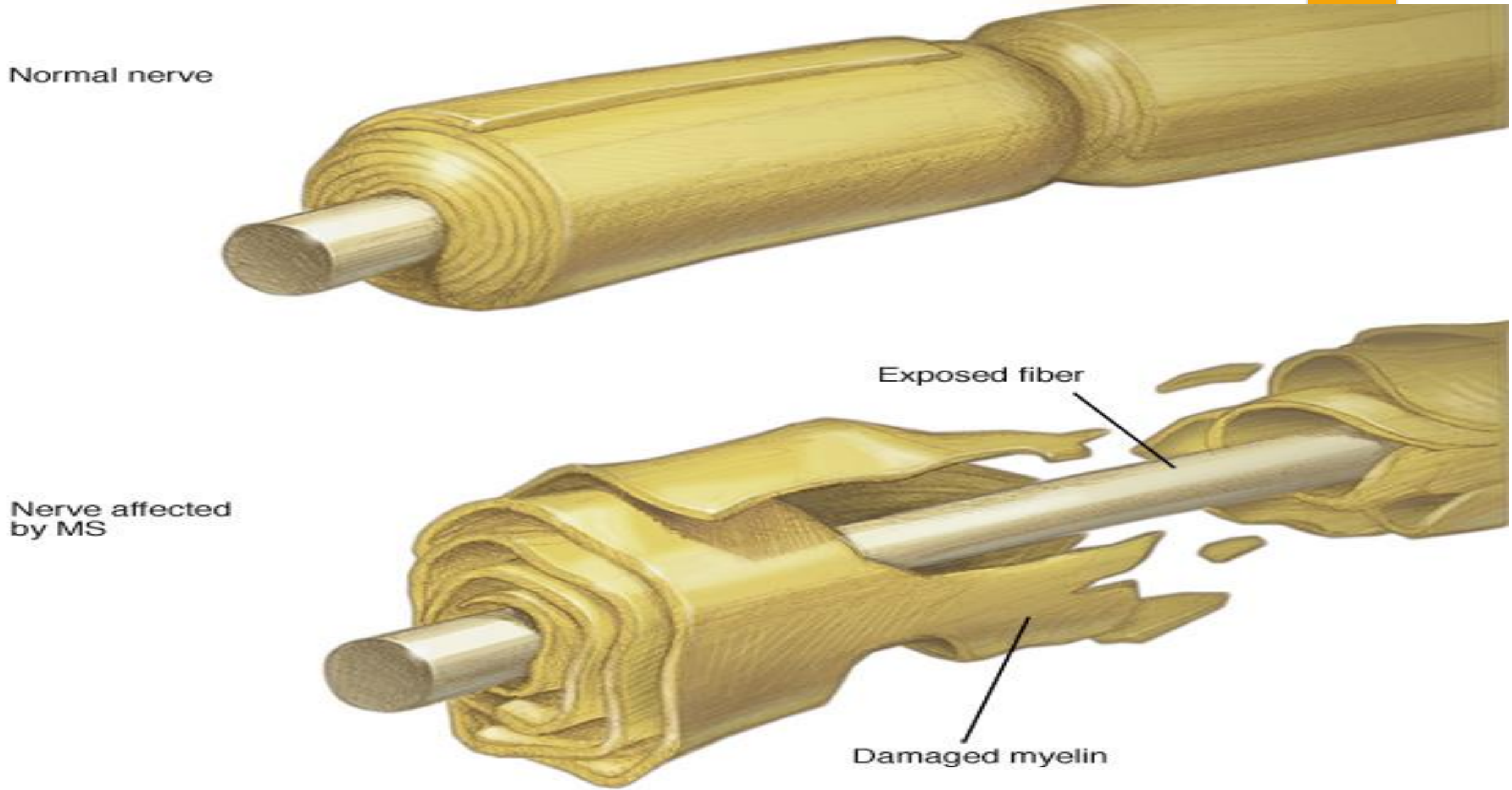
(1) True demyelinating diseases: **multiple sclerosis**
(2) Sphingolipidoses: **lipid storage diseases**

Multiple sclerosis: loss of both phospholipids (particularly **ethanolamin**e **plasmalogen**) and of sphingolipids from white matter.

