MSS

PATHOLOGY

#Sheet 1

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*This year the only change that we'll have is an extra lecture about skin pathology, specifically skin tumors.

Mentioned in slides—-> Blue

Doctor and writer's notes —> Black

Let's start our lecture talking about bone functions.

The bone functions:

1- mechanical support

2- force transmission

Remember that the weight is a force , so your body weight or even the weight you carry on , will be equally transmitted and distributed on your bony structures.

3- protection

Brain is protected by the skull , pelvic organs are protected by the pelvic bone and so on

4- mineral homeostasis

Specifically, calcium and phosphorus homeostasis

5- Hematopoiesis

(formation of blood cellular components) which occurs in the bone marrow inside the bones.

These are the major functions of the bone , which means if any systemic disease in the bone , all of these functions would be affected. On the other hand, if there's a local disease in a certain bone , the functions of that local area's bone will be affected only.

For instance if you have a fracture in the skull , you'll not suffer from any problem in the femur.

Bone structure :

1- matrix (osteoid 35% and minerals 65%)

- osteoid : (the organic part) predominantly organic type 1 collagen, which is the strongest type of collagen and other things such as glycosaminoglycan and other proteins.

- Inorganic hydroxyapatite [Ca10(PO4)6(OH)2]

2- Cells

- osteoblasts: osteo = bone / blast = forming, so these are the cells that are responsible for bone formation predominantly the osteoid. for example if you had a fracture, these osteoblasts will work to face the demand in the osteoid.

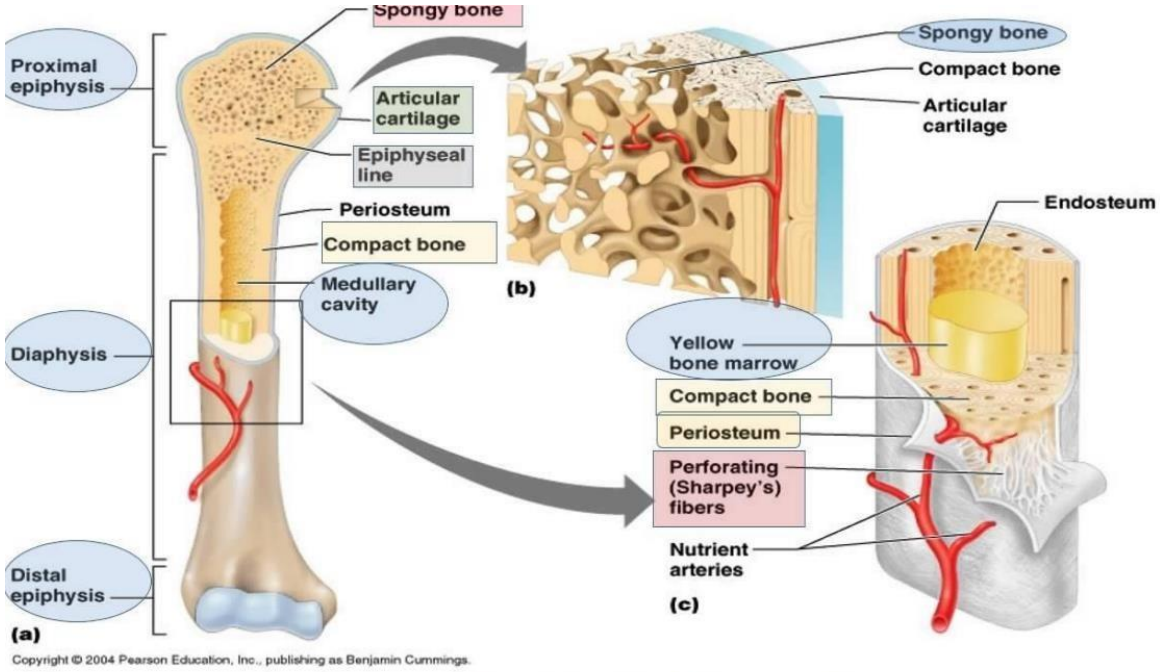
Note: osteoblast has an abundant cytoplasm so more Golgi apparatus to synthesis collagen and other component (it is highly metabolically active)

- Osteoclasts: the exact opposite function to that of osteoblasts, it resorbs (eat) the bone , extra collagen for example or even extra calcium , these cells will work to get rid of these extras as it also plays an important role in phosphorus and calcium homeostasis.

