جامعة الملك سعود
King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Biochemistry437

Biochemistry of Myelin

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

Neuropsychiatry block

EDITING FILE

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MED437
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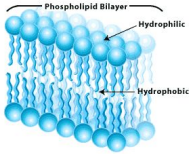
Objectives

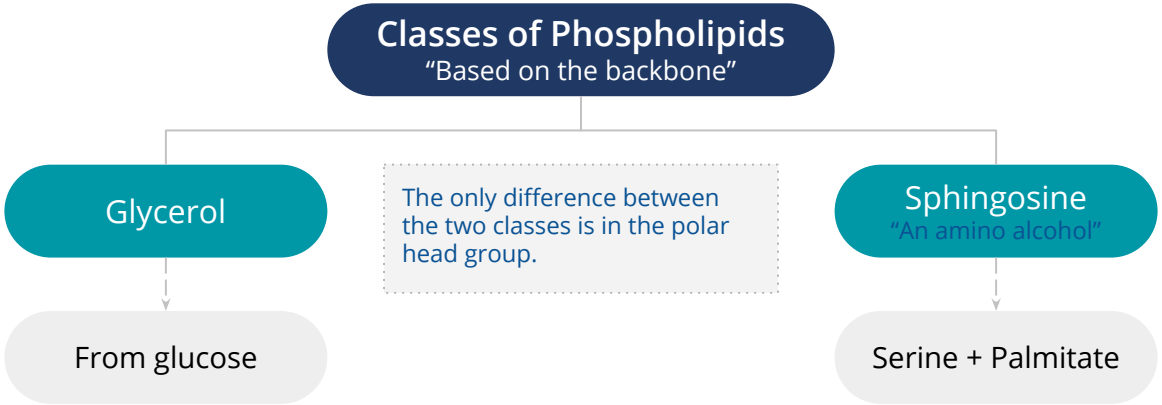
By the end of this lecture, you should be able to:

- 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 Sphingolipidoses.

Recall

- Myelin is a sheath that forms around nerves, which insulates the nerve fiber, and help it regenerate.
- Mylien is the extension of the cell membrane of schwann cells.
- Cell Membranes are composed of some proteins and a lipid bilayer, which is mainly formed by phospholipids
- Phospholipids are composed of fatty acid chains and a phosphate containing alcohol that attach to a lipid backbone.
- The fatty acid chains make the hydrophobic tail which attach to the membrane, and the polar phosphate containing alcohol makes the hydrophilic head which reacts with the aqueous environment, Making the entire molecule amphipathic.
- Inner leaflet of the plasma membrane is interacting with the cytoplasm while the outer leaflet is interacting with the extracellular fluid.





Importance of Phospholipids

- Essential component of membranes.
- Abundant in nervous tissue.
- Also exist extra-nervous tissue:
  e.g. Receptors for (Recognition of):
  - Cholera toxins
  - Diphtheria toxins
  - Viruses
- Regulation of growth and development.
- Cell transformation. (by engulfing of exogenous genetic material through the membrane).
- Very antigenic*:
  - Blood group antigen.
  - Embryonic antigen.
  - Tumor antigen.

* Antigenic because of the presence of complex phospholipids, which means that there's a non phospholipid part attached to it. like glycosphingolipids which have a carbohydrate group attached to it, making it antigenic.

How would the tumor antigens work? these sphingolipids they keep on changing. So, when the cell is going under transformation, say it becomes cancerous the carbohydrates in the cell membrane keep changing, and that's the marker for cell transformation.. "team 436"

Key Principles

- Chemical structure of Sphingolipids
  - A backbone of sphingosine with fatty acid chains and a polar head group attached to it.
  - If the polar head group has phosphate, then it is a sphingophospholipid
  - If the polar head group does not contain phosphate, but contains a carbohydrate group, then it becomes a glycosphingolipid “not a phospholipid”
- Types:
  - Glycosphingolipids (Glycolipids)
  - Sphingophospholipids, e.g. Sphingomyelin. “The only important sphingophospholipid”
- Myelin structure and function
- Sphingolipidoses

Dr said: you don't have to memorize any chemical structure

Sphingolipids: Structure and Types

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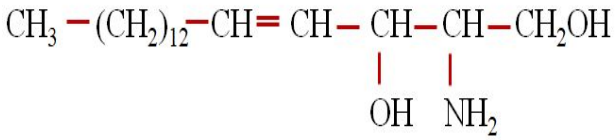
Sphingosine

Long chain, unsaturated amino alcohol



Composed of:

- Serine "amino acid"
- Palmitoyl COA "alcohol"

When a long fatty acid joins the amino group it makes an amide bond and converts the molecule into ceramide.

