MSS

pathology

LEC no.1 V2

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MUSCULOSKELETAL PATHOLOGY-1 CONGENITAL DISEASES

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CONGENITAL DISEASES

- **Dysostosis** خلل العظم: localized abnormal bone formation
- Failure of migration and condensation of mesenchyme
- Examples: absence of bone or digit (aplasia)
- Supernumerary digits or ribs
- Abnormal fusion of bones (craniosynostosis, syndactyly)
- Results from mutations in homeobox genes, cytokines or cytokine-receptors genes.

localized : **it affects single or few bones**

Example of Abnormal fusion is the bones of the skull in newborns, they are separated, then a fusion takes place

Just to understand

- Craniosynostosis: a condition where one or more of the sutures in an infant's skull close prematurely, before the brain has fully formed
- Syndactyly: when fingers are fused together.

Homeobox genes : a DNA sequence, that regulates large-scale anatomical features in the early stages of embryonic development.

CONGENITAL DISEASES

- **Bone Dysplasia:** abnormal pattern of growth
- Not a premalignant lesion
- Generalized abnormality, affecting the entire skeleton
- Disorganization of bone and/or cartilage
- Mutations in genes that control development or remodeling of the entire skeleton (they are not a specific mutations)

Note that here we have generalized dysplasia, unlike the previous one. Also be noticed that here in MSS the word " Dysplasia "means Abnormality in the bones, it's congenital and systemic.. This is not premalignant , unlike the Dysplasia in epithelial cells which we took last semester.

OSTEOGENESIS IMPERFECTA

(BONE GENERATION/FORMATION)

- **Most common inherited disorder of connective tissue**
- Mutation in type-1 collagen gene, protein becomes defective and prematurely degraded
- Different types of mutations, variable in severity, may affect α1 or α2 subunits
- Bone matrix amount is too little, results in bone fragility, deformity

just for clarification:

remember that Type I collagen is made up of α1 chains and α2 chain, which come together to form a triple helical structure. This structure is essential for the collagen's strength and function. In this case, mutations often occur in the genes that code for the α1 or α2 subunits of type I collagen,

Bone Matrix Deficiency: this matrix is composed of collagen and minerals like phosphate and calcium, A deficiency in collagen disrupts the normal deposition and mineralization process leading to complications like:

Bone Fragility: They may break easily, even from minor incidents

Deformity: The reduced quality or quantity of collagen affects the bone's ability to maintain its proper shape, leading to deformities.

SYMPTOMS

- Skeletal deformity
- Repeated fractures
- Also affects skin, joints, and eyes (blue sclera) -->
- Hearing loss (conduction defects in the middle and inner ear bones)
- Small misshapen teeth are a result of dentin deficiency
- Type 1: most common, normal life expectancy
- Type 2: severest, death early in life or in utero (severe fractures)

Because all these have collagen, so patients complain from hemorrhage "repeated bleeding" in these structures and it might develop to arthritis (if we talk about joints)
Sclera : white part of the eye

this happens because hearing is dependent on the bones conductivity

type 1 is not life threatening, it's just affects the quality of life, type 2 is much more severe

ACHONDROPLASIA

The (A) in achondroplasia means NON

Chondroplasia : abnormality in the cartilage

- Most common skeletal dysplasia
- Major cause of dwarfism
- Autosomal dominant transmission
- 90% of cases represent new acquired mutation, mostly paternal side

It is the most common one after the OSTEOGENESIS IMPERFECTA

just for clarification:(the last point)

If a parent has achondroplasia (carries one mutated copy of the FGFR3 gene), there is a 50% chance of passing the mutation to the child