- important note: we have a strong balance between osteoclasts and osteoblasts. However, if this balance is disturbed and osteoclast wins (more differentiation so more activity) for example, this would be abnormal and we'll have osteoporosis (هشاشة عظام)

- Osteocytes: mature small well- differentiated bone cells. when the osteoblast finishes the building up process of the bone it will become inactive and now it is an osteocyte.

- less cytoplasm than osteoblast and osteoclast and smaller than them too.



Structure of a Typical Long Bone

Here we have the structure of a typical long bone , proximal epiphysis , diaphysis and distal epiphysis

Note : the area in between each epiphysis and diaphysis is called metaphysis.

In this metaphysis there's the epiphyseal line where we had our growth and elongation, so if we have a fracture in this area and we still able to grow (until a certain age). our bone growth and elongation will be affected.

Let me clarify more if you can't remember these details from the 1st year histology course:

Your bones still can elongate until a certain age , approximately 21-24

Now before this age you'll have in the metaphysis area something called epiphyseal or growth plate (which is a hyaline cartilage that can undergo mitosis and elongate) now

once you're not able to elongate more , this epiphyseal plate will be closed and we'll have epiphyseal line instead, which is a bony structure not a cartilage anymore.

It's important to know these structures because there are certain diseases affect diaphysis , while others epiphysis and so on.

Now let's move to another topic , there are 2 main types of bone :

woven VS lamellar bone , so what is the difference between them?

- Lamellar bone : the mature bone , it is linear and organized where we have equal distribution of osteocytes and equal homogenous intensity of the osteoid

تتذكروا لما كنا نحكي بالهيكل مخطوط متجانس و بدون هيئ جميع اجزاء المحلول بتحتوي على النسبة نفسها من المكونات وهاد الشي بينطبق على هاد النوع من العظام

- woven bone : the immature bone found in embryos and newborns , so if you see woven bone in adults you should know that there's something abnormal , for example we see it when our fracture's being healed (when we have a fracture, we'll have initial woven bone , then it will be converted into lamellar once it has been healed) but on the other hand it can imply the presence of cancer

* also here we have more cells and it's disorganized.

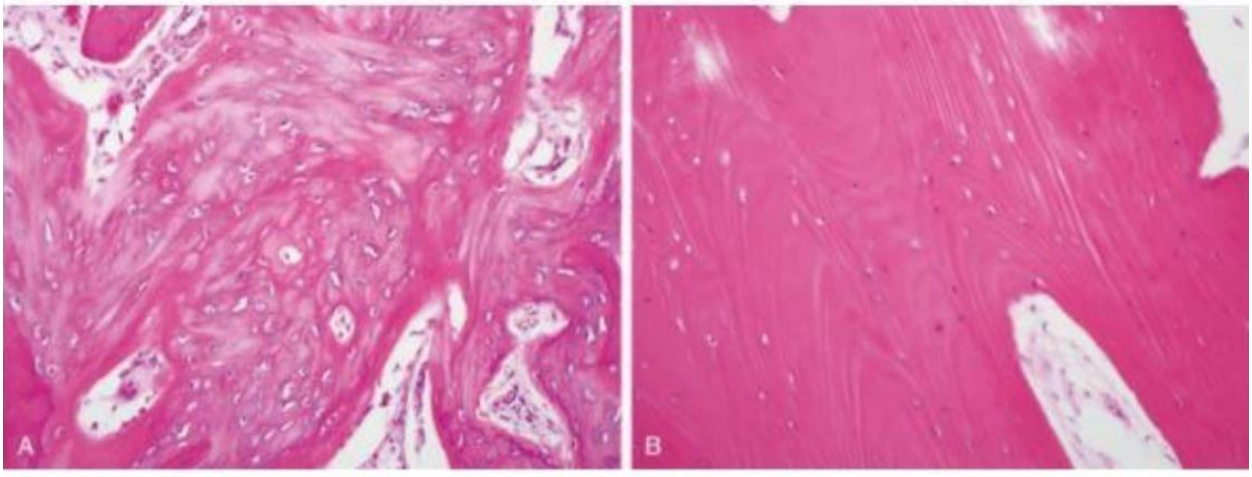
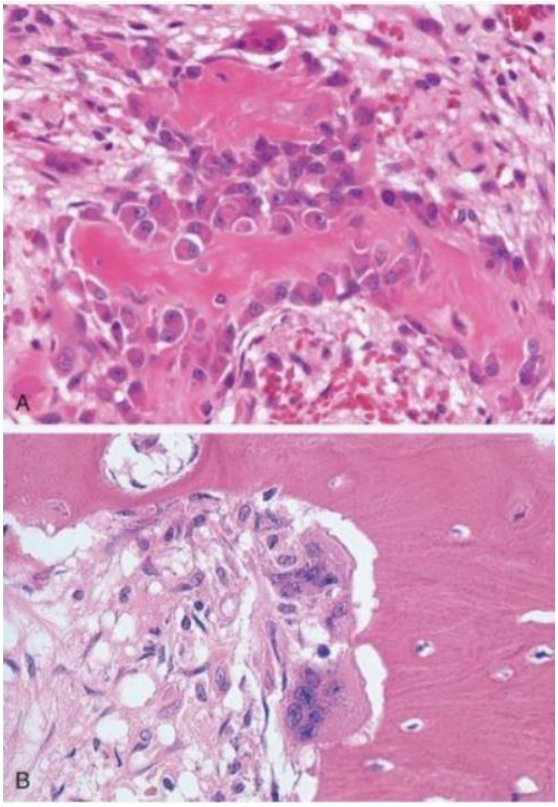