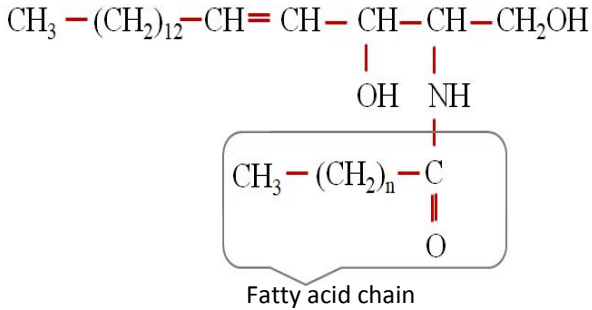
First, we start with a molecule of sphingosine, then we add a fatty acid chain to it to make it ceramide

Ceramide is the parent molecule for the sphingolipids, each time we add something to it and make it into a different molecule.

"More details on next slide"

Ceramide

Sphingosine + Fatty acid



- Ceramide play a key role in maintaining the skin's water-permeability barrier.
- Decreased ceramide levels are associated with a number of skin diseases.
- Because of its effect Ceramide is actually a component in skin lotions.

Dr said: you don't have to memorize any chemical structure

Sphingolipids: Structure and Types

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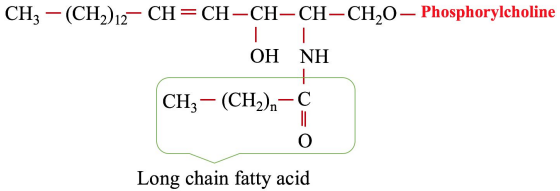
Sphingomyelin

Ceramide + Phosphorylcholine

Sphingosine+fatty acids

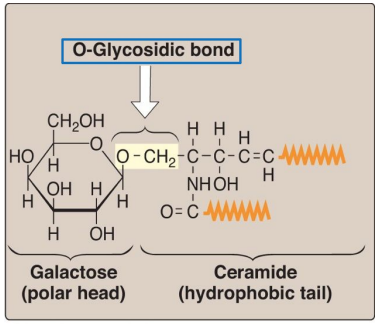


- Sphingomyelin is the only significant sphingolipid in humans.
- Phosphorylcholine: Is the polar head group of some phospholipids, which is composed of phosphate bonded to a choline group.

Cerebrosides

Ceramide + Monosaccharides*

e.g. Galactocerebroside



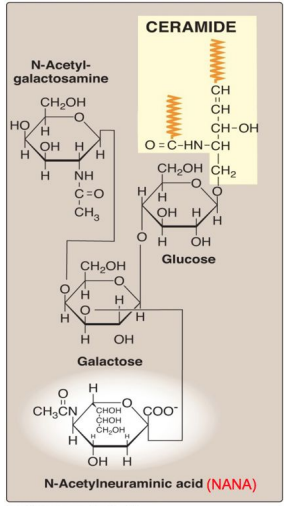
1- The polar head can either be glucose or galactose but galactose is more common.
2- When the polar head is galactose it is called galactocerebroside.
3- When it is glucose it is called glucocerebroside.
4- Cerebrosides are the simplest and most neutral glycolipids.
5- The bond that join Ceramide with the monosaccharides is an Oxygen glycosidic bond.

Gangliosides

Ceramide oligosaccharides + NANA

e.g. GM2 :

- *G=ganglioside*
- *M=mono molecule of NANA "B will stand for Bi, and T will stand for tri and so on"*
- *2=the monomeric sequence of the carbohydrate attached to the ceramide "2 monosaccharides, glucose and galactose"*



1- Oligosaccharides mean that there's 3 or more monosaccharide group attached to the ceramide.
2- The ceramide must be attached to at least one NANA molecule to be considered a ganglioside.
3- If accumulated can cause many storage diseases.
4- In picture we can find a ceramide with a glucose and a galactose attached to it "oligosaccharides" and one NANA group, this molecule is called: GM2.