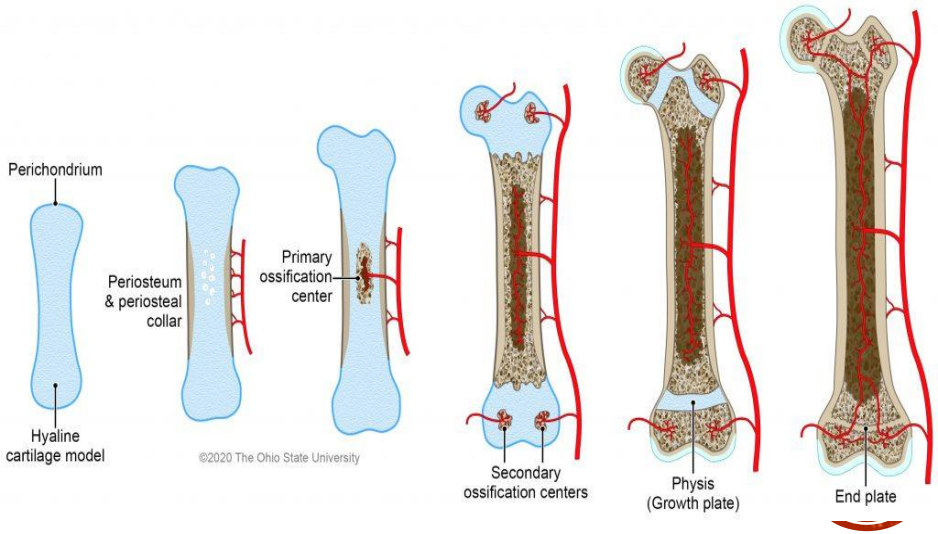
Interestingly, about 90% of achondroplasia cases are the result of new mutations in the FGFR3 gene, meaning the mutation occurs spontaneously **in the sperm or egg before conception**, and the child is the first in the family to have the condition.The majority of new mutations causing achondroplasia occur in the paternal germline (sperm), and there is a strong correlation with increased paternal age at the time of conception. Older fathers are more likely to have sperm with the FGFR3 mutation

الفكرة باختصار إنه عنا حالتين :إما أحد الأبوين بكون حامل لـ الطفرة فـ يورثها للطفل
أو الحالة الثانية يلي تشكل أغلب الحالات وهي انه الأهل سليمين لكن الجاميت نفسه (بويضة/حيوان منوي) حصلت فيه طفرة تم توريثها للطفل ، وغالبًا الطفرة تحدث في جاميت الأب "الحيوان المنوي" خاصةً عند تقدم الأب في العمر

PATHOGENESIS

- Point mutation in the fibroblast growth factor receptor 3 (FGFR3) that results in permanent activation
- Activated FGFR3 inhibits chondrocyte proliferation; as a result, the normal epiphyseal growth plate of the long bones is suppressed
- Patients have normal head and trunk, but short bowing limbs
- Normal life expectancy and mental function

just for clarification: to understand this let's remember the process(endochondral ossification):
1 Proliferation: Chondrocytes divide rapidly in the growth plate.
2 Maturation: These cells then mature and enlarge (hypertrophy).
3 Ossification: Finally, the cartilage is replaced by bone.
)الصورة اضافية فقط للفهم (
But in this case, the point is that patients have a mutation which increases abnormally active FGFR3
,this inhibits chondrocyte proliferation , as a result , they have shorter bones .



THANATOPHORIC DYSPLASIA

Could be called thanatophoric morphism. FYI, Thanato means death.

- A lethal form of dwarfism
- FGFR3 mutation, but more increase in signaling activity
- Short limbs, frontal bone bossing, macrocephaly, small chest, belly-like abdomen
- Respiratory insufficiency
- Die at birth or shortly after
- Its like a more severe form of **achondroplasia**

OSTEOPETROSIS تصخر العظم

Petro means rocks, remember **Petra** البتراء

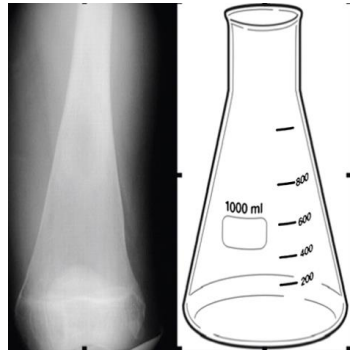
- Marble-like bone, they are very hard and thick bones
- Rare genetic disorders characterized by reduced osteoclast-mediated bone resorption and therefore defective bone remodeling
- Bone shows diffuse symmetric sclerosis(very thick wall), yet can fracture easily (because the orientation is not perfect)

These bones can fracture easily despite being thick, because of their **abnormal shape**.

Remember : **osteoclasts** **resorb** (degrade) bones while **osteoblasts** **build** bones.

INHERITANCE

- Multiple variants based on both the mode of inheritance and severity of symptoms
- All variants share a problem in the acidification process of osteoclasts that is responsible for bone resorption, so osteoclasts number is decreased
- Autosomal dominant variant is the mildest (symptoms appear in adolescence or adulthood)
- Repetitive fractures
- Cranial nerve deficits
- Anemia, because there is less bone marrow
- Erlenmeyer-Flask deformity of long bones



The autosomal **dominant** variant is **mild**
The autosomal **recessive** variant is **severe**