The CSF shows raised phospholipid levels.

phospholipid=glycerol+2 fatty acid +phosphate.
it completely different from sphingolipid.

sclerosis >> التصلب اللويحي>>it related to degradation of nervous system specifically protection shell the nerve cells most exposed or most important in this disease .



Sphingolipidoses

(lipid storage diseases) are a group of inherited diseases that are caused by a genetic defect in the catabolism of lipids containing sphingosine. **(lysosomal disorders)**

Features:

(1) Complex lipids containing ceramide accumulate in cells, particularly neurons, causing neurodegeneration and shortening the lifespan.

(1) The rate of **synthesis** of the stored lipid is **normal**.

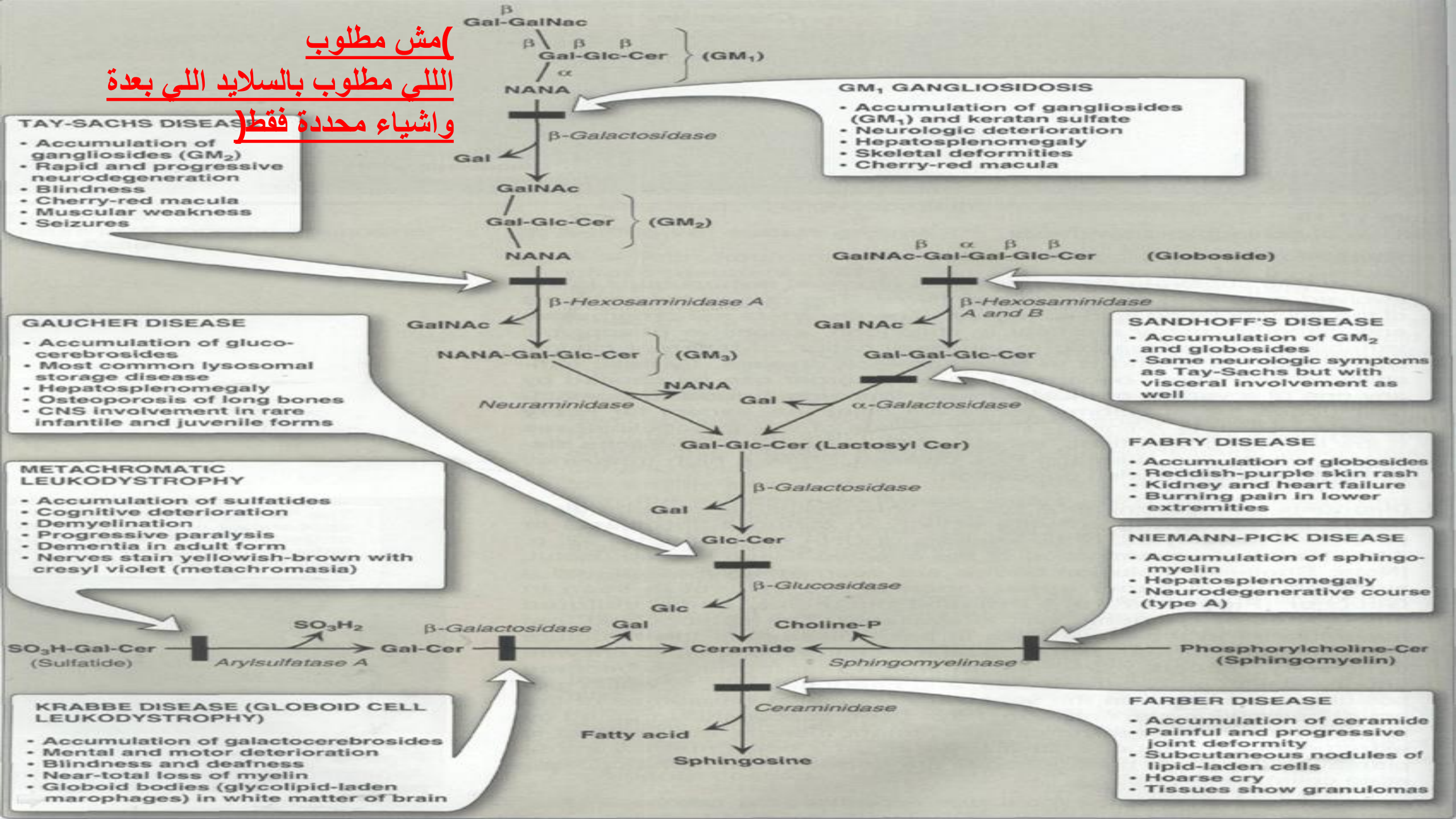
(1) The enzymatic defect is in the **lysosomal degradation pathway** of sphingolipids.