FIG. 21.1 Woven bone (A) is more cellular and disorganized than lamellar bone (B).

Again we'll go back to the osteoblasts and osteoclasts but with histological sections:

- **Osteoblasts** : small mononuclear cells
- **Osteoclasts** : big multi-nucleated giant cells



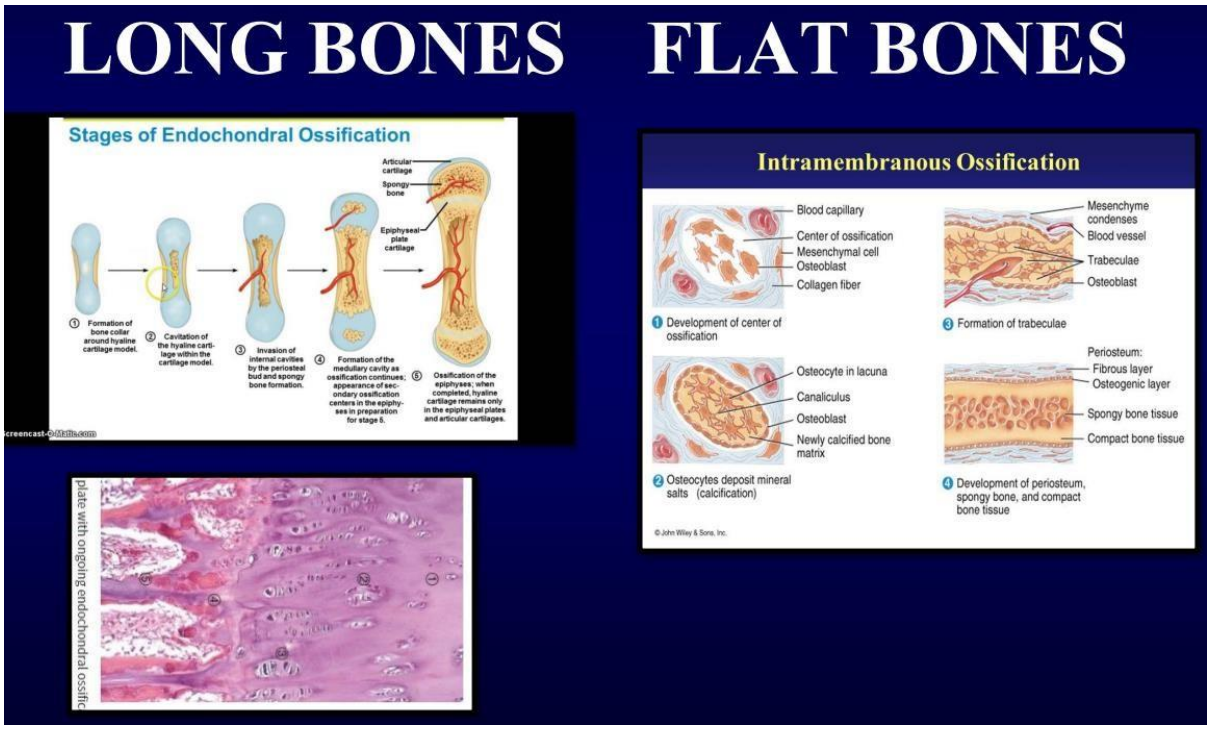
The development of the bone

There are 2 major ways by which the development of bone occurs:

1- endochondral ossification : it's the way by which the long bones are formed , humerus , radius , ulna , femur and so on. As the name implies, the formation of bone here happens by the conversion of cartilage into bone but not the whole cartilage, you'll still have the articular cartilages when you're adult.