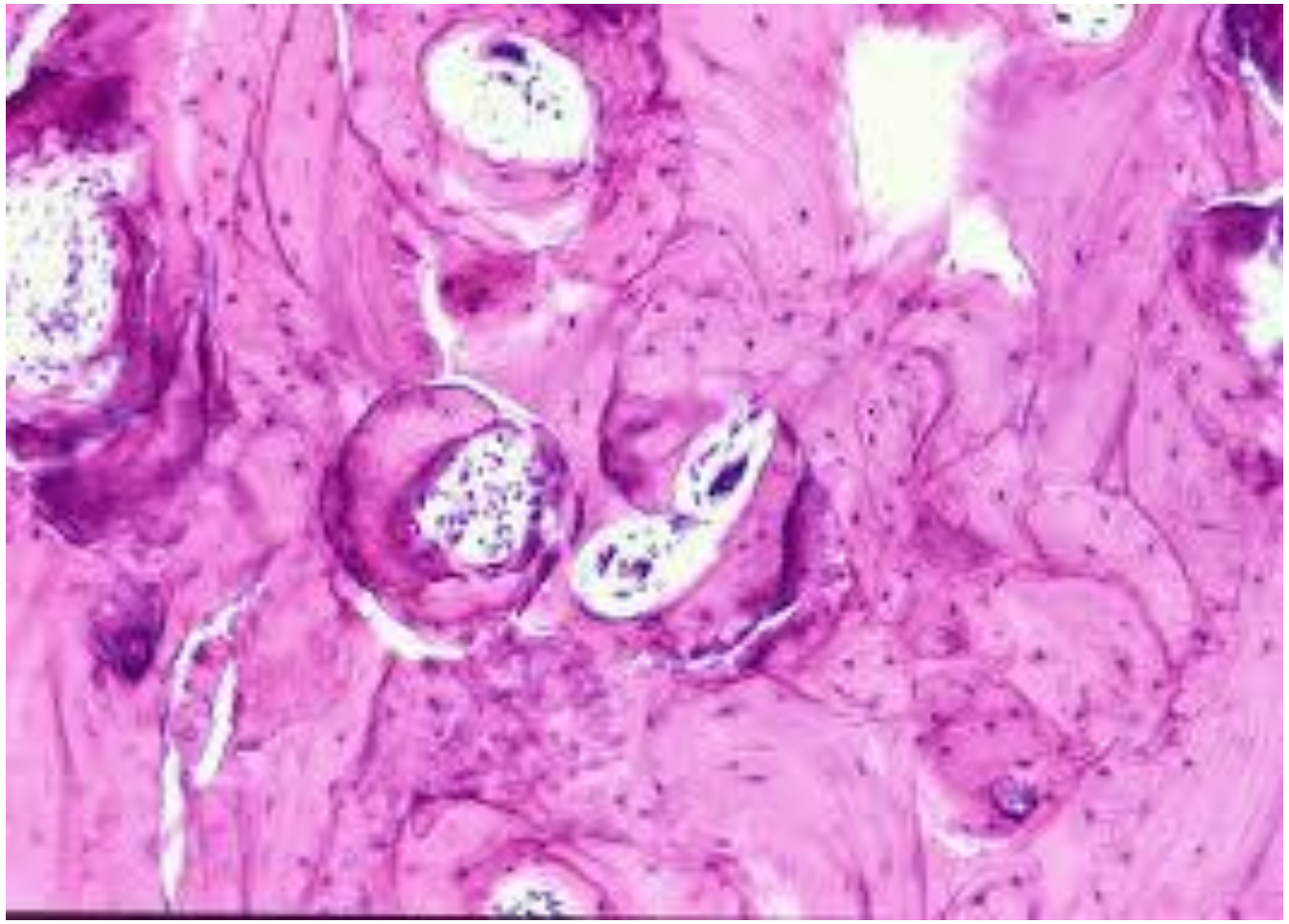
SEVERE INFANTILE OSTEOPETROSIS

- Autosomal recessive
- Severe symptoms, appear early in life
- Leukopenia, that means that there are **no white blood cells**, because of severe decrease of bone marrow mass and that's fetal
- Hepatosplenomegaly (extramedullary hematopoiesis), the liver and spleen are trying to compensate for the absence of white blood cells production in the bone marrow.
- Fatal

Extramedullary hematpoiesis : the production of blood cells outside the bone marrow.