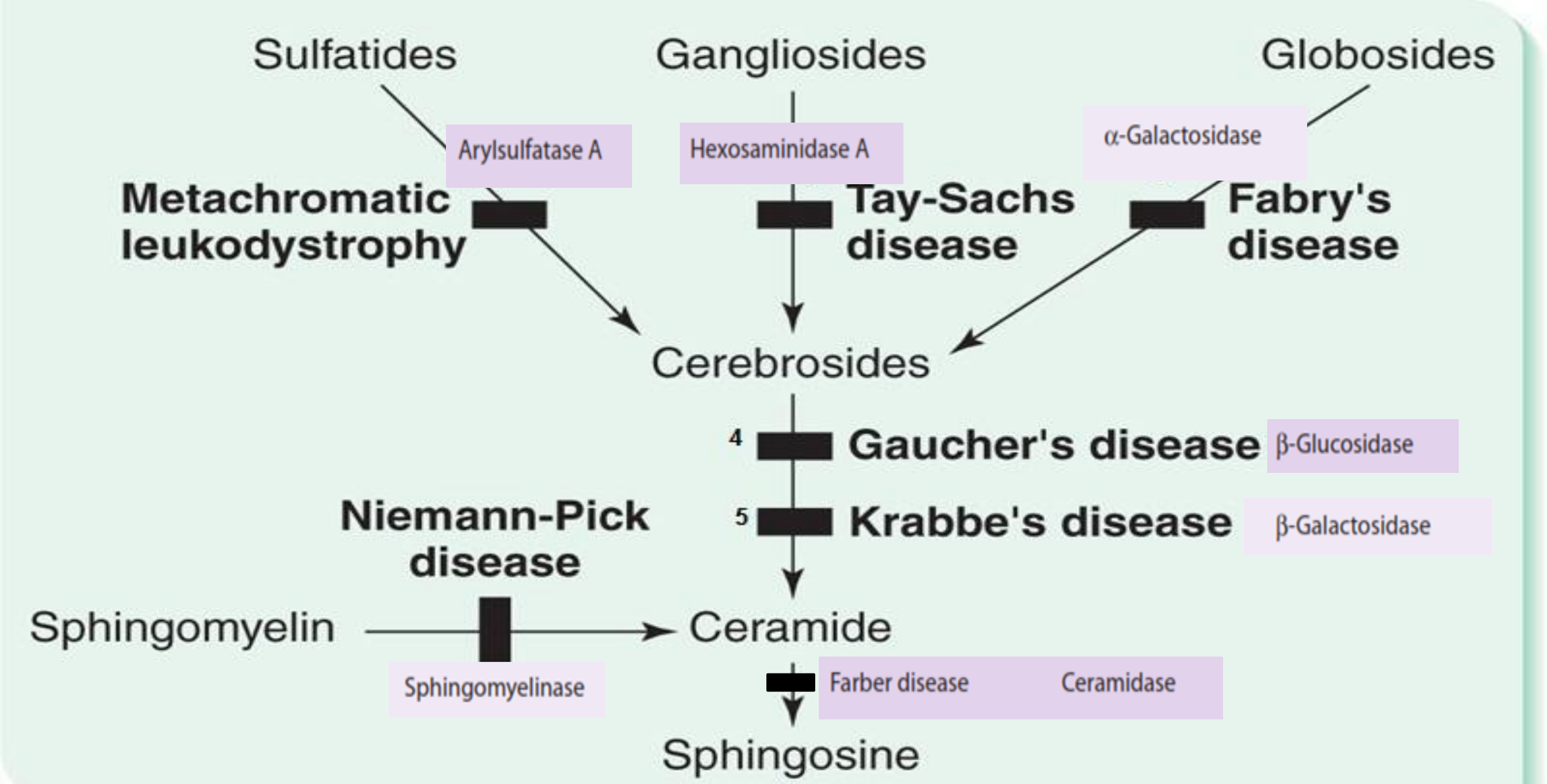
(1) The extent to which the activity of the affected enzyme is decreased is similar in all tissues.