2- intramembranous ossification: the process by which the flat bones are formed, clavicle, sternum and so on. Here the process is a little bit complicated but it's mainly the conversion of a membrane into a bone

The doctor asked us to see the video regarding the intramembranous ossification to remember the difference very well.



Remodeling and homeostasis

From google (just to understand the concept) :

Bone remodeling: is a lifelong process where mature bone tissue is removed from the skeleton by osteoclasts and new bone tissue is formed by osteoblasts.

It is a Continuous and dynamic complex process even in adult mature skeleton (microscopic level)

So at any time if you took a histological section from the bone , you will find that osteoblast and osteoclast are both working together.
-Don't forget that once something disrupts the balance between them you'll suffer from a disease.

For example if the balance shifted towards the osteclasts , you'll have osteoporosis (low bone density)

Peak bone mass is reached in early adulthood (25-35) years old after completion of skeletal growth , after that the osteoclastic activity will prevail over the osteoblasts means Resorption > bone formation on the 4th decade. This is why when you reach the 4th decade , you should be already prepared to prevent the occurrence of osteoporosis.
Note : the prevention of this disease is more important than it's treatment.

We have many factors that stimulate osteoclast activity while others inhibit as well , these include :

+ Osteoclast differentiation	- Osteoclast differentiation
PTH **IL-1** **Steroids**	**BMPs (bone morphogenic proteins)** **Sex hormones (estrogen & test.)**

When they increase , You'll have high osteoclastic activity —> less bone density —> osteoporosis

This is a cartoon explanation about how the osteoclast becomes mature and active
“ Dr mousa said that it will be explained later on “

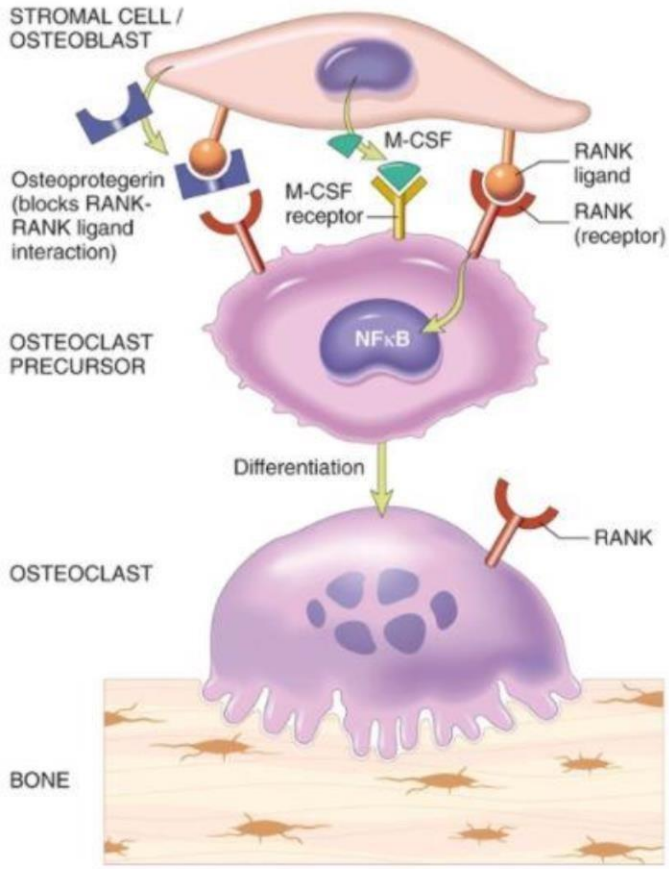


FIG. 21.4 Paracrine molecular mechanisms that regulate osteoclast formation and fun.