Sphingolipids Synthesis

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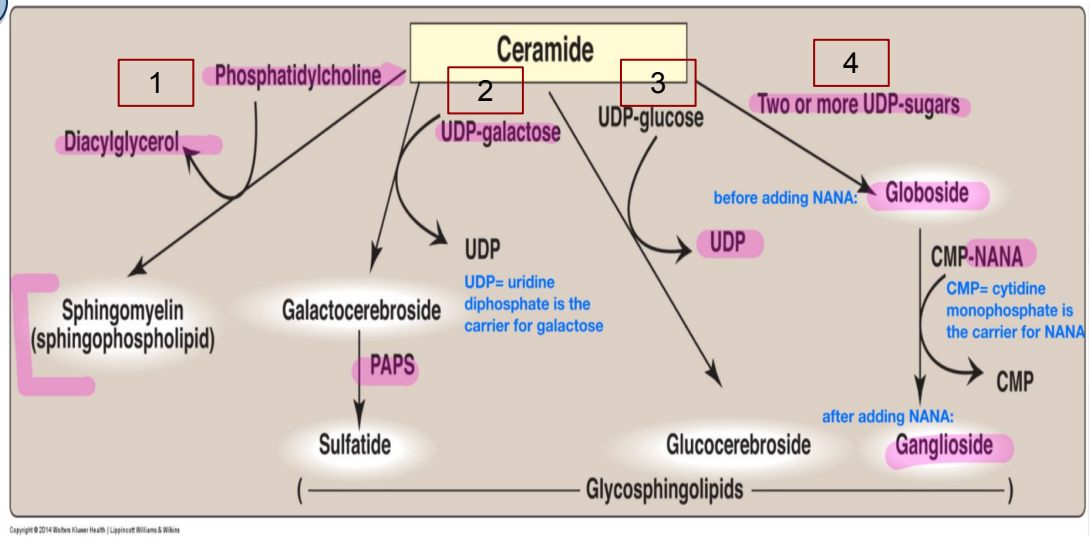
You have to know all of what is in the slides, doctor said the carriers came in the exam before!



1. Phosphatidylcholine interacts with ceramide, diacylglycerol goes out and gives us sphingomyelin "the only important sphingophospholipid".
2. Galactose is added to ceramide by the carrier UDP "uridine diphosphate", UDP goes out and we get galactocerebroside.
   We can modify it further by adding a sulfate group with the carrier PAPS, giving us sulfatide.
3. Glucose is added to ceramide by the carrier UDP, UDP goes out and we get glucocerebroside.
4. Two or more UDP sugars are added to ceramide and we get: globosides.
   If NANA was added to it by the carrier CMP "cytidine monophosphate", we get gangliosides.

Myelin Structure and Function

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Definition

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

Produced by

- **Schwann cells:** Peripheral nerves
- **Oligodendrocytes:** CNS

Composition

- **Lipids (80%):**

Main component:
Cerebrosides
(main is Galactocerebroside)
Other component:
Sphingomyelin

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

Structure

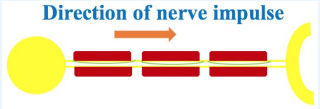
Fatty acid of Sphingomyelin:
Myelin sheath:
Very long chain fatty acids
Lignoceric 24:0
Nervonic 24:1(15)

- 24: refers to the number of carbon atoms
- 1: is the number of double bonds
- 15: is the position of the double bond

- Lignoceric: 24 carbon atoms with 0 double bond.
- Nervonic: 24 carbon atoms with One double bond in the 15th carbon atom.

Function

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



Multiple Sclerosis

- Neuro-degenerative, auto-immune disease.
- The proteins present in the myelin sheath are attacked by the immune cells.
- Breakdown of myelin sheath (demyelination).
- Defective transmission of nerve impulses.

Sphingolipidoses

- A partial or total missing of a specific lysosomal acid hydrolase leads to accumulation of a sphingolipid.
- Lysosomal lipid storage diseases caused by these deficiencies are called **sphingolipidoses**.
- Synthesis **(Normal)**; Degradation **(Defective)**.
- Substrate accumulates in organs.
- Progressive, early death.
- Phenotypic[1] and genotypic[2] variability.
- Autosomal recessive **(mostly)**[3].
- Rare, **Except in** Ashkenazi Jewish.
- *Usually only a single sphingolipid accumulates in the involved organs in each disease.*

Also called lysosomal storage disease, When the enzymes responsible for the degradation of the sphingolipids are deficient, it leads to accumulation of these lipids and later degeneration of the neurons.