We have deficiency in catabolism .

بشبه كثير>>>glycogen storage disease
deficiency بالانزيمات المسؤولة عن ادا كان عنا
degradation of glycogen .

so we have glycogen storage disease like pompe disease.


مش مطلوب)
اللي مطلوب بالسلايد اللي بعدة
واشياء محددة فقط)
β Gal-GalNac
β β β
Gal-Glc-Cer (GM1)
α
NANA
β-Galactosidase
Gal
GalNAc
Gal-Glc-Cer (GM2)
NANA
β-Hexosaminidase A
GalNAc
NANA-Gal-Glc-Cer (GM3)
Neuraminidase
NANA
Gal-Glc-Cer (Lactosyl Cer)
β-Galactosidase
Gal
Glc-Cer
β-Glucosidase
Glc
Ceramide
Ceraminidase
Fatty acid
Sphingosine
GalNAc-Gal-Gal-Glc-Cer (Globoside)
β-Hexosaminidase A and B
Gal NAc
Gal-Gal-Glc-Cer
α-Galactosidase
Gal
SO3H2
SO3H-Gal-Cer
(Sulfatide)
Arylsulfatase A
Gal-Cer
β-Galactosidase
Gal
Choline-P
Sphingomyelinase
Phosphorylcholine-Cer
(Sphingomyelin)
GM1 GANGLIOSIDOSIS
- Accumulation of gangliosides (GM1) and keratan sulfate
- Neurologic deterioration
- Hepatosplenomegaly
- Skeletal deformities
- Cherry-red macula
TAY-SACHS DISEASE
- Accumulation of gangliosides (GM2)
- Rapid and progressive neurodegeneration
- Blindness
- Cherry-red macula
- Muscular weakness
- Seizures
GAUCHER DISEASE
- Accumulation of gluco-cerebrosides
- Most common lysosomal storage disease
- Hepatosplenomegaly
- Osteoporosis of long bones
- CNS involvement in rare infantile and juvenile forms
METACHROMATIC LEUKODYSTROPHY
- Accumulation of sulfatides
- Cognitive deterioration
- Demyelination
- Progressive paralysis
- Dementia in adult form
- Nerves stain yellowish-brown with cresyl violet (metachromasia)
KRABBE DISEASE (GLOBOID CELL LEUKODYSTROPHY)
- Accumulation of galactocerebrosides
- Mental and motor deterioration
- Blindness and deafness
- Near-total loss of myelin
- Globoid bodies (glycolipid-laden marophages) in white matter of brain
SANDHOFF'S DISEASE
- Accumulation of GM2 and globosides
- Same neurologic symptoms as Tay-Sachs but with visceral involvement as well
FABRY DISEASE
- Accumulation of globosides
- Reddish-purple skin rash
- Kidney and heart failure
- Burning pain in lower extremities
NIEMANN-PICK DISEASE
- Accumulation of sphingo-myelin
- Hepatosplenomegaly
- Neurodegenerative course (type A)
FARBER DISEASE
- Accumulation of ceramide
- Painful and progressive joint deformity
- Subcutaneous nodules of lipid-laden cells
- Hoarse cry
- Tissues show granulomas



السبب

*Metachromatic leukodystrophy >>> Arylsulfatase A deficiency

*Tay sachs disease one of lipid metabolism disorder >>> السبب Hexosaminidase A deficiency .