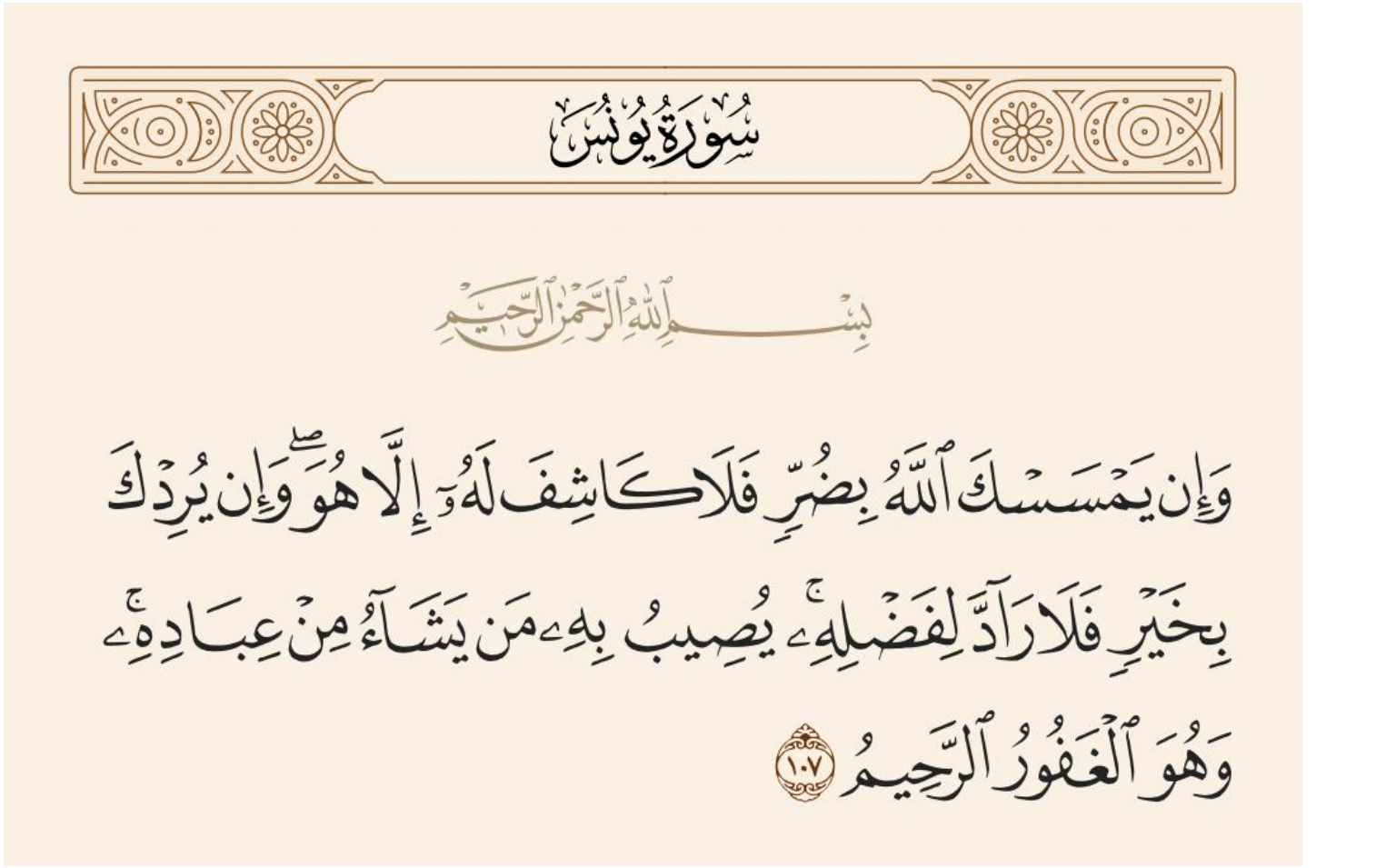
Hepato = liver , spleno = spleen , megaly = enlargement
Hepatosplenomegaly = enlargement in the liver and spleen

Let's understand :Because there is little bone marrow, which produces many blood cells, the liver and spleen compensate for this function until they enlarge in size. It is important to remember that in infants, the spleen and liver are the primary sites for blood cell production, a role that gradually diminishes as bone marrow activity increases.



- Osteopetrosis: markedly thickened bone trabeculae, marrow spaces are minimal, that explains the anemia and leukopenia

The white in pic = bone marrow


سُورَةُ يُونُسَ
بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ
وَإِن يَمْسَسْكَ ٱللَّهُ بِضُرٍّ فَلَا كَاشِفَ لَهُۥٓ إِلَّا هُوَ ۖ وَإِن يُرِدْكَ
بِخَيْرٍ فَلَا رَآدَّ لِفَضْلِهِۦ ۚ يُصِيبُ بِهِۦ مَن يَشَآءُ مِنْ عِبَادِهِۦ ۚ
وَهُوَ ٱلْغَفُورُ ٱلرَّحِيمُ ١٠٧

V2

- Slide 9
- macrocephaly instead of microcephaly