Congenital disorders of the bone

Divided into two major groups:

1- Dysostosis (dys: abnormal ... ostosis: bone).
2- Dysplasia (doesn’t mean preneoplastic that we took in first semester pathology)

Dysostosis:

This group of diseases are characterized by:

➢ Abnormal condensation and migration of the mesenchyme, (something went wrong during growth and development of mesenchyme) which is the embryonic connective tissue that give rise to many tissues including bones.

➢ Caused by genetic abnormalities in certain genes called the homeobox genes (responsible for the development of the musculoskeletal system), and abnormalities in the cytokines and their receptors (we said that they have a function in inflammation, now an extra information about then that they have a role in condensation and migration of mesenchyme)

Examples:

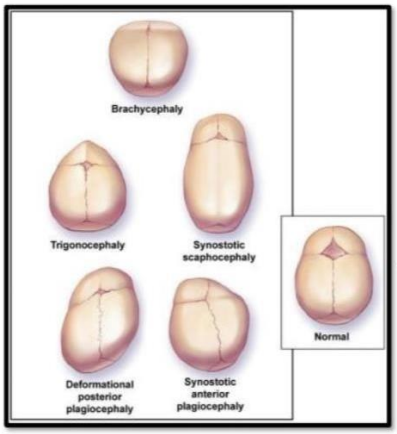
1- Aplasia: " plasia = formation/ aplasia = no formation "
absence of formation of a certain finger for example (4 fingers instead of 5).

2- Syndactyly & craniosynostosis:

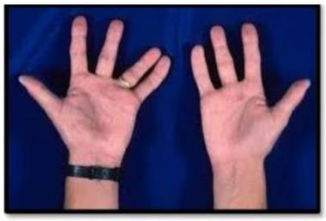
-Syndactyly: Fusion of the fingers (for some reason the apoptosis that was supposed to happen to the cells between fingers was stopped).

-Craniosynostosis: an abnormality in the sutures of the skull that affects the brain growth.

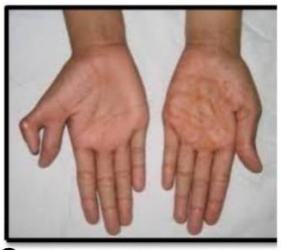
3- Supernumerary digit: an additional finger or toe.



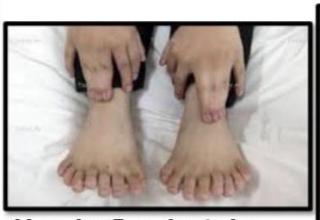
Craniosynostosis



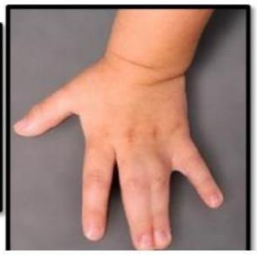
Aplasia



Supernumerary digit



Hands: Syndactyly.
Feet: supernumerary digit



Syndactyly

Dysplasia:

➢ The basic pathology of this disorder is disorganization of the bone and cartilage.
➢ Caused by genetic mutations in the gene that control the development and remodeling of the bone (usually point mutation)
-Remember that dysplasia of the bone , as here is not premalignant

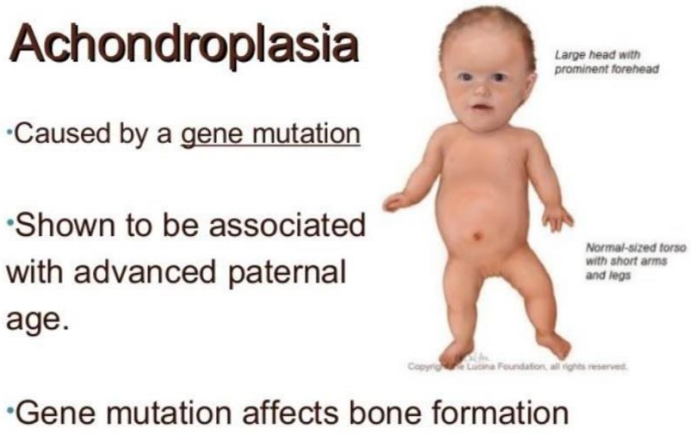
Examples:

1-Achondroplasia (the most common cause of dwarfism): here we have a problem with the growth of long bones via endochondral ossification that we have mentioned so far
.
➢ Caused by many mutations but the major one is in Fibroblast Growth Factor Receptor #3 (FGFR3) gene.

➢ The most important concept that you must understand that there is no impact on longevity, intelligence, or reproductive status...they live a normal life.

- sometimes they have a big head and frontal bossing.
- They have a big chest wall
- ➢ AD: Autosomal Dominant.

Peter Dinklage: 48-years-old, married with 2 children from USA, New Jersey
"Game of thrones"



2-Thanatophoric dysplasia:

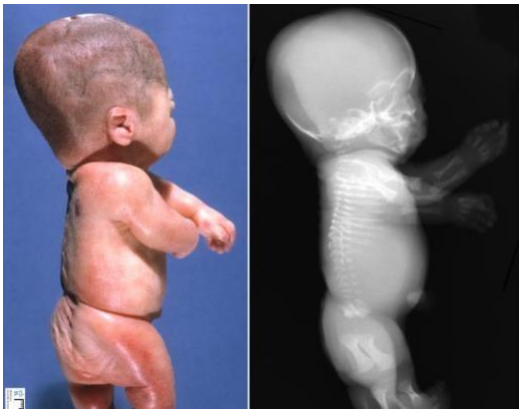
➢ it is the Most common lethal form of dwarfism

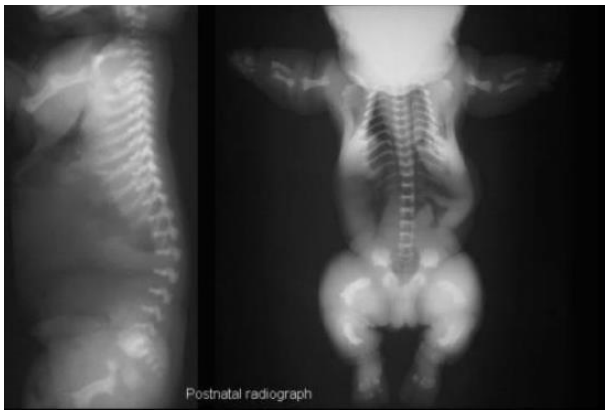
➢ caused by FGFR3mutations (different from Achondroplasia), different mutation's location (locus) than that of Achondroplasia.

➢ most of the babies with this condition, die in the uterus or at birth or shortly after birth and the leading cause of death is that there's small chest leading to respiratory insufficiency (there's a compression by the chest on the lungs)

- can be diagnosed early by ultrasound.
- Worst than the Achondroplasia because it is lethal.

Note : The doctor said that when i give you in the exam a senario and i told you that the baby died early on , you should know that this is Thanatophoric dysplasia.





3- Osteogenesis imperfecta (imperfect bone formation)

➢ Most common inherited disorders of connective tissue.

➢ Group of disorders: it's not a single disease, group of disorders classified according to the severity of disease (type 1, type 2 ...)

➢ AD: Autosomal Dominant.

➢ characterized mainly by Deficiency of type I collagen synthesis Or abnormal collagen.

➢ Too little bone; fragility.

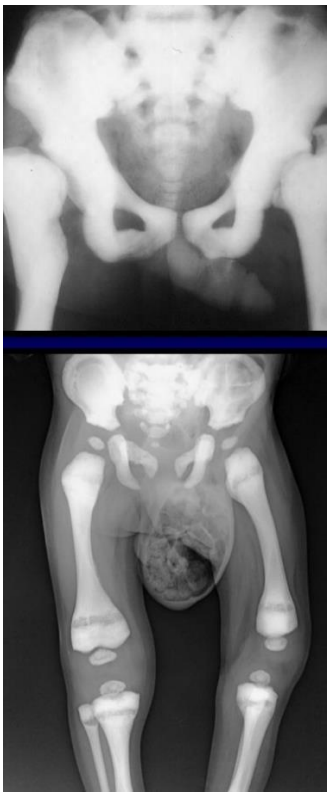
➢ Patient has blue sclera; hearing loss (the bones of the middle ear are impaired); teeth abnormalities.

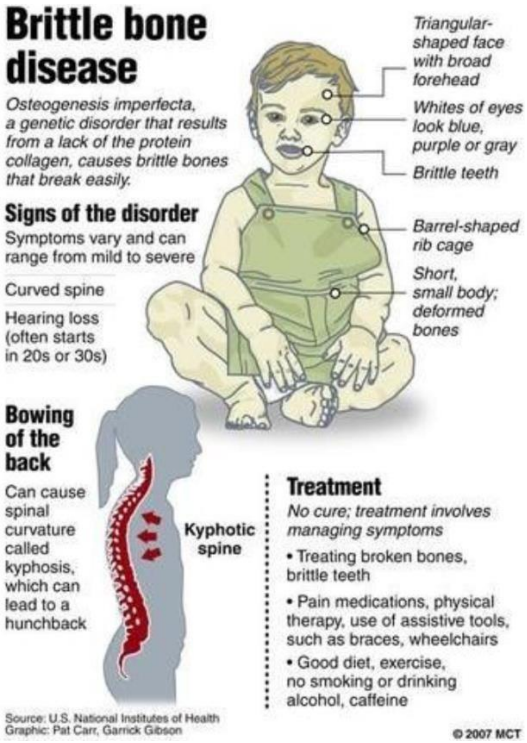
(remember that connective tissue includes many structures, including sclera)

➢ Type 2 is the most severe, patients die early (lethal), and Type I (relatively normal life so good prognosis) so type 1 is the most benign.

➢ It's also called "Brittle bone disease": the quantity or quality of the bone is not normal; it will be weaker (easy to break).

The doctor asked us to look for the reason behind the blue sclera in these patient.





Osteopetrosis:

➢ Marble bone disease "stone bone" , so very hard bone.

➢ Exactly the opposite of osteoporosis.

➢ Group of disorders; rare.

➢ Impaired osteoclast function: reduced bone resorption leading to diffuse sclerosis (hardening of the bone due to increase in collagen synthesis)

➢ Dx: X-ray.

➢ Fractures and leukopenia in severe forms

-Leukopenia is caused as a result of the closure of the bone marrow site following by bone replacement.

- fractures are caused by the decrease in shock absorption that happened as a result of decrease in osteoclasts' activity.

Summary

Congenital Disorders of Bone and Cartilage

Abnormalities in a single bone or a localized group of bones are called **dysostoses** and arise from defects in the migration and condensation of mesenchyme. They manifest as absent, supernumerary, or abnormally fused bones. Global disorganizations of bone and/or cartilage are called **dysplasias.** Developmental abnormalities can be categorized by the associated genetic defect.

- FGFR3 mutations are responsible for achondroplasia and thanatophoric dysplasia, both of which manifest as dwarfism.
- Mutations in the genes for type I collagen underlie most types of osteogenesis imperfecta (brittle bone disease), characterized by defective bone formation and skeletal fragility.
- Mutations in *CA2* and *TCIRG1* result in osteopetrosis (in which bones are hard but brittle) and renal tubular acidosis.

Past papers :

1. Which of the following is true regarding lamellar bone :
a. It is found in the fetus
b. Fibers are disorganized
c. Has stronger structural integrity than woven bone
d. It's formation is rapid

2. Which of the following is true about osteocytes?
a. They are large and multinucleated
b. They have high metabolic activity
c. They are mature bone cells
d. They are essential for bone resorption

3. Which of the following is false regarding bone?
a. Lamellar bone is the mature bone
b. Formation of woven bone is much faster than lamellar bone
c. Both types have similar composition at general
d. The presence of woven bone in adults is normal

4.Which one of the following statements best describe bone structure and its Physiohistology ?
a. The osteoid constitutes 85% of the matrix.
b. Type Il collagen is the main protein in matrix
c. Lamellar bone is less cellular than woven bone
d. Osteocytes are large multinucleated cells
e.Osteoclasts are small bone forming cells

5. A 2-year-old boy is treated for recurrent fractures of his long bones. Physical examination reveals blue sclerae, loose joints, abnormal teeth, and poor hearing. Molecular diagnostic studies will most likely demonstrate a mutation in the gene encoding which of the following proteins?
a) Collagen
b) Dystrophin
c) Lysyl hydroxylase
d) Fibrillin
e) Fibroblast growth factor receptor.

6. A 30-year-old man with dwarfism is admitted to the hospital for hip replacement due to severe osteoarthritis. He has short arms and legs and a relatively large head. His parents do not show signs of this congenital disease. This patient most likely has a spontaneous mutation in the gene encoding which of the following proteins?
a) Collagen type I
b) Collagen type II
c) Fibroblast growth factor receptor
d) Growth hormone receptor
e) Insulin-like growth factor

Ans: 1-c. 2-c. 3-d. 4-c. 5- a 6.c

Best wishes

V1