*Fabry's disease >>> alpha -galactosidase deficiency

*Niemann-pick disease on of the common ..... disease >>>sphingomyelinase deficiency.

*Farbar disease more rapidly accumulation of ceramide molecule that deficiency in ceramidase enzyme .

*Gaucher's disease >>> beta-glucosidase enzyme.

*krabbe's disease >>> beta-galactosidase.

TABLE 24–1 Examples of Sphingolipidoses

Disease	Enzyme Deficiency	Lipid Accumulating	Clinical Symptoms
Tay-Sachs disease	Hexosaminidase A	Cer—Glc—Gal(NeuAc)–÷–GalNAc G_{M2} Ganglioside	Mental retardation, blindness, muscular weakness
Fabry disease	α-Galactosidase	Cer—Glc—Gal—÷–Gal Globotriaosylceramide	Skin rash, kidney failure (full symptoms only in males; X-linked recessive)
Metachromatic leukodystrophy	Arylsulfatase A	Cer—Gal—÷–OSO_3 3-Sulfogalactosylceramide	Mental retardation and psychologic disturbances in adults; demyelination
Krabbe disease	β-Galactosidase	Cer—÷–Gal Galactosylceramide	Mental retardation; myelin almost absent
Gaucher disease	β-Glucosidase	Cer—÷–Glc Glucosylceramide	Enlarged liver and spleen, erosion of long bones, mental retardation in infants
Niemann-Pick disease	Sphingomyelinase	Cer—÷–P—choline Sphingomyelin	Enlarged liver and spleen, mental retardation; fatal in early life
Farber disease	Ceramidase	Acyl—÷–Sphingosine Ceramide	Hoarseness, dermatitis, skeletal deformation, mental retardation; fatal in early life

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Abbreviations: Cer, ceramide; Gal, galactose; Glc, glucose; NeuAc, *N*-acetylneuraminic acid; ÷, site of deficient enzyme reaction.

Multiple sulfatase deficiency

Multiple sulfatase deficiency results in accumulation of:

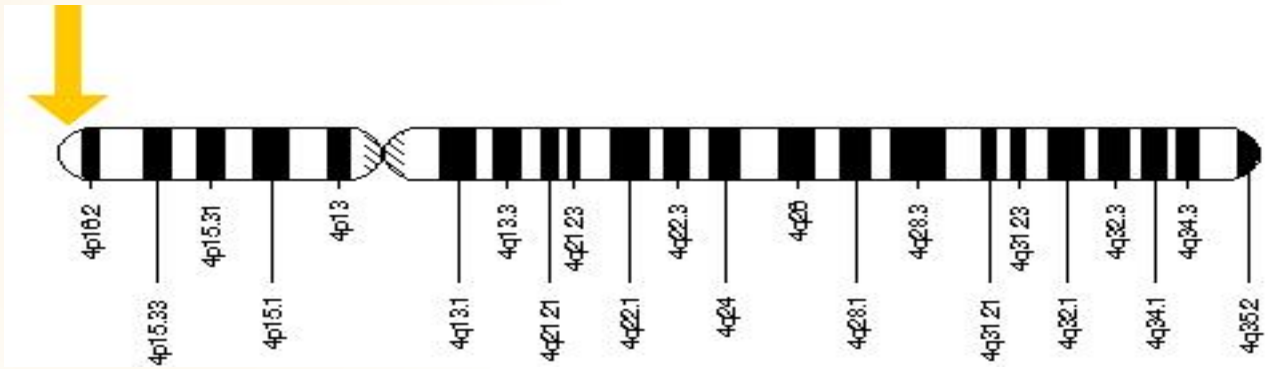
1. *Sulfogalactosylceramide*.
2. Steroid sulfates.
3. ***Proteoglycans*** owing to a combined deficiency of arylsulfatases A, B, and C and steroid sulfatase.

This kind of disease is related to unusual molecule (sulfo galactosylceramide molecule)>> نفسه galactosylceramide لكن مضاف اليه sulfate .