1 Phenotypic: Depends on how much the enzyme is defected, whether its completely absent or not.

2 Genotypic: Is when there's a mutation in a gene that is causing the disease.

3 Except Fabry disease (X-linked).

Sphingolipidoses

Diagnosis:

- Measure enzyme activity:
  - Cultured fibroblasts or peripheral leukocytes.
  - Cultured amniocytes or chorionic villi (prenatal)[1].
- Histologic examination.
- DNA analysis[2].

Treatment: e.g. for Gaucher disease:

- Replacement Therapy (e.g. recombinant human enzyme).
- Bone marrow transplantation.

[1] If we know the parents are carrier of the disease we can do the 2nd test.

[2] Only if i know what disease it is and what are all the mutations that might cause it.

Sphingolipidoses

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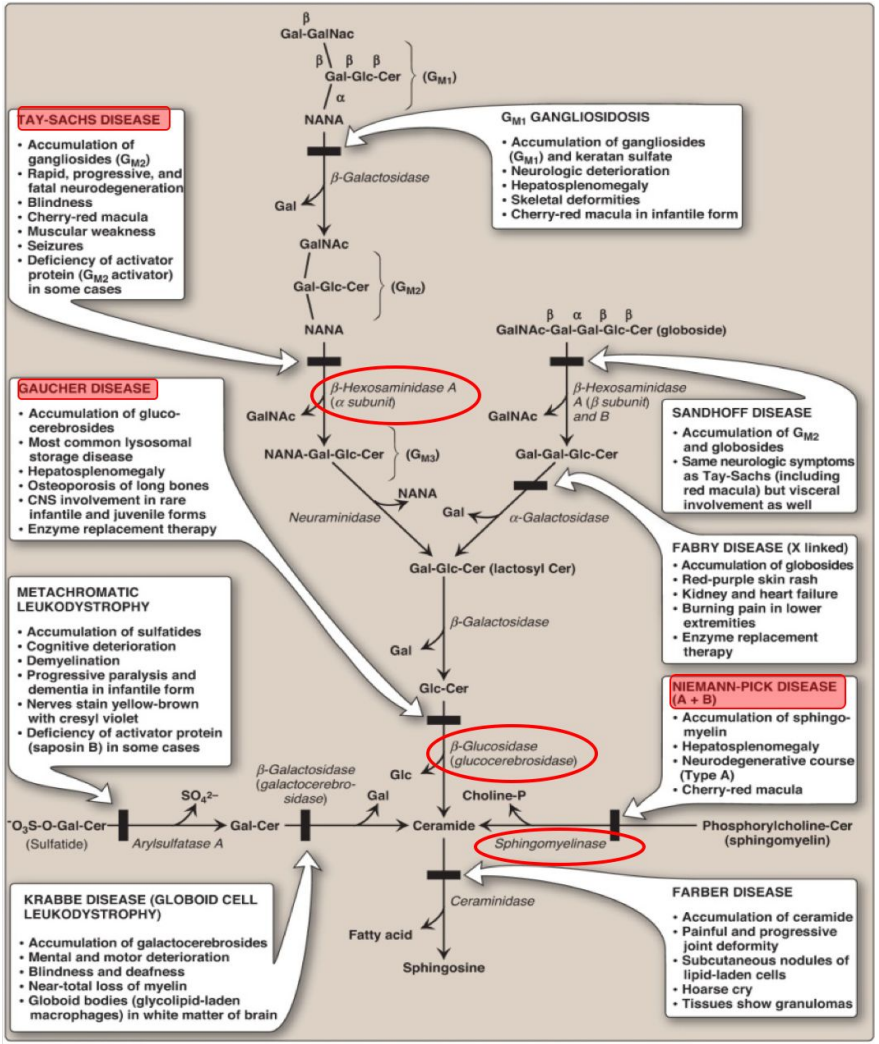


tip

Doctor said focus on deficiencies and accumulations, but also know the characteristics since the question might come as a case.

- Myelination usually starts at the 3rd trimester, and continues after the child is born.
- Most of the myelination happens in the early infantile stage “when the baby is learning to walk, talk..etc” this is why most of these diseases happen early in childhood.
- If the disease was severe, it leads to cognitive disabilities and then later death.
- Less severe forms happen later in life and might not lead to neurodegeneration.