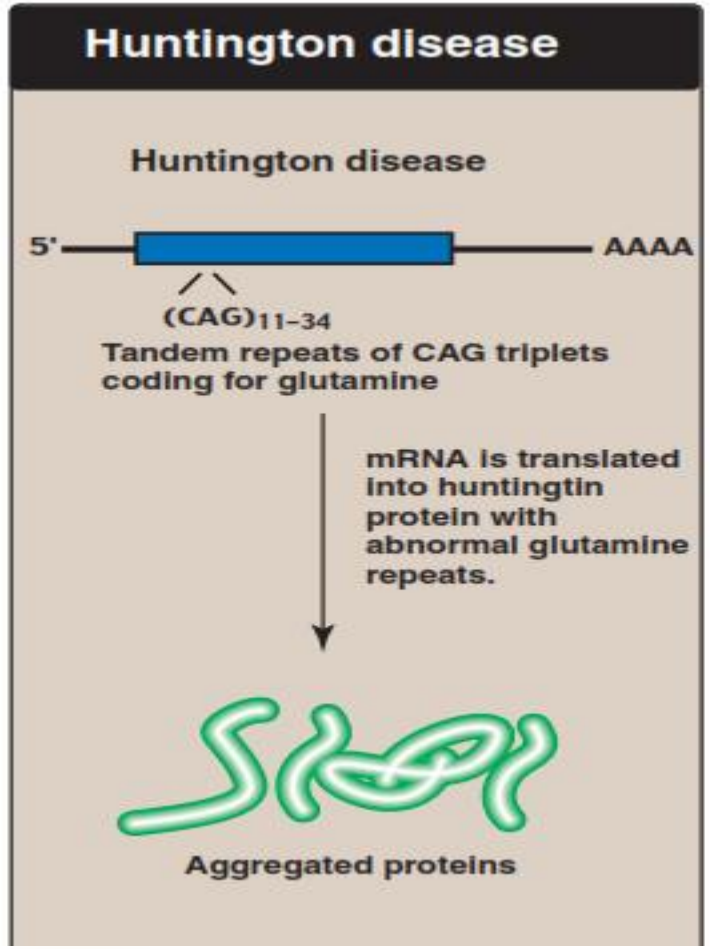
so their accumulation of this molecule or steroid sulfates or proteoglycans in the nervous system .

Huntington disease

- 1983—The gene for Huntington disease is mapped. 4p
- Trinucleotide sequences ((CAG)) repeated in abnormal # in *HTT* gene
- ***Associated with aggregation of amyloids***
- Adult-onset Huntington disease



Cytogenetic Location: 4p16.3



gene in short arm on chromosome 4.
CAG is coded for >>>glutamine .
CAG >>> بتعطينا ما بين11-34 glutamine
in huntington disease>>>aggregation of this protein and they noticed that >>> أنه البروتين عندهم فيهrepeats أكثر من الناس الطبيعية
so they assumed the repeats of glutamine they cause aggregation of this protein which will cause the huntington disease development.
and this disease is age related in progression the disease is called age onset disease >> يعني في فترة معينة يكون الإنسانadult فجأه بصير يتفاقم المرض
* ما بكون ظاهر في بدايات العمر بالنسبة للشخص اللي رح ينصاب*
ممكن يكون المرض موجود بالعائلة جينياً لكن ما يتم اكتشافه عند هذا الشخص ال بعد ما يصير adult او حاجة الجسم هو السببnervous system لإنتاج هذا النوع من البروتين
كثير يصير عنا هذا المرض ؟ repeat السؤال المهم؟ عل شرط لما يكون عنا الجواب هو لا مش شرط
وهذا بوضح انه المرضgenetically factorial

Huntington disease

I. Huntington disease affects an estimated 3 to 7 per 100,000 people of European ancestry

I. Normally, the CAG segment is repeated 10 to 35 times within the gene.

I. Huntington disease, the CAG segment is repeated 36 to more than 120 times.

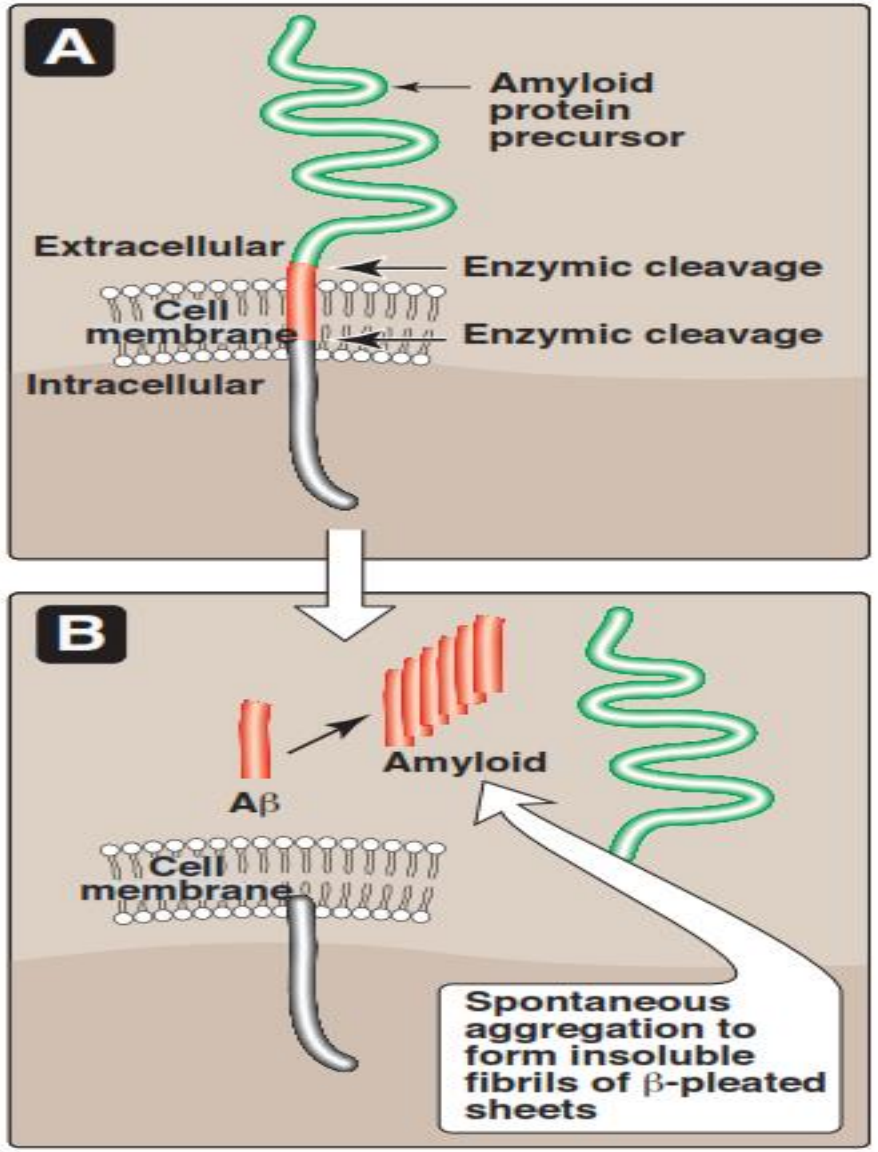
I. This condition is inherited in an **autosomal dominant** pattern

Alzheimer's Disease

i. Refolding or misfolding of another protein endogenous to human brain tissue, β-amyloid, is a prominent feature of the Alzheimer's disease.

i. A 4.3-kDa polypeptide produced by proteolytic cleavage of a larger protein known as amyloid precursor protein.

i. Protein undergoes a conformational transformation from a soluble a helix-rich state to a state rich in β sheet and prone to self-aggregation.



related to damage in brain cells due to the presence of beta-amyloid .
(beta-amyloid)>> عبارة عن جزء من بروتين كبير اسمه amyloid precursor protein هذا البروتين الكبير موجود في membrane of nervous system .
so due to unknown reason >>> يصير ح activation for certein enzyme .
proteolytic enzyme will cleavage large protein and this cleavage happen in extracellular and intracellular domain and the central part of protein which is membranous domain (hydrophobic) لهيك همه موجودين في ال brain
وتشيله لحاله رح يأدي الى as hydrophobic protein وبالتالي وجودهم في هذا المكان
وبالتالي بصير >>> accumulation of this hydrophobic protein شي من aggregation of beta amyloid يعمل
and accumulation of this protein in nervous system will cause damage of brain cell.
and will be one of the cause of Alzheimer's Disease.