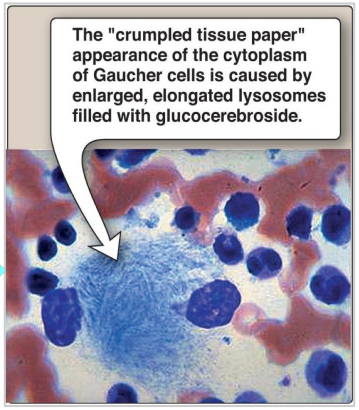
Sphingolipidoses

Tay-sachs

- **Accumulation of gangliosides (GM2).**
- **Deficiency of the enzyme B-Hexosaminidase.**
- Rapid, progressive and fatal neurodegeneration.
- Cherry red macula "red spot found in the retina"
- Muscular weakness.

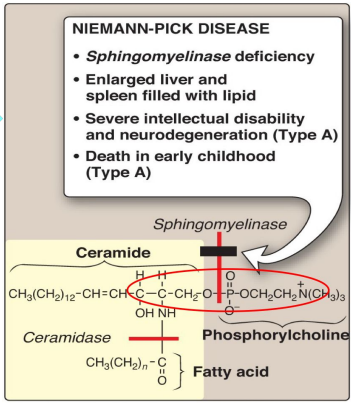
Gaucher

- **Accumulation of glucocerebrosides in liver and spleen.**
- **Deficiency of the enzyme b-glucosidase (glucocerebrosidase).**
- Most common.
- Causes osteoporosis in long bones
- Causes hepatosplenomegaly "in liver and spleen".
- Causes crumpled tissue paper appearance of the cytoplasm.
- Treated with replacement therapy and bone marrow transplantation.



Niemann-pick

- **Sphingomyelinase deficiency.**
- **Accumulation of sphingomyelin.**
- Enlarged liver and spleen filled with lipids.
- It has two types, A and B.
- Type A is more severe because the enzyme has almost no activity, it causes severe intellectual disability and death in early childhood.
- Type B is less severe, has a later onset and causes little to no neurodegeneration.



Take Home Messages

- Sphingolipids are complex lipids that includes sphingophospholipids 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.

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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 (PNC) and Oligodendrocytes (CNS). 3. It is composed of 80% lipids and 20% proteins.
Function	Nerve insulation: to avoid signal leakage, and to increase velocity of impulse transmission.

Diseases					
	1. Multiple sclerosis	**2. Sphingolipidoses** (lysosomal lipid storage diseases)			
General Information	**It is a neurodegenerative, autoimmune disease.** **Cause : demyelination**	**There is A partial or total missing of a specific lysosomal acid hydrolase leads to accumulation of a sphingolipid.** **It is :** **1. Autosomal recessive disease.** **2. Progressive.** **3. Rare, except in Ashkenazi Jewish.** **4. There is Phenotypic and genotypic variability.**			
Diagnosis	-	**1. Measuring enzyme activity.**	**2. Histological examination.**	**3. DNA Analysis.**	
Examples	-	**1. Tay Sachs disease**	**2. Niemann Pick disease**	**3. Gaucher disease**	**4. Fabry disease**
Lipid accumulated	-	**Gangliosides (Gm2) due to : β-Hexosaminidase (α subunit) deficiency.**	**Sphingomyelin due to : Sphingomyelinase deficiency.**	**Glucocerebrosides due to : β-glucosidase (glucocerebrosidase) deficiency.**	-
Treatment	-	-	-	**1. Replacement therapy.** **2. Bone marrow transplantation.**	-

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. -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 Sphingolipidoses

MCQs

Q1/ Decreased ceramide level is usually associated with..?

A. Lung disease
B. Liver disease
C. Skin disease
D. Kidney disease

Q2/ Which of the following is the combination of ceramide and monosaccharides?

A. Sphingomyelin
B. Cerebrosides
C. Gangliosides
D. Sphingosine

Q3/ Myelin in the central nervous system is produced by?

A. Oligodendrocytes
B. Schwann cells
C. Monocytes
D. Epithelial cells

Q4/ In SPHINGOLIPIDOSES the defective function leading to accumulation of substrate in organ is the.. ?

A. Synthase
B. Degradation
C. Transformation
D. Storage

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

Team leaders

- رهام الحلبي
- معاذ الحمود

Boys team

- طارق العميم
- نايف المطيري
- عبدالعزيز العبدالكريم
- محمد الصويغ
- صالح الوكيل
- عبد الملك الشرهان
- سعيد القحطاني
- نواف اللويمي
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Girls team

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