Alzheimer's Disease

I. Apolipoprotein E has been implicated as a potential mediator of this conformational transformation.

I. Researchers have found that this form of the disorder can result from mutations in one of three genes: *APP*, *PSEN1*, or *PSEN2*.

I. Most cases of Alzheimer disease are not genetically based, although at least 5–10% of cases are familial.

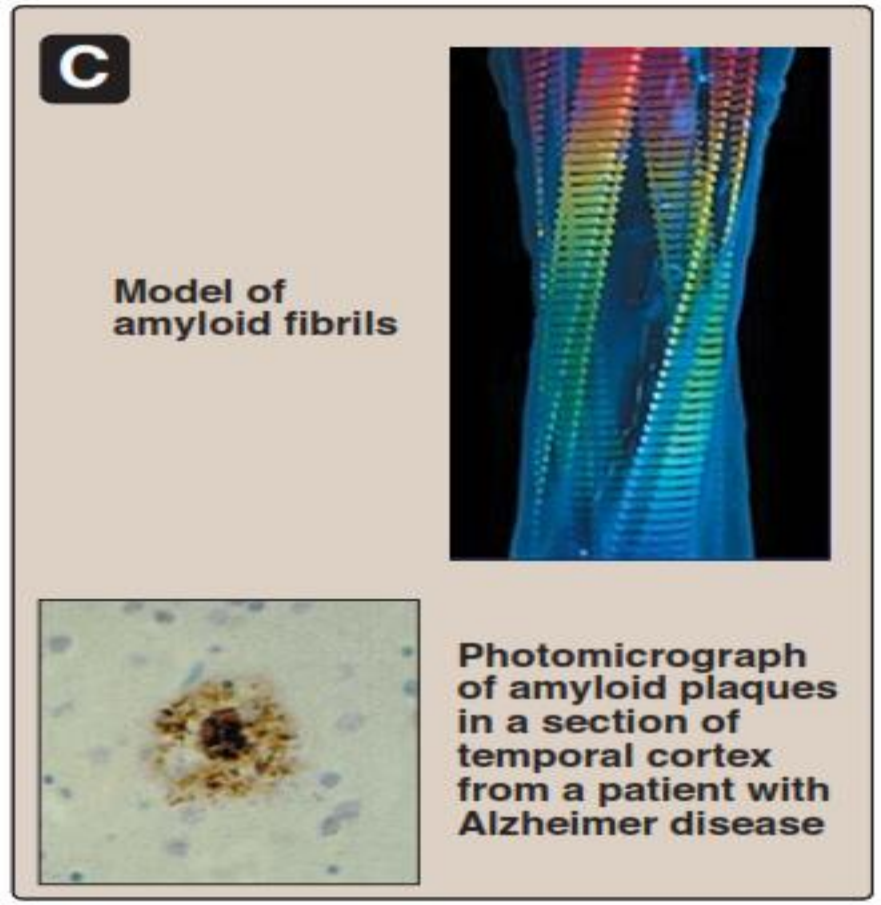


Figure 2.13
Formation of amyloid plaques found in Alzheimer disease.

Alzheimer's Disease and Tau protein

I. A second biologic factor involved in the development of Alzheimer disease is the accumulation of neurofibrillary tangles inside neurons.

I. A key component of these tangled fibers is an abnormal form of the tau (τ) protein, which in its healthy version helps in the assembly of the microtubular structure.

I. The defective τ, however, appears to block the actions of its normal counterpart.

فما لذة الحياة دون تحدي ....وما قيمة الحلم ان كان سهلاً

موفقين شغف (: