Inherited disorders

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Introduction

- Human cells have 23 pairs of chromosomes made up of 22 pairs of non sex chromosomes called autosomes and 1 pair of sex chromosome giving a total of 46.
- The sex chromosomes are X and Y.
- XY for males and XX for females.
- Genetic disorders are split into categories such as: Chromosomal, Single Gene, and Multifactorial.
- Penetrance is defined as the proportion of individuals bearing a mutated allele who develop the disease phenotype.
- Expressivity describes the level of severity of each aspect of the disease phenotype.

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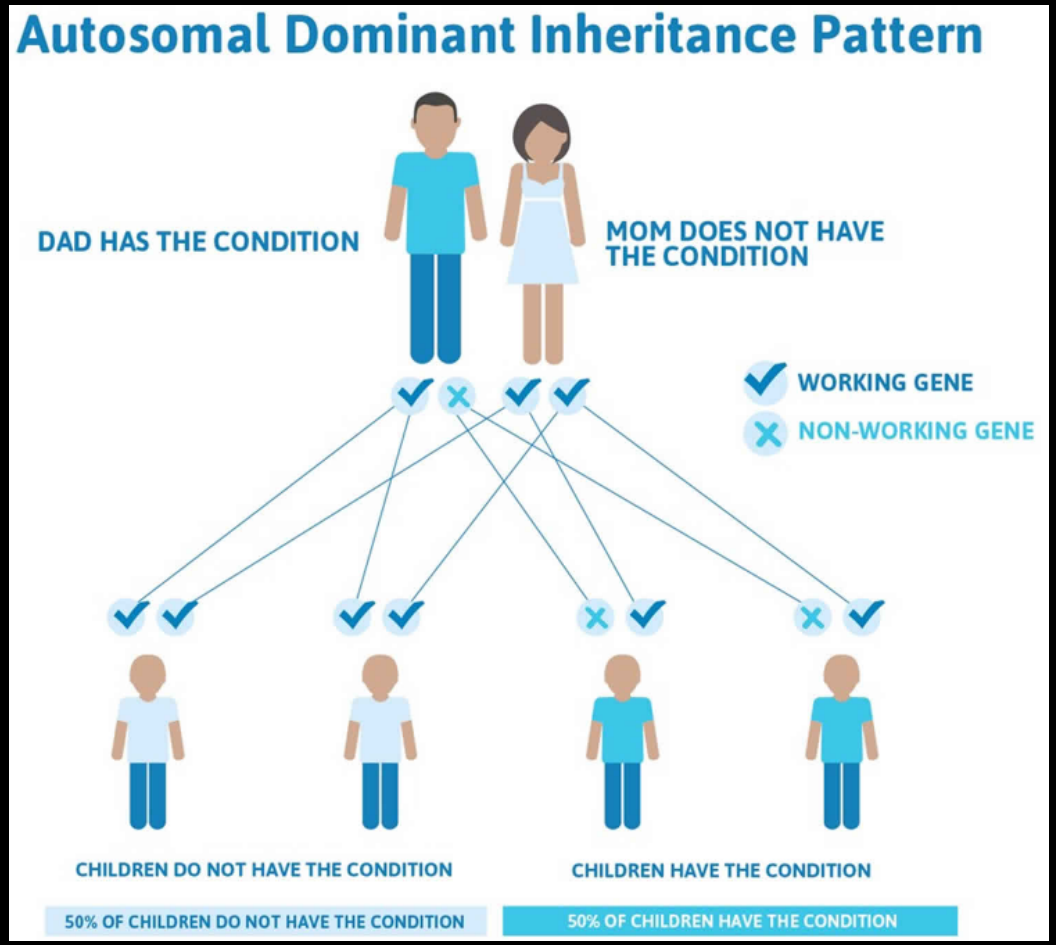
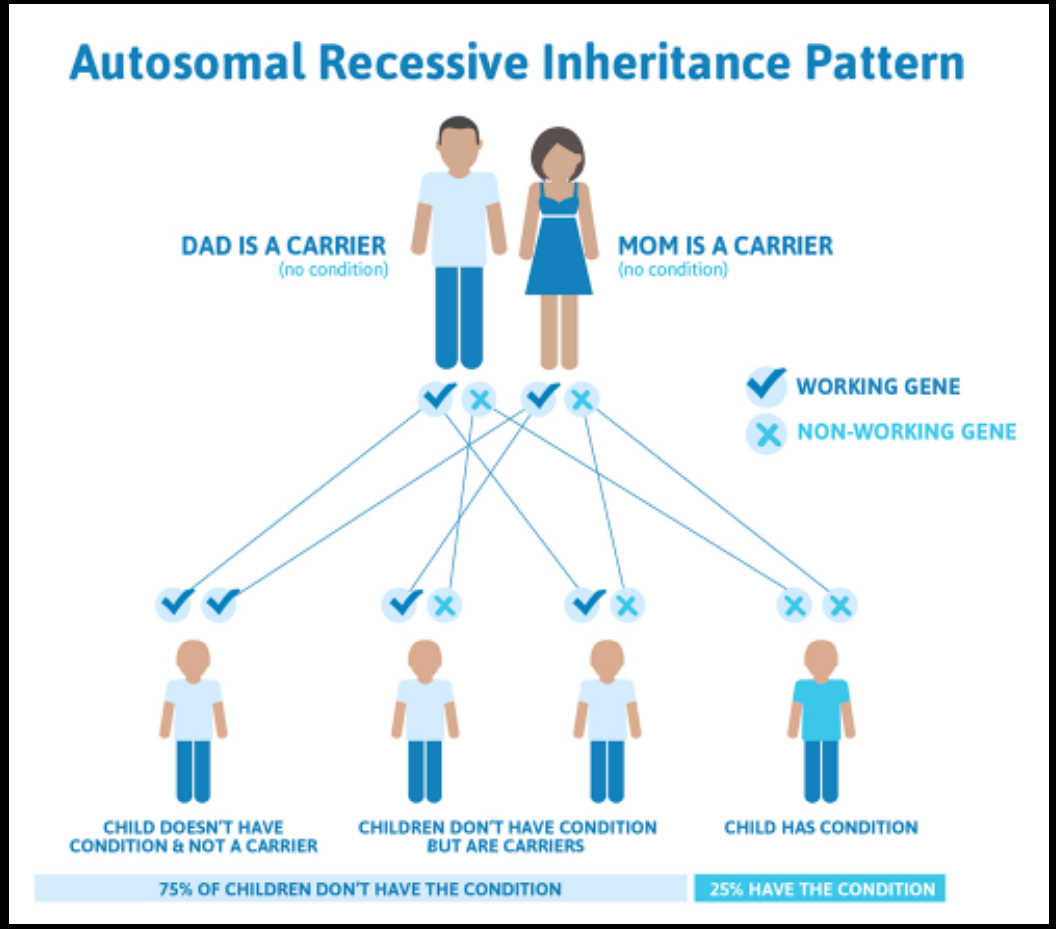
Single gene (Autosomal Dominant)

- Usually represented in diagrams using an UPPERCASE letter (R)
- Autosomal means involving the non sex chromosomes.
- Dominant means that one copy of an abnormal gene is enough to cause the disorder. (Rr) or (RR) have the disorder.
- Examples include Huntington's Disease and Polycystic Kidney Disease



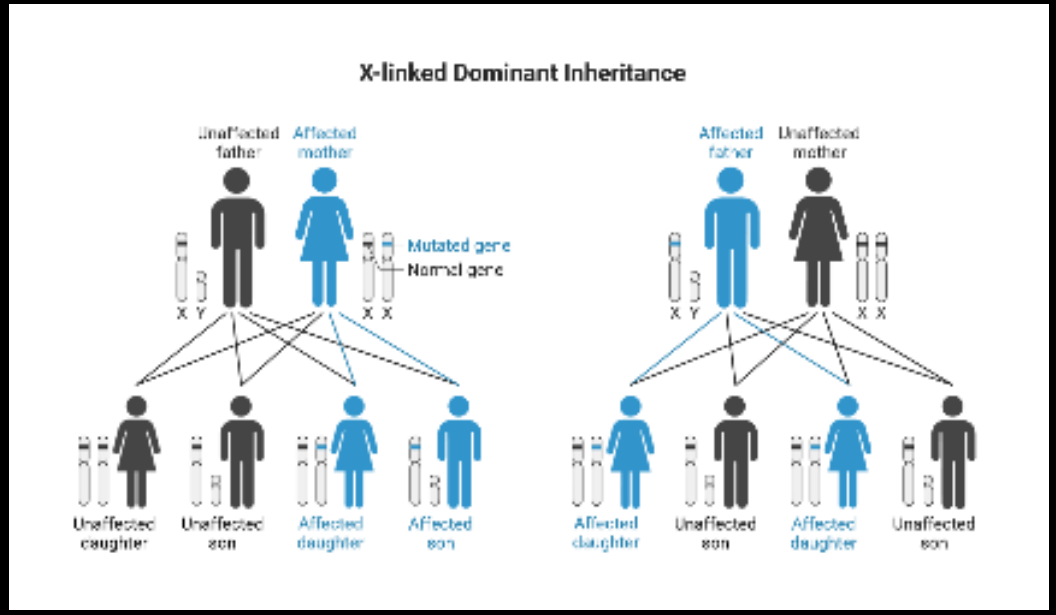
Single gene (Autosomal Recessive)

- Usually represented in diagrams using a lowercase letter. (r)
- Recessive means that if the individual has one copy of the abnormal gene, they are carriers. (Rr)
- But if they have both copies of the abnormal genes they have the condition. (rr)
- Examples include Thalassemia, Sickle Cell Anemia, and Cystic Fibrosis.



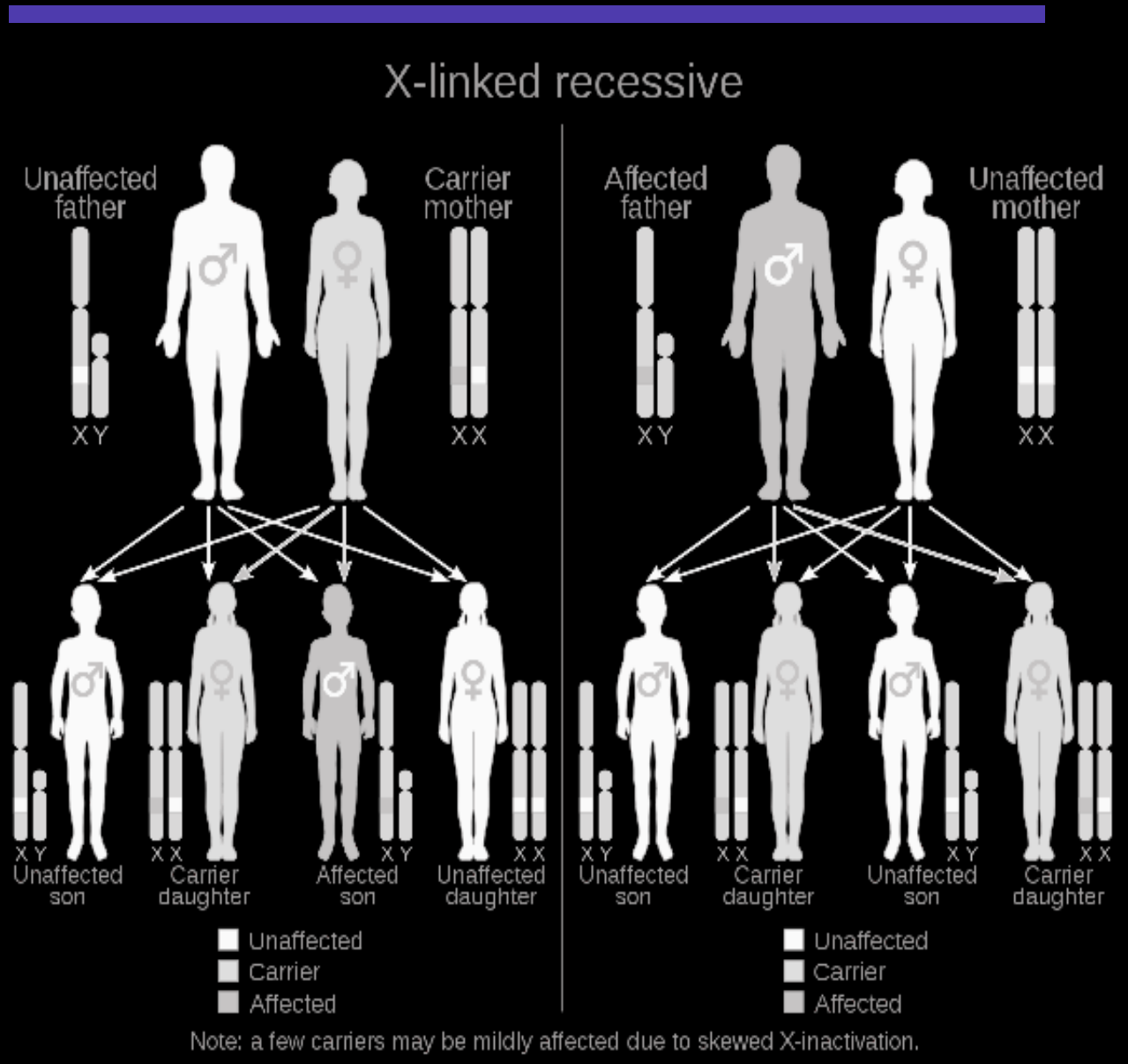
Single gene (X linked dominant)

- The dominant gene is carried on sex chromosome X. and only one is enough to cause the disorder.
- Common in both males and females.
- Vitamin D resistant rickets also called Hypophosphatemic rickets is an example.



Single gene (X linked recessive)

- The recessive gene is on the X chromosome.
- Since males have one X chromosome it is much more common in males.
- Duchenne's Muscular Dystrophy is an example.



Single gene (Mitochondrial)

- Mutation in non-nuclear DNA of the mitochondria. Since egg cells keep their mitochondria during fertilization and sperm cells don't. This is always inherited from the mother to her children.
- The eye disease Leber's hereditary optic neuropathy is an example.

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Multifactorial and chromosomal abnormalities

- Multifactorial: Caused by a combination of factors such as the environment and mutations in multiple genes. Studies into breast cancer have shown different genes that influence susceptibility. High blood pressure, diabetes, and Inflammatory Bowel Diseases are multifactorial.
- Chromosomal abnormalities are large scale mutations of the chromosome. Either excess or deficient. Usually due to a problem in cell division. Such as Down Syndrome Trisomy 21.

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Progressive Inherited disorders

- Conditions such as Huntignton's and Cystic Fibrosis are progressive. Meaning that symptoms get worse over time as the damage accumulates and with the lack of a cure or treatment the decline in health and function gets worse as well over time.
- This can lead to frustration, depression, and suicide attempts in patients diagnosed with progressive disorders.
- Making coping and dealing with the stress of the disorder a very important part in maintaining quality of life.

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Duchenne's muscular dystrophy

- Is an X linked recessive disorder. In which there is a lack of dystrophin. Predominantly in males, although some female carriers may show manifestations.
- Characteristic: NO inflammation.
- Symptoms begin to show at the age of 5 and teenage patients need wheelchairs.
- 1/3500 live birth males have DMD. 2/3 are inherited and 1/3 are spontaneous.
- The average lifespan is 30 and causes of death include cardiac complications (Dilated Cardiomyopathy and Arrythmias) and respiratory failure.

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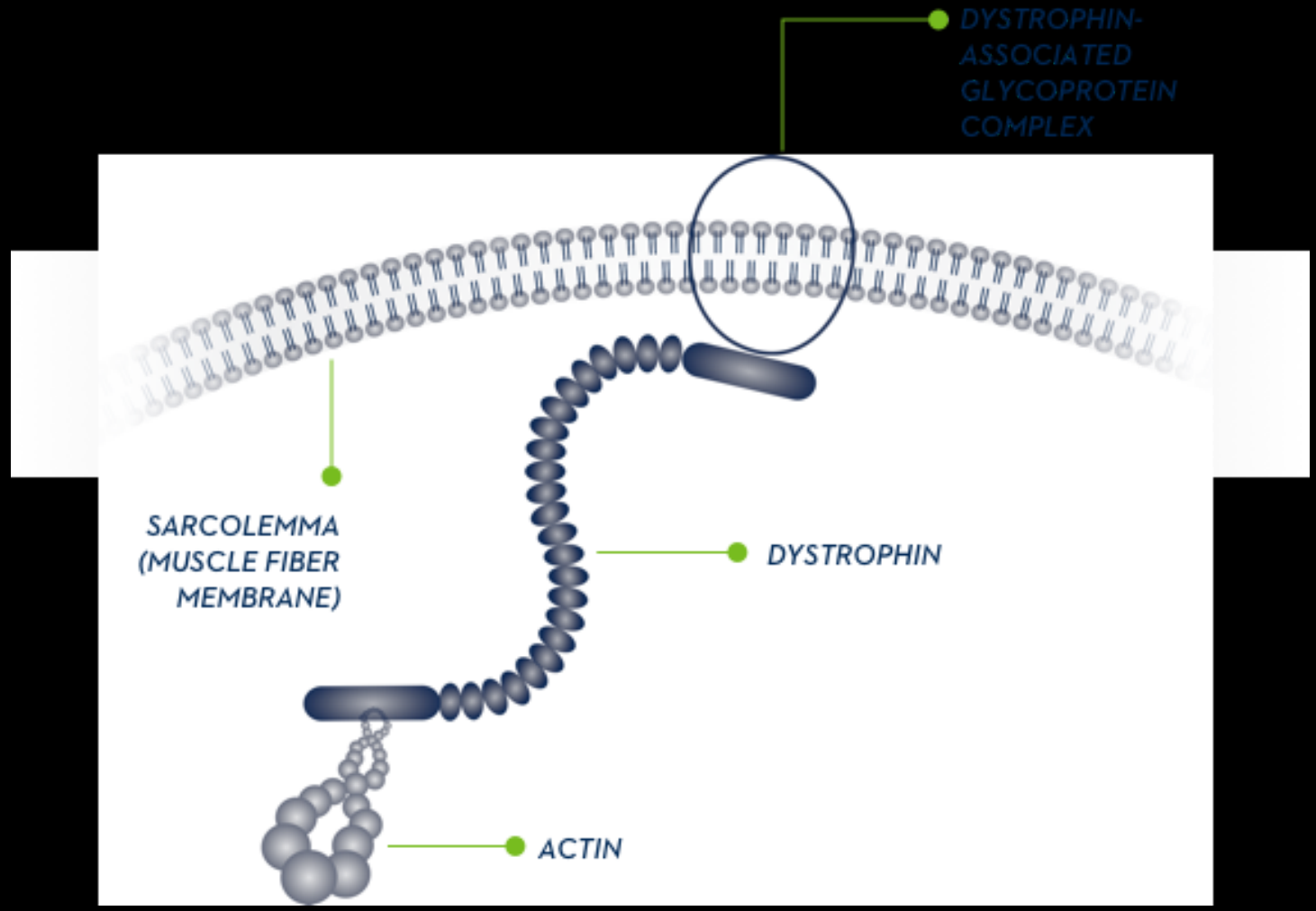
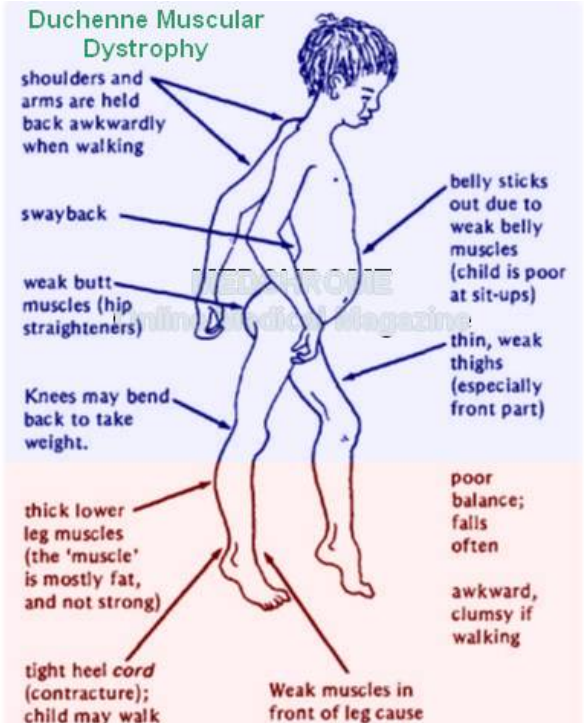
Dystrophin

- Dystrophin is the anchor or the glue. It links actin to the Dystrophin associated glycoprotein complex that are anchored to ECM. This stabilizes the Sarcolemma.
- Without dystrophin the sarcolemma is weak and unstable. With time Calcium enters the cell (Cell death) and Creatine Kinase leaves the cell(Diagnostic tool)





Clinical features

- Muscle weakness is progressive and symmetric involving proximal muscles primarily (pelvic girdle). In the short term there is regeneration. But long term atrophy.
- Gowers maneuver (use of hands to get up) and waddling gait.
- Calf pseudohypertrophy: due to fat replacing muscles
- Ultimately results in wheelchair use, respiratory muscle involvement and failure, and death.

Diagnosis

- Through high creatine kinase
- Mutations in Dystrophin (DNA test or western blot)
- Muscle biopsy
- No cure is available. Treatment is symptomatic to improve quality of life.
- Screening is necessary for cardiac abnormalities.
- Becker's Muscular Dystrophy is a similar less severe and less common muscular dystrophy in which there is some dystrophin present.

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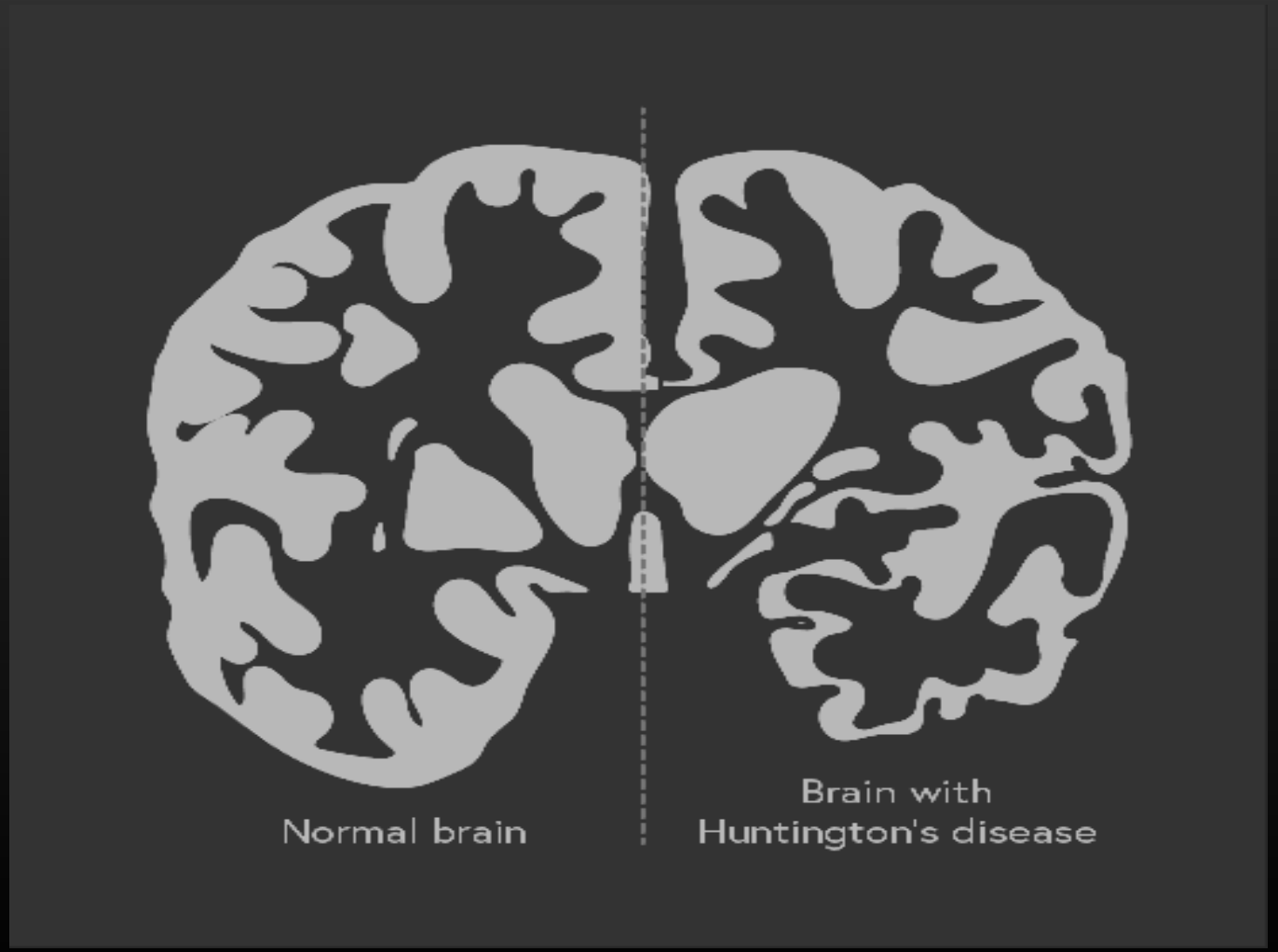
Thank You!

Huntingtons Disease



HD disease def.?

- progressive neurodegenerative disorder characterized by choreiform movements)appear to be minor problems with coordination(, psychiatric problems, and dementia.

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Huntingtons protien

- This protein is involved in chemical signaling, transporting materials, attaching (binding) to proteins and other structures, and protecting the cell from self-destruction (apoptosis).

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EPIDEMIOLOGY

- The worldwide prevalence of HD was 2.7 cases per 100,000 persons.
- In studies from Europe, North America, and Australia, the prevalence of HD was 5.7 cases per 100,000 persons
- The prevalence rate in Middle Eastern Arabs is estimated to vary from 3 to 4 per 100,000.

- A 2012 meta-analysis that evaluated HD epidemiology studies published since 1985 made the following observations:

Genetics of HTT

- HD disease is caused by $(CAG)_{glu}$ trinucleotide repeat expansion in the Huntington(HTT) gene on chromosome 4p and inherited in an autosomal-dominant pattern.

HUNT 4 DATE:-

HUNTingtons on chromosome **4** ,with cau**DATE** nucleus involvment

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CAG portion in normal

- CAG repeats normally in healthy individual are 28 or less, but in diseased one symptoms will appear when the repeats exceeds the 40 repeats and the HD symptoms will appear.
- Repeats between 28-40 will place the next generation in a risk to develop expansion.

NB:- As with all trinucleotide disorders, there is genetic instability. Expansion of the repeat number between successive generations, which causes an earlier and more severe phenotype, is termed "anticipation".Paternal inheritance results in the largest increase. Thus, children with juvenile-onset HD will have typically inherited the pathological allele with expansion from the father.

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Pathophysiology of HD

- Their will be accumulation of CAG repeats in HTT gene (norm 28 or less) and their aminoacid(glutamine) in HTT protien too.
- The huntingtin protein is thought to become toxic with the CAG expansion ("gain of function") but continues to serve a function that is critical to survival in early development.

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How neuro cells will die?

1) HTT protien aggregation will triger the autophagic degraditon patheways,then disregulated cell injury death.
2) Abnormal HTT protien□binding of various transcriptional regulators□sucibtability of oxidative strees,protective genes damage□neuronal death.

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What cells will be mostly effected?

- The most common effected cells are those found in the Dorsal striatum (caudate and putamen) which are in charge of the movement inhibition.
- So most symptoms will be related to these sites function,like chorea(HDvsRHD),athetosis, abnormal eye movments and poor coordination.
- Hypotonia with hyperreflexia is a feature of early disease. Dystonia (prolonged, sustained, abnormal postures) may be seen in the hands with such activities as walking. Mild bradykinesia is also observed.

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Chorea

- **movement disorder that causes involuntary, irregular, unpredictable muscle movements**. The disorder can make you look like you're dancing (the word chorea comes from the Greek word for “dance”) or look restless or fidgety. Chorea is a movement problem that occurs in many different diseases and conditions.

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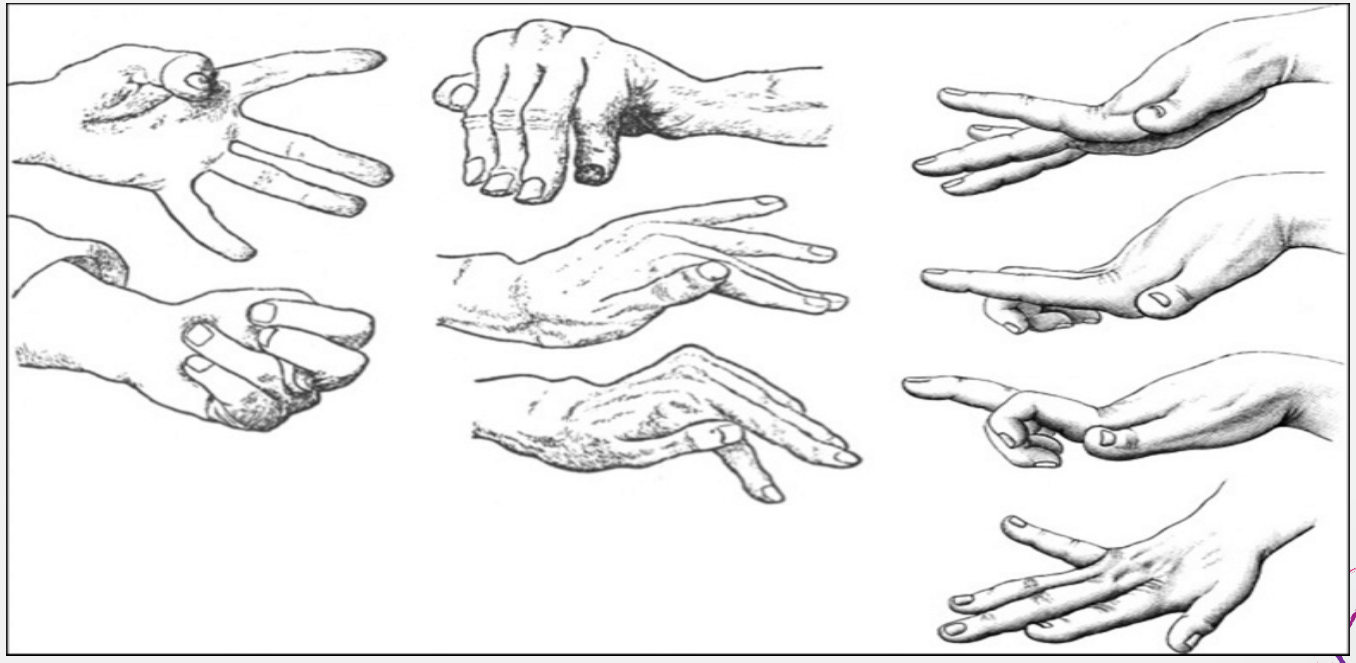
Athetosis

- **slow, involuntary, and writhing movements of the limbs, face, neck, tongue, and other muscle groups**. The fingers are also affected, with their flexing happening separately and irregularly. The hands move, and the toes and feet may also experience the effect.



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Psychiatric complications

- Patients with HD may present with irritability, depression, and/or disrupted social relationships up to several years prior to onset of chorea Depression, paranoia, delusions, and hallucinations can develop at any point in the illness.
- HD is associated with an increased risk of suicide for diagnosed patients and at-risk family members while rates of suicidal ideaiton among HD mutaiton carriers are as high as 20 percent.

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Signs and symptoms summary

- Motor :- hyptonia and hyperreflexia (chorea,athetosis,dystonia,eye movments slows and gait abnormalities)
- Psychatric:-apathy,irritability,depression,delusions and paranoia.
- Cognetive:- progressive dementia,decreased concentration and memory loss.
- Weight loss and cachexia

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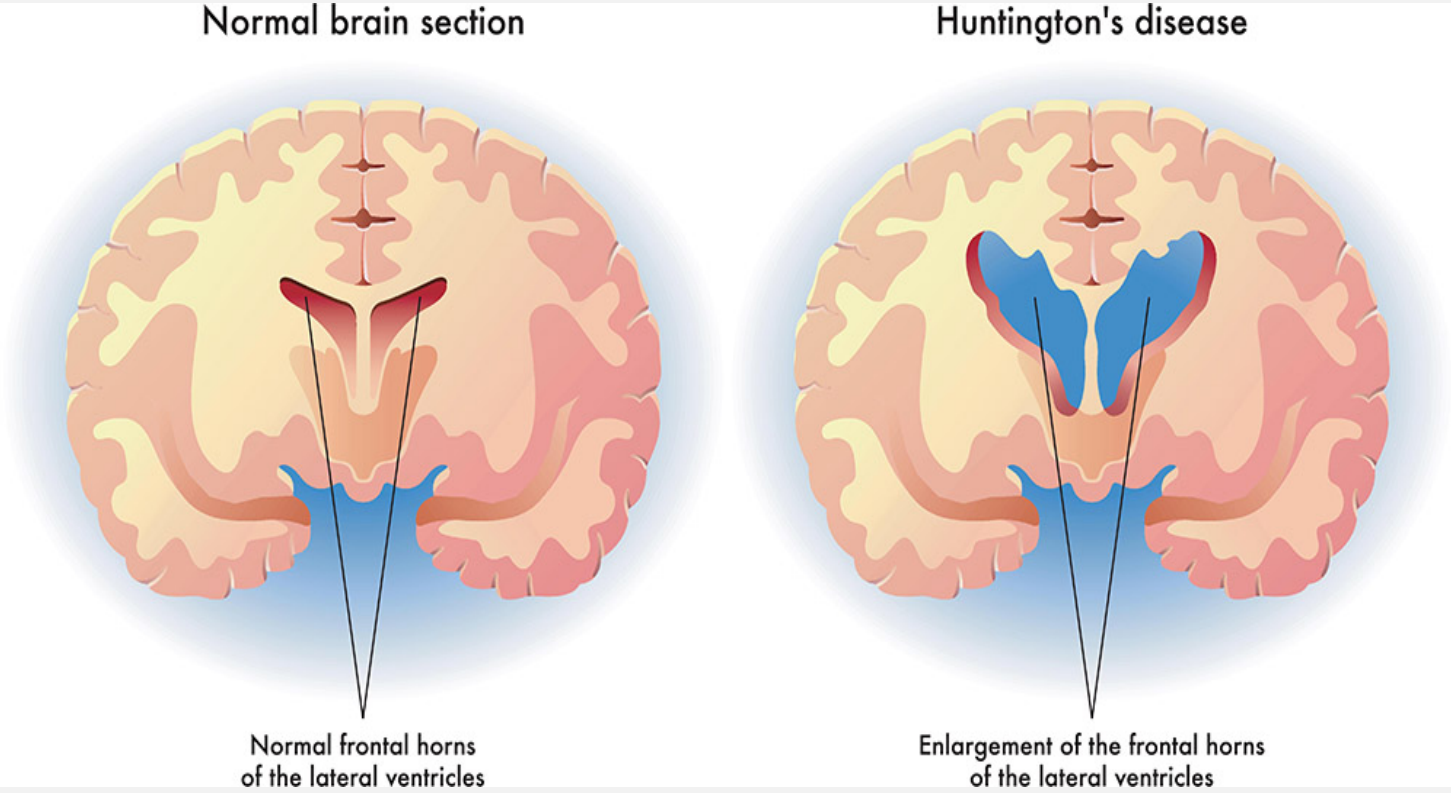
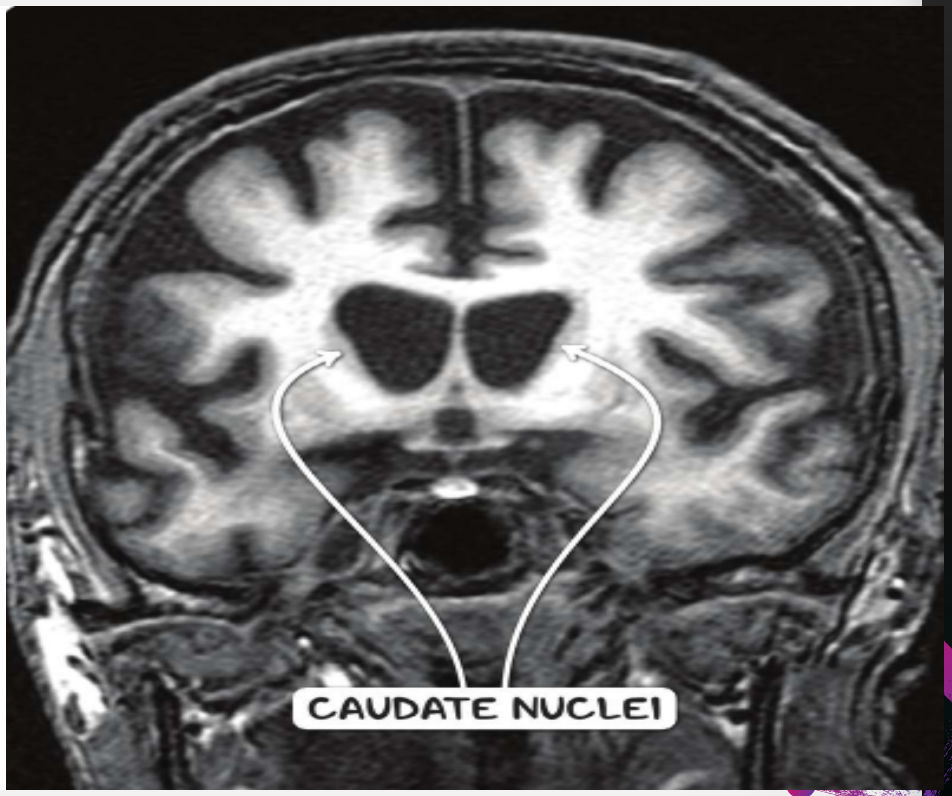
Diagnosis

- Imaging

MRI ☐atrophy of head of caudate nuclei





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Diagnosis cont..

- LAB results

Genetic test for CAG repeats in HTT (>36repeats)

- Other Diagnistics

  History,physical ex

  Neurological (motor and mental)status examination.

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Summary

- HD is a neurodegenerative disorder
- Caused by (CAG) trinucleotide repeat expansion in the Huntington(HTT) gene (return to menomic)
- charctrized mainly by motor problems such as chorea and athetosis and psychatric problems as depression and sucidal trials.
- Diagnosed through

MRI,history,physical ex and neurological (motor and mental) status.

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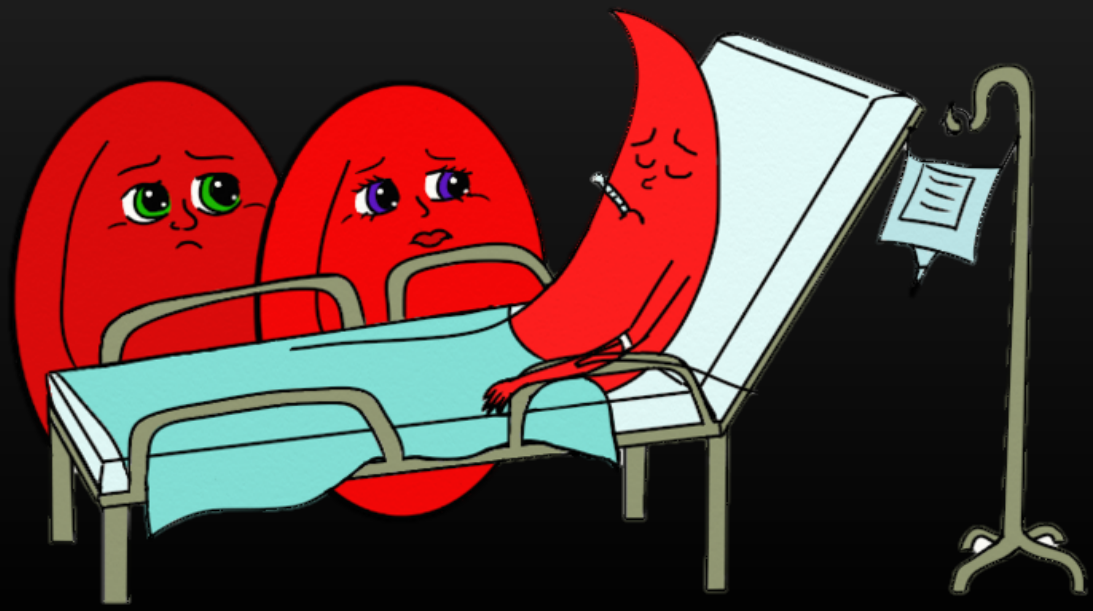
Thank
You

Sickle cell anemia..

By : rahaf Ibrahim al-hwetat



SICKLE CELL ANEMIA..

- Sickle cell anemia is one of a group of disorders known as sickle cell disease.
- Sickle cell anemia is an inherited red blood cell disorder in which there aren't enough healthy red blood cells to carry oxygen throughout your body.

- Normally, the flexible, round red blood cells move easily through blood vessels.
- In sickle cell anemia , the red blood cells are shaped like sickles or crescent moons . And that change allows them to be easily destroyed which cause anemia .These sticky cells can get stuck in small blood vessels , which can slow or block blood flow and oxygen to parts of the body.

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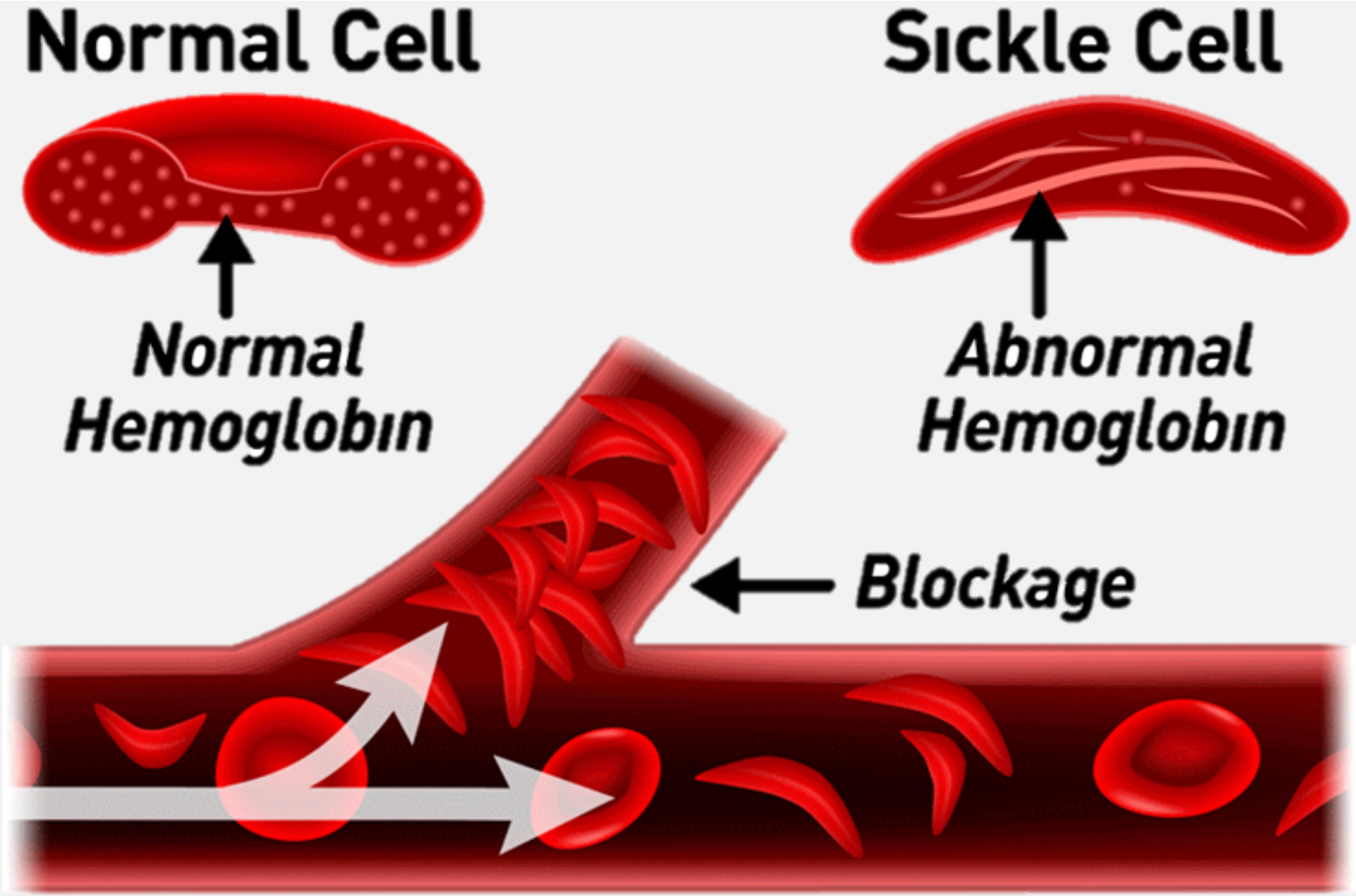

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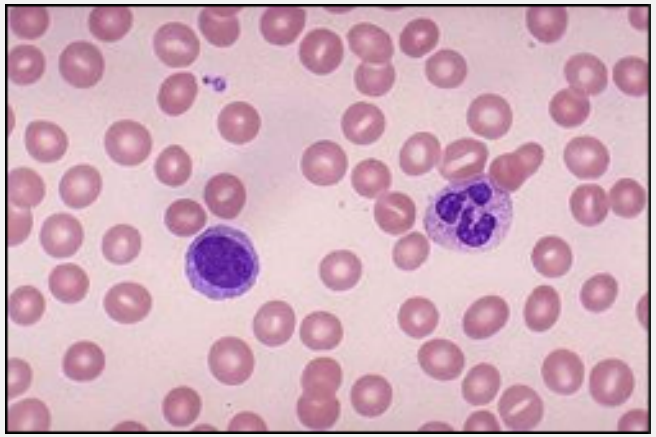
Normal Vs. Sickle Red Cells

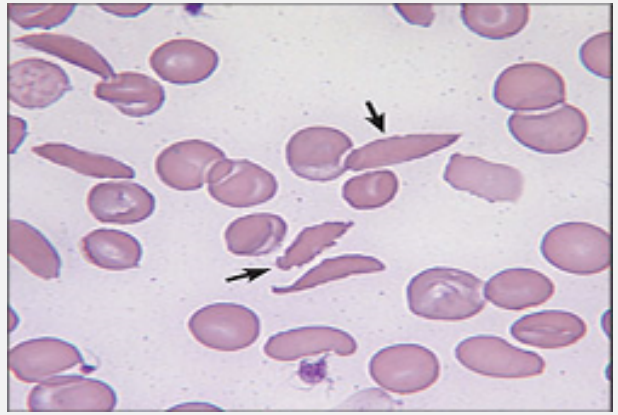
Normal

- Biconcave disc-shaped
- Deformable
- Life span of 120 days



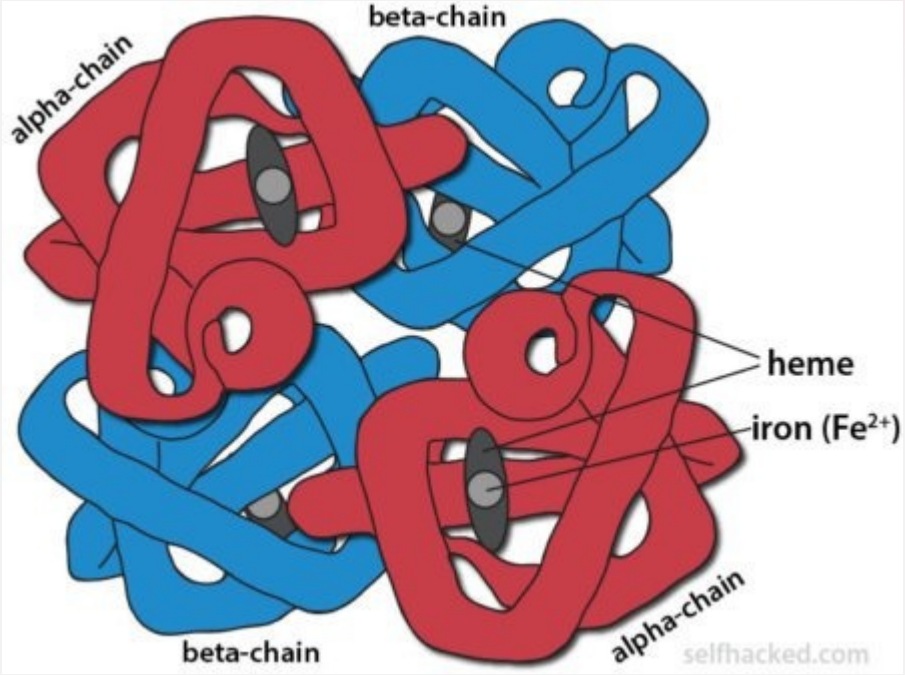
Sickle

- Sickle-shaped
- Rigid
- Life span of 20 days or less
- Sticky surface, abnormal properties



SICKLE CELL ANEMIA..

- Sickle cell disease is caused by defective hemoglobin ,which is oxygen-carring protein in red blood cells, hemoglobin is actually made of four peptide chains, each bound to heme group, different hemoglobin's have different combination of these groups .
- Hemoglobin A (HbA) is made up of two alpha globin and two beta globin chains.
- This is the primary hemoglobin affected in sickle cell, specifically the beta globin chain become misshapen, this is because of mutation in HBB gene.



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SICKLE CELL ANEMIA..

- Sickle cell disease is an autosomal recessive disorder which means both mother and father must pass the defective form of the gene for a child to be affected.
- If only one parent passes the sickle cell gene to the child, that child will have the sickle cell trait. With one normal hemoglobin gene and one defective form of the gene, people with the sickle cell trait make both normal hemoglobin and sickle cell hemoglobin.
- Their blood might contain some sickle cells, but they generally don't have symptoms, unless the person exposed to extreme conditions, e.g. high altitude, dehydration, hypoxia, stress, low temperature, acidosis, infection. They're carriers of the disease, however, they can pass the gene to their children.

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SICKLE CELL ANEMIA..

- sickle-cell patient have a missense non-conservative mutation at a single point in the DNA. The alpha subunit is normal but the beta subunit has the amino acid valine at position 6 instead of the glutamic acid that is normally present.
- Non conservative mutation means that the new amino acids (valine) which is hydrophobic has different property than the one that replace (glutamine) which is hydrophilic.
- This causes the body to produce a new form of hemoglobin called (HbS), which behaves very differently to regular hemoglobin (HbA) . This, in turn, causes the entire shape of blood cells to be different.

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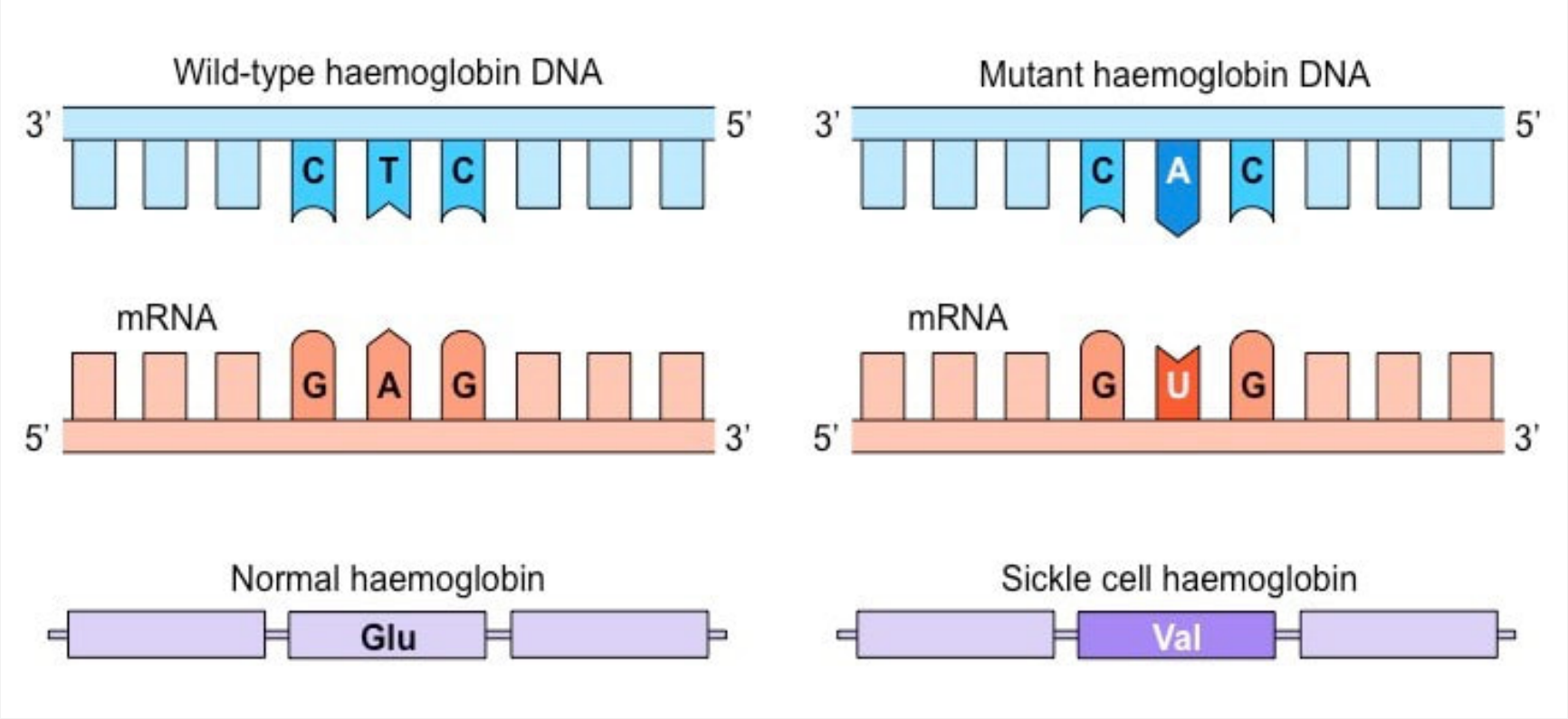
SICKLE CELL ANEMIA..



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SICKLE CELL ANEMIA..

- In oxygenation HbS carrys oxygen well, but in deoxygenation, HbS changes in shape which allows cells to aggregates with other HbS proteins and form long polymer that destroyed red blood cells and become crescent shape (sickling).
- But If your hemoglobin level is too low, like in acidosis which is decrease Hb affinity for oxygen, you may not be able to supply the cells in your body with the oxygen they need to survive, and sickling will occur

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SICKLE CELL ANEMIA..

- Recurrent episodes of sickling weakening cell membrane and become not capable of resuming biconcave shape upon re-oxygenation
- Deformed sickle cells adhere to endothelium & macrophages and contribute to erythrophagocytosis and the hemolytic process.
- This hemolysis leads to anemia which is deficiency of RBCs, and lots of hemoglobin spills out.
- Free Hemoglobin in the plasma is bound to molecule called haptoglobin and then get recycled, that's why low level of haptoglobin is sign for intravascular hemolysis.

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SIGNS AND SYMPTOMS..

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1- anemia

As the cells are abnormal, chronic hemolysis of the cell occur which leads to anemia .
Patient presented with fatigue, shortness of breath and feeling cold ,dizziness, headache and fast heartbeat .

Pale and dry skin and conjunctiva

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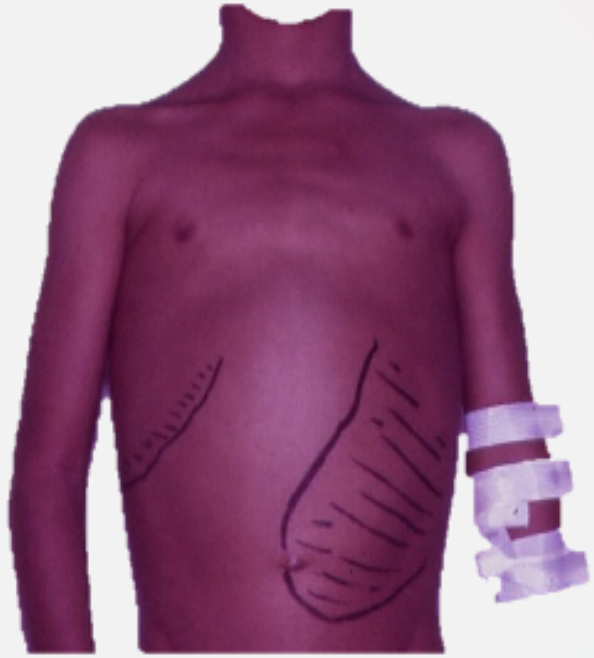
2- splenomegaly

- The incidence of splenomegaly in sickle cell anemia (defined as a spleen easily palpated below the costal margin in quiet respiration) appears to be around 10% after 10 years of age.
- Sickle cells can block the blood vessels leading out of the spleen. When this happens, blood stays in the spleen instead of flowing through it. This causes the spleen to get bigger.



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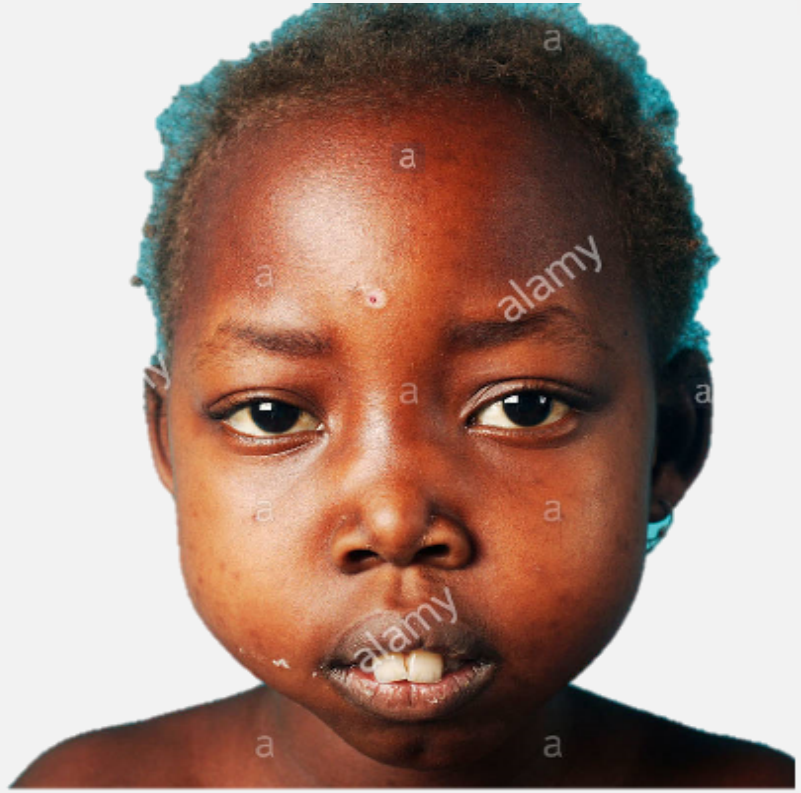
3- enlarged cheeks

- To counteract the anemia, the bone marrow increase number of reticulocytes which are immature red blood cells which cause new bone formation and the medullary cavities of skull expanded outward which cause enlarged cheeks and “ hair-on-ends” appearance in skull X-ray



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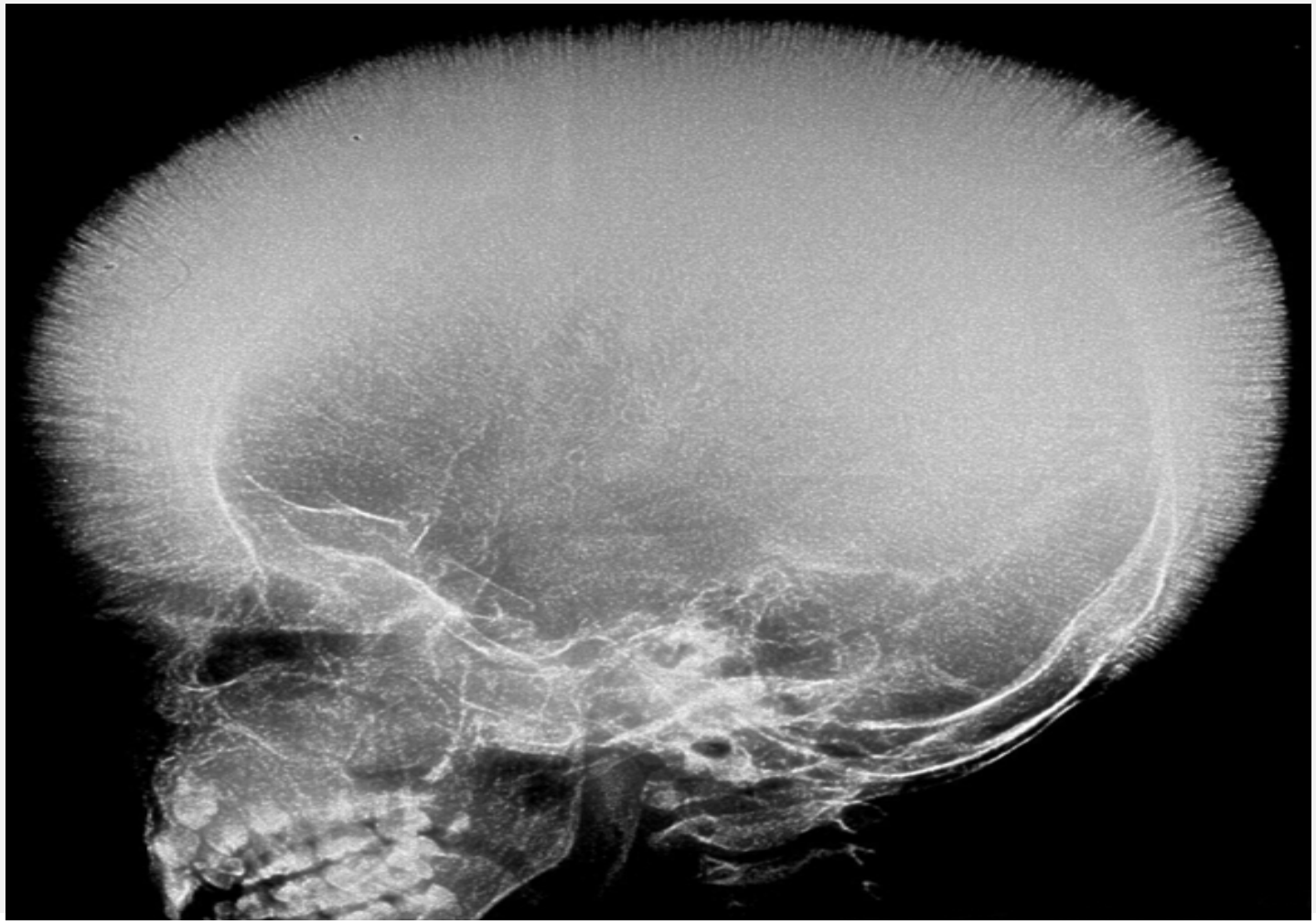
“hair-on-ends” appearance in X-ray



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4- jaundice

- Chronic hemolysis leads to break down hemoglobin continuous, recycling of heme group yield uncongugated bilirubin to buildup in the blood and cause jaundice which is a yellowish pigmentation of the skin and whites of the eyes (scleral icterus)
- Jaundice may be treated with drugs that reduce the sickling of red blood cells. It may also be treated with blood transfusions that increase the number of healthy red blood cells.

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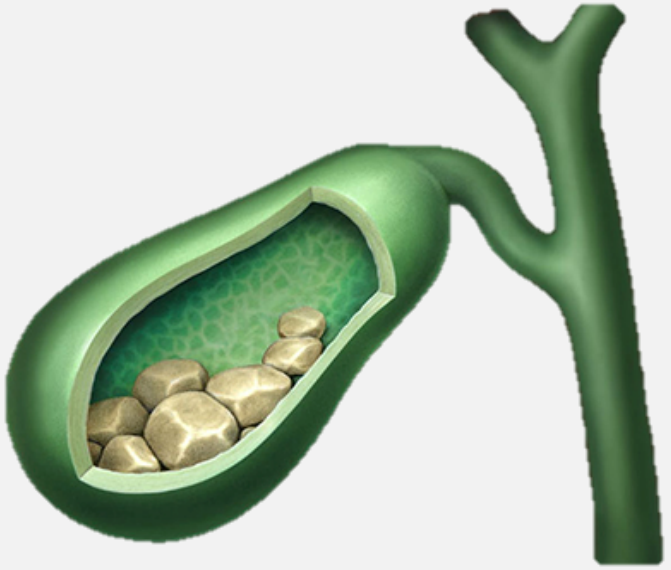
5- acute abdomen

- Gallstones form in SCD when bilirubin builds up in the gallbladder. These stons are solid, rock-like structures that form in the gallbladder. The condition is also called cholelithiasis.
- Gallstone migration can block the common bile duct and leads to gallbladder inflammation and the patient presented with acute abdomen .



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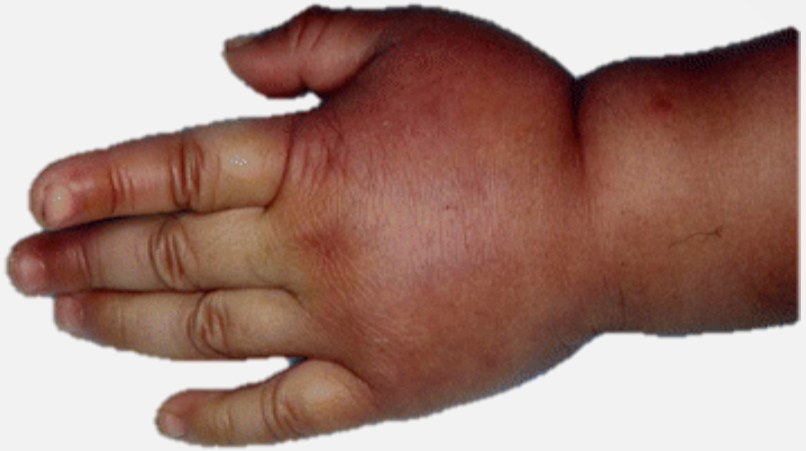
6- swelling of the hand and feet

- Swelling in the hands and feet usually is the first symptom of SCD. This swelling, often along with a fever, is caused by the sickle cells getting stuck in the blood vessels and blocking the flow of blood in and out of the hands and feet .



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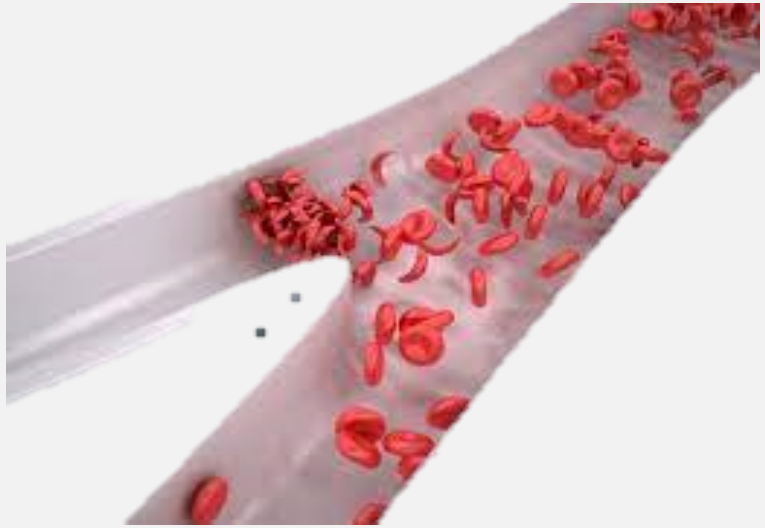
another Manifestations

- 1- Bacterial sepsis or meningitis
- 2- Splenic sequestration
- 3-Aplastic crisis
- 4-Acute chest syndrome
- 5- Stroke
- 6-Restrictive lung disease
- 7-Leg ulcers

Complications…

DVT / PE

- People with sickle cell disease (SCD) are at greater risk than the general population for forming blood clots. The cells stick with each other and can form a clot in one of the large veins, usually in a person's leg or arm, is called a deep vein thrombosis (DVT). If a DVT is not treated, it can get bigger or break off and travel to the lungs and cause PE which increase the pulmonary pressure and lead to right side heart failure



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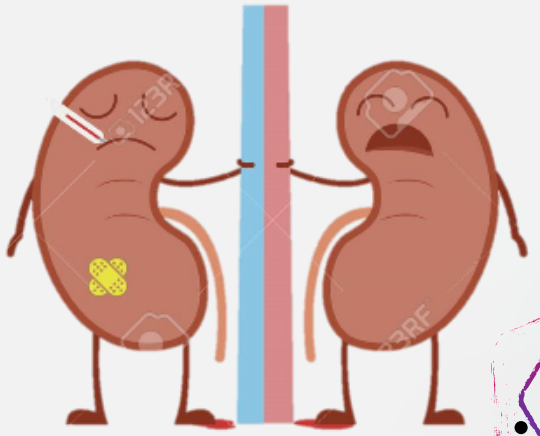
Sickle cell nephropathy (SCN)

- Sickle cell nephropathy (SCN) is a group of renal complications that can develop chronic kidney disease because of reduced blood flow to the kidney. It include hematuria, proteinuria, hyposthenuria, renal papillary necrosis, renal tubular disorders, acute and chronic kidney injury, sickle cell glomerulopathy, and renal medullary carcinoma . Chronic kidney disease can lead to end-stage renal disease (ESRD) and is a common cause of death for people with SCD



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Blindness / glaucoma

- People who have sickle cell disease can sometimes have vision problems. Blood cells that change shape, or "sickle," can get trapped in blood vessels, increasing eye pressure and lead to glaucoma .
- The clot can block the blood flow in the small blood vessels in the retina of the eyes, it can cause vision loss

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Sickle cell disease and malaria

- Sickle cell trait has repeatedly been identified as a major human malaria resistance factor.
- Various mechanisms to explain malaria resistance have been proposed, including sickling of the infected red blood cells (RBCs), increased splenic phagocytosis , premature hemolysis and leak of the nutrients that the parasites need to survive then the cells eventually get eliminated fast by the body , and the parasite died

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Treatment

- Management of sickle cell anemia is usually aimed at avoiding pain episodes, relieving symptoms and preventing complications. Treatments might include medications and blood transfusions. For some children and teenagers, a stem cell transplant might cure the disease.

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thank you…

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Thalassemia

Made by: Azhar Alsmady

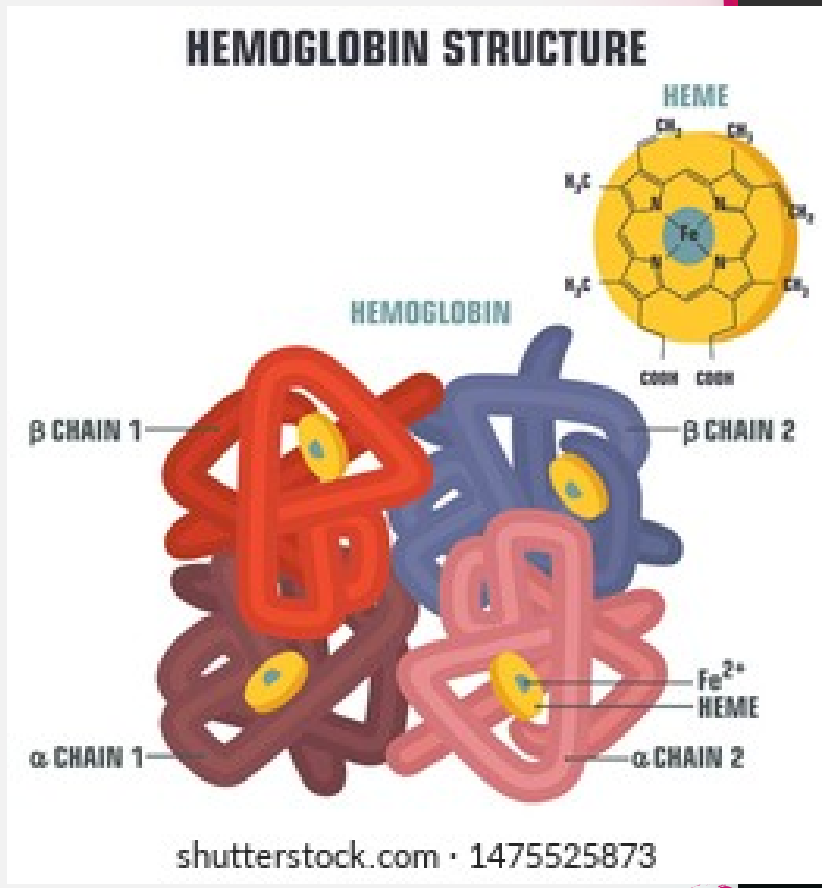
Introduction:

- Thalassemia from the Greek word “thalassa”, which means “the sea” and “emia” means “related to blood”.
- It refers to a group of inherited hemoglobinopathies that arose in certain regions of the world.

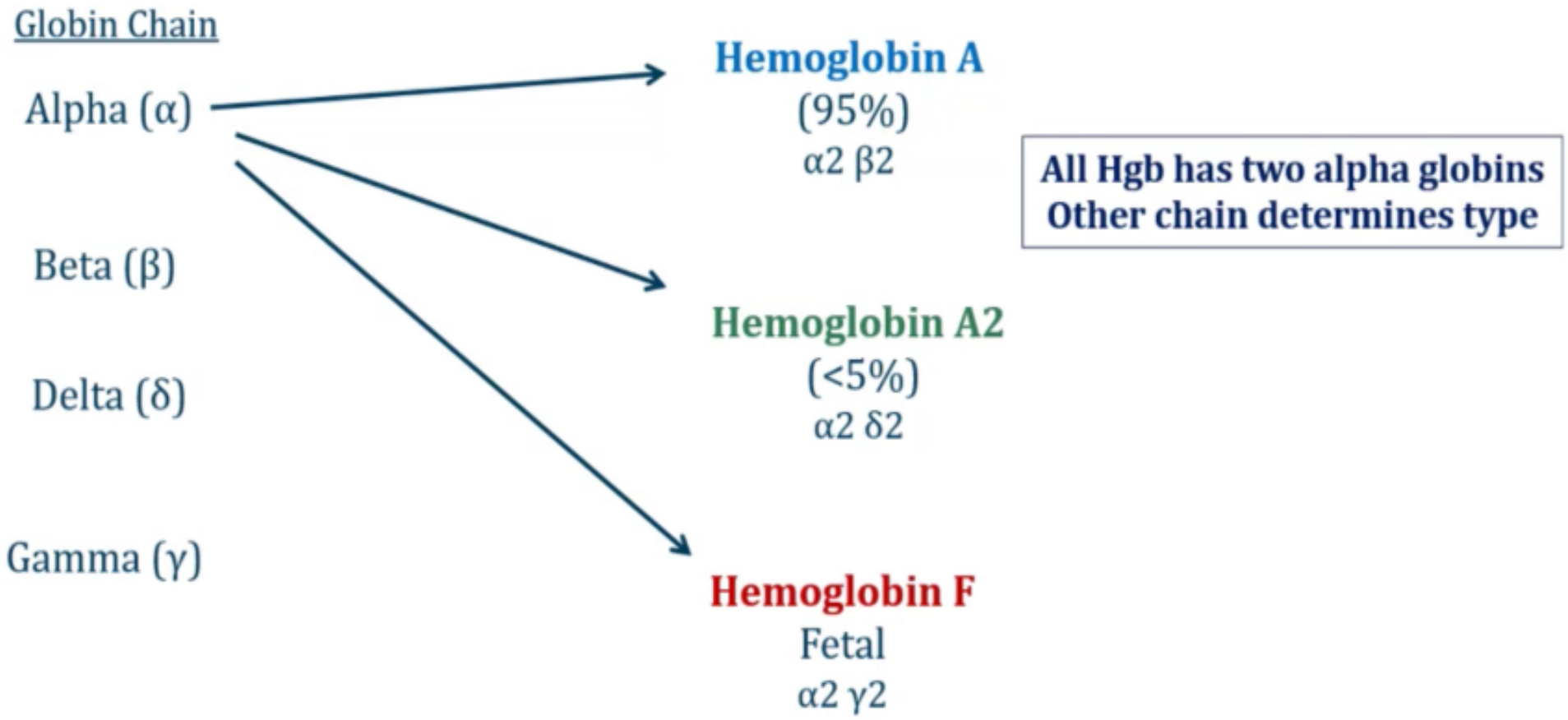
Hemoglobinopathies

Hemoglobin disorder

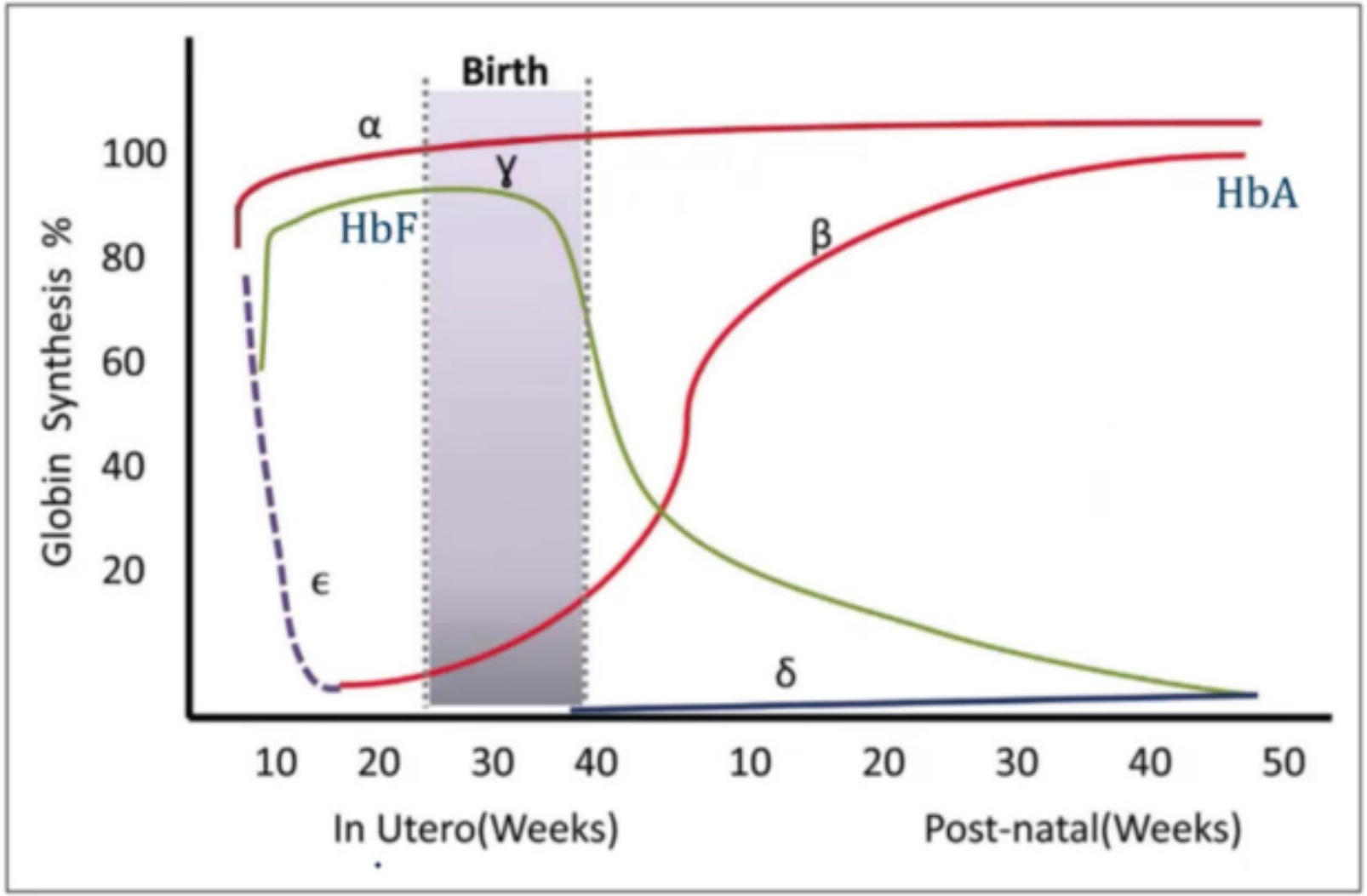
- Structural disorders: sickle cell disease.
- Thalassemia there is **decreased globin chain production.**
- Alpha thalassemia: alpha globin
- Beta thalassemia: beta globin



Globin Chains and Hemoglobin



Globin Chains and Hemoglobin



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What is thalassemia?

Inherited blood disorder characterized by reduced production of either the α- or β- globin chain of hemoglobin. This disorder results in excessive destruction of RBCs, which leads to anemia. Thalassemia is inherited, meaning that at least one of the patient's parents must be a carrier of this disorder.

Thalassemia is one of the causes of microcytic anemia, where MCV< 80.

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thalassemia

- **Spectrum of severity**
- **Thalassemia minor**
  - Often asymptomatic
  - Identified on routine blood testing or blood smear
  - May have microcytosis with ↑ red cell count
- **Thalassemia major**
  - Severe loss of globin production
  - Lifelong transfusion or death

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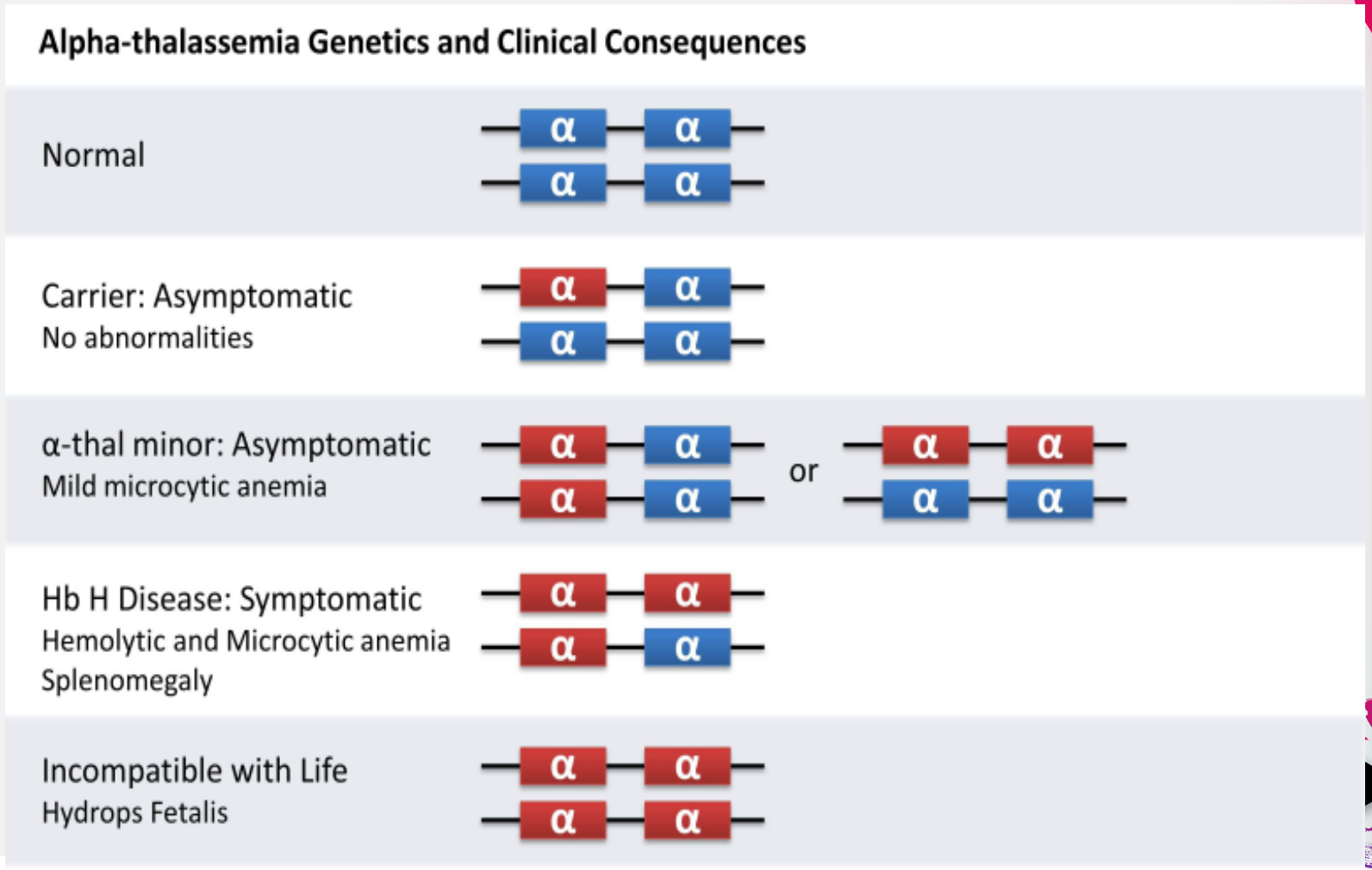
Alpha thalassemia

- Four gene codes for alpha chains
- Two on each copy of chromosome 16
- Often caused by gene deletions → ↓ α chains → alpha thalassemia



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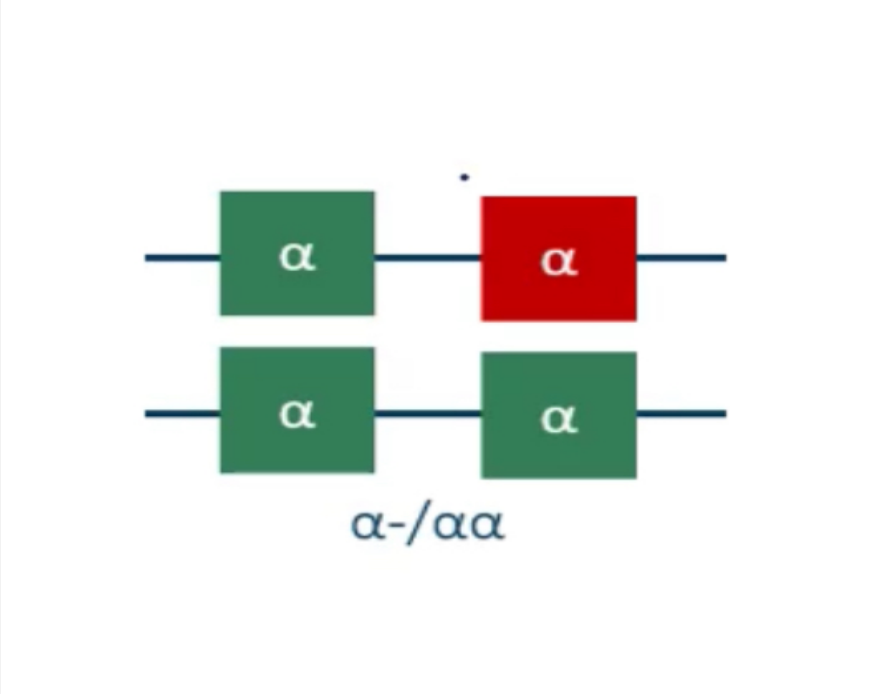
Alpha thalassemia minima

- Normal red cells
- No symptoms
- Carrier state



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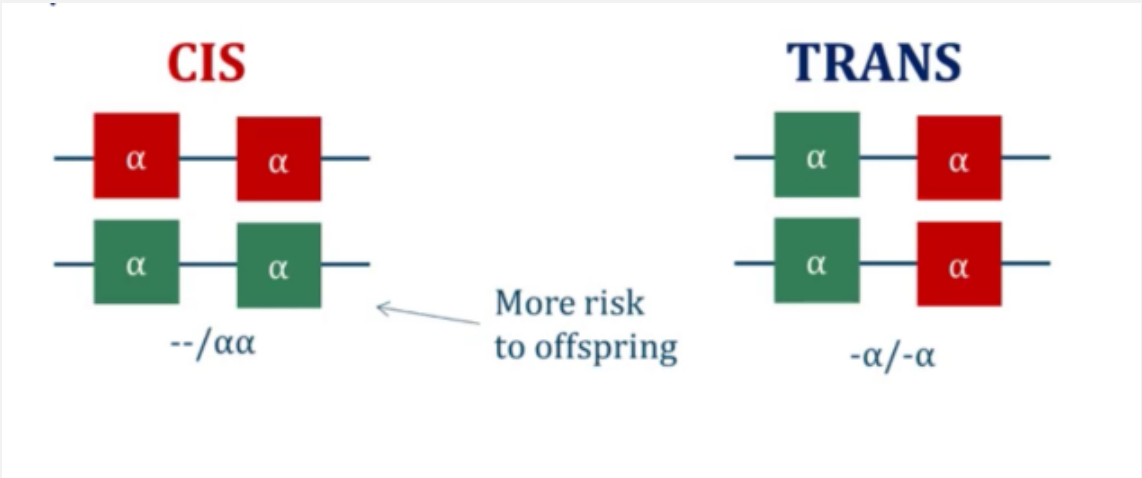
Alpha thalassemia minor

alpha thalassemia trait

- No symptoms
- ↓ MCV/ MCH/MCHC
- Electrophoresis: usually normal
- Diagnosis: genetic testing



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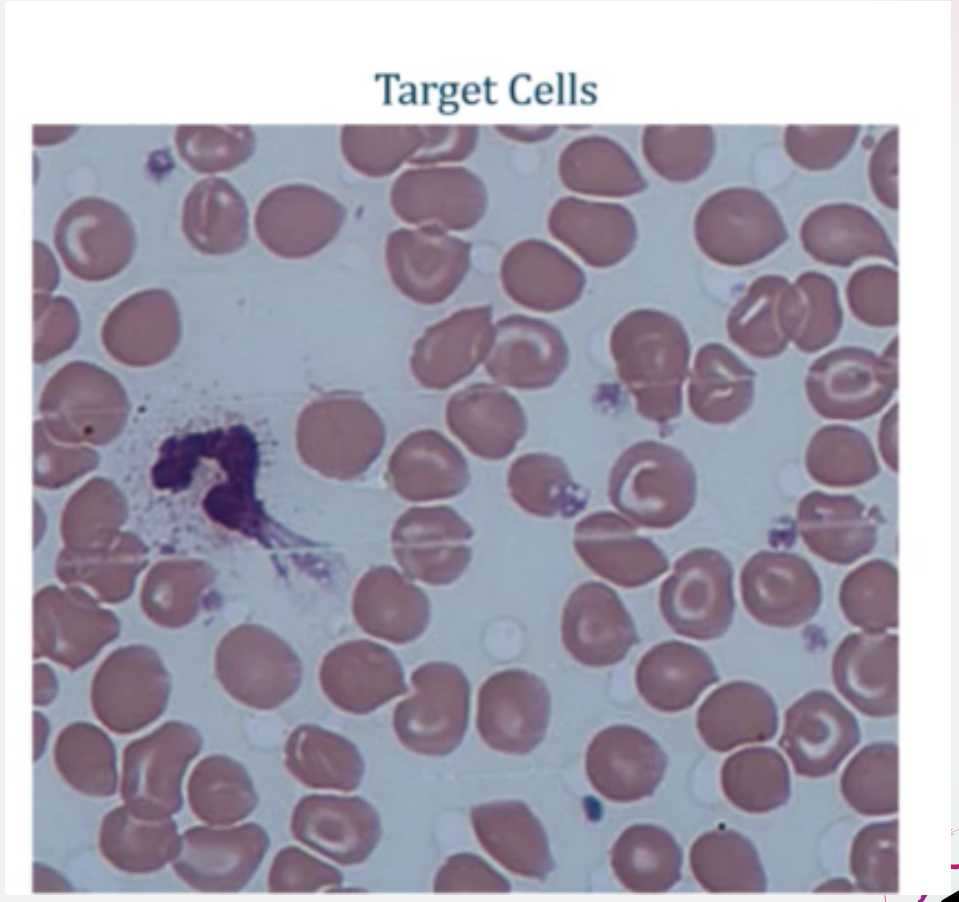
Thalassemia minor

differential diagnosis

- Alpha and beta minor can mimic iron deficiency
- Both may lead to low MCV & MCH
- Key distinguishing factors for thalassemia:
  - Red cell count normal or increased
  - RDW normal
  - Iron & ferritin normal or increased (increased turnover)
- Target cells
  - Classic finding in thalassemia
  - Caused by increased surface to volume ratio
  - Rarely seen in iron deficiency.



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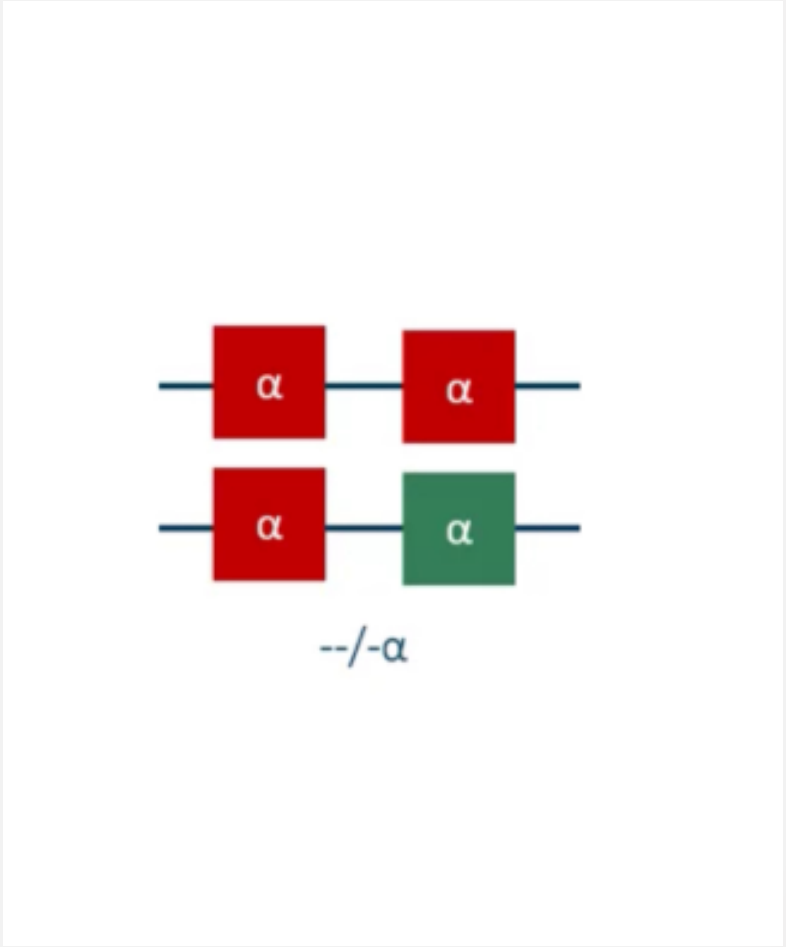
Hemoglobin H disease

alpha thalassemia intermedia

- Very little alpha globin production
- Excess beta globin
- HbH forms: four beta chains
  - Easily damaged
  - Affinity for oxygen 10x HbA
  - Poor oxygen delivery



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Hemoglobin h disease

clinical features, diagnosis & treatment

- **Clinical features:**
  - Highly variable presentations
  - Often asymptomatic in infancy
  - Hypochromic, microcytic anemia
  - Low MCV, MCH, MCHC
  - Extravascular hemolysis
    - Abnormal RBCs deformability
    - Splenomegaly
    - Indirect hyperbilirubinemia
    - May cause neonatal jaundice
  - Bizarre red cell morphologies

- **Diagnosis**
  - Electrophoresis
    - HBH
    - Decreased HbA, HbA2, HbF
  - DNA testing

- **Treatment**
  - Blood transfusions
  - Splenectomy
  - Bone marrow transplantation

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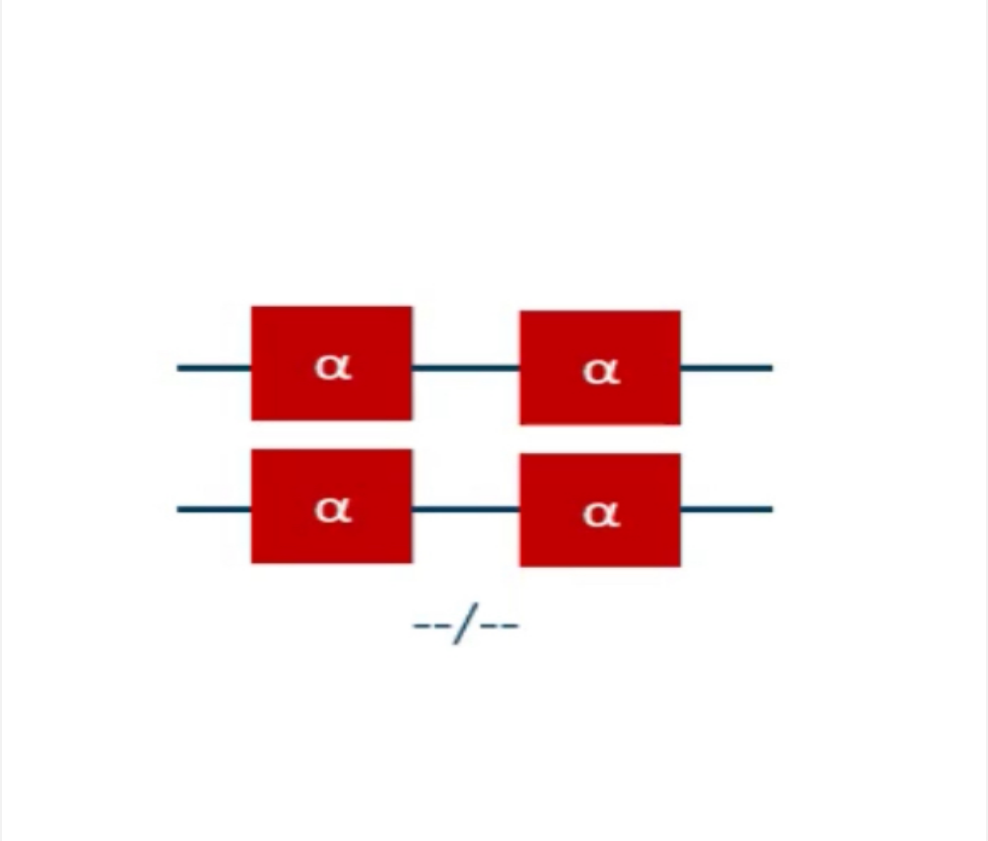
Hemoglobin barts

alpha thalassemia major

- No alpha globin
- Can not form HbF
- HgB Barts
  - Forms in utero
  - Four gamma globin chains
  - Can not release oxygen to tissues
- Hydrops fetalis
  - Massive total body edema
  - High output heart failure
- In utero death or death hours after birth



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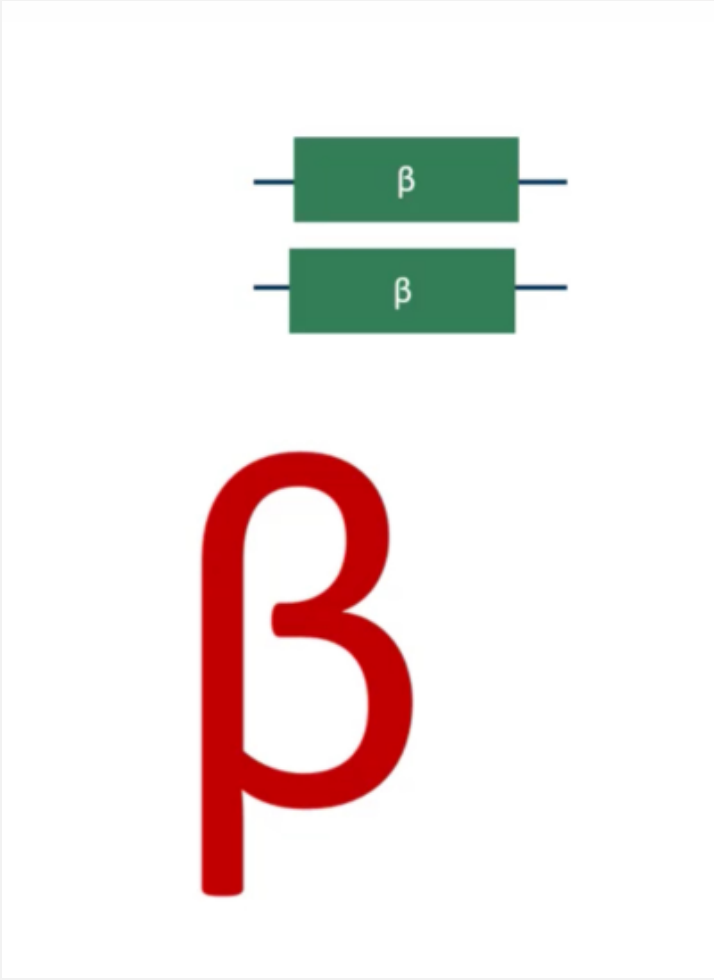
Beta thalassemia

- ↓β globin chain synthesis
- Two genes code for beta chains
- One on each copy of chromosome 11
- Often caused by mutations (not deletions)
- Wide spectrum of disease depending on mutation
- β^0 = no function, β^+ = some function



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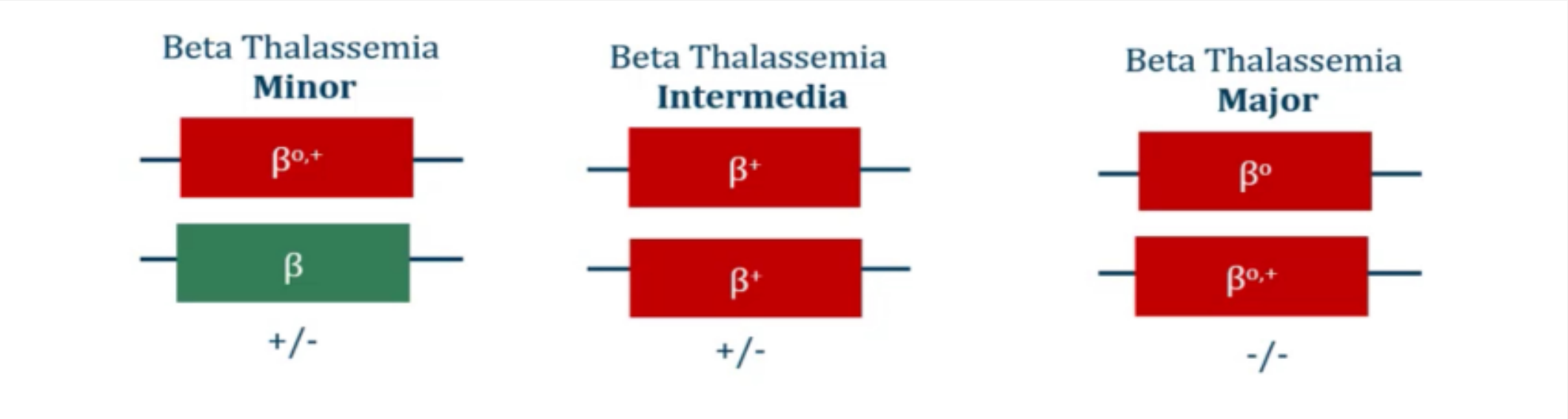
Beta thalassemia

- Previously classified as; minor, intermedia or major
- Now classified as **transfusion-dependent** or **transfusion-independent**



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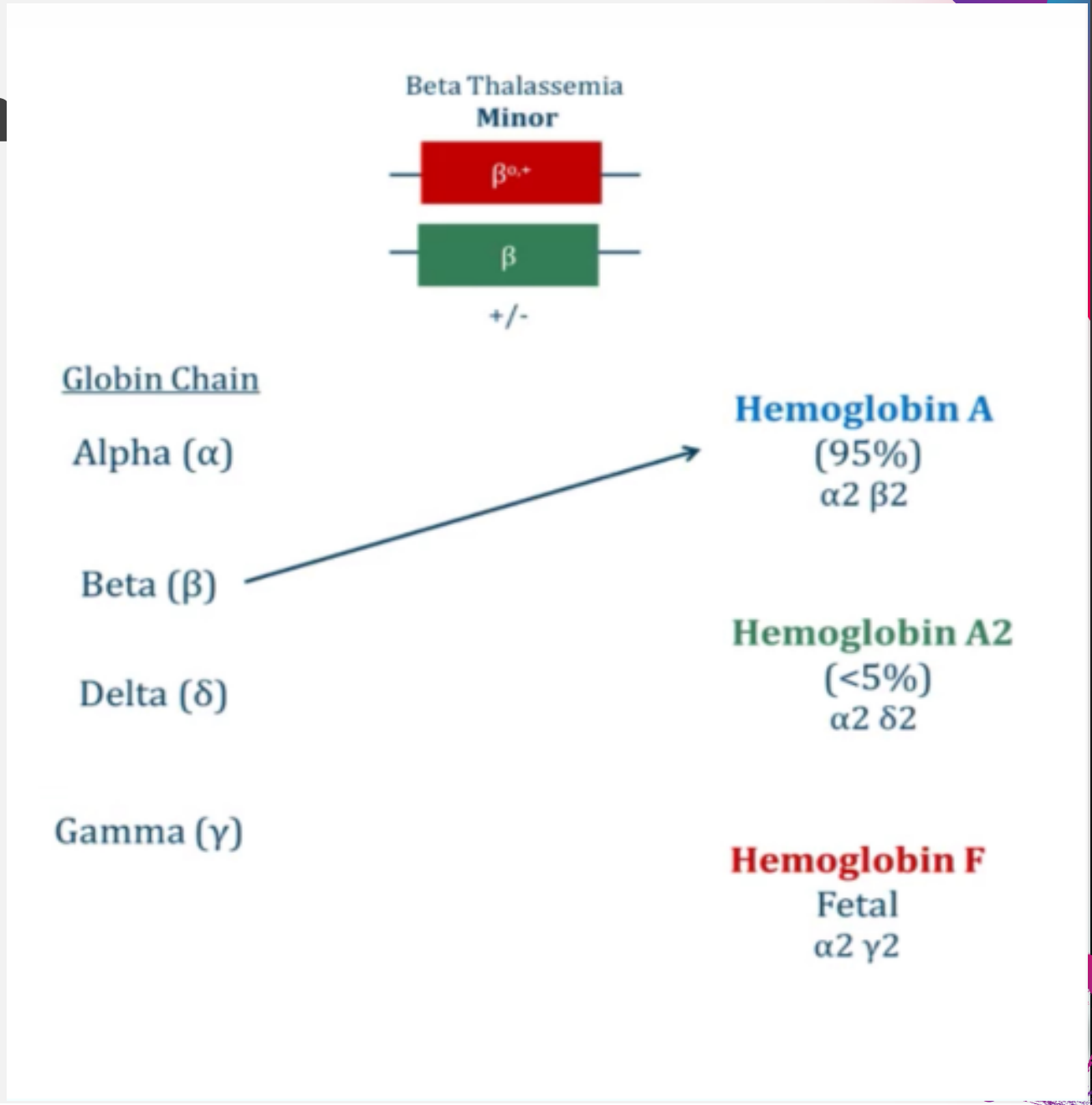
Beta thalassemia n

beta thalassemia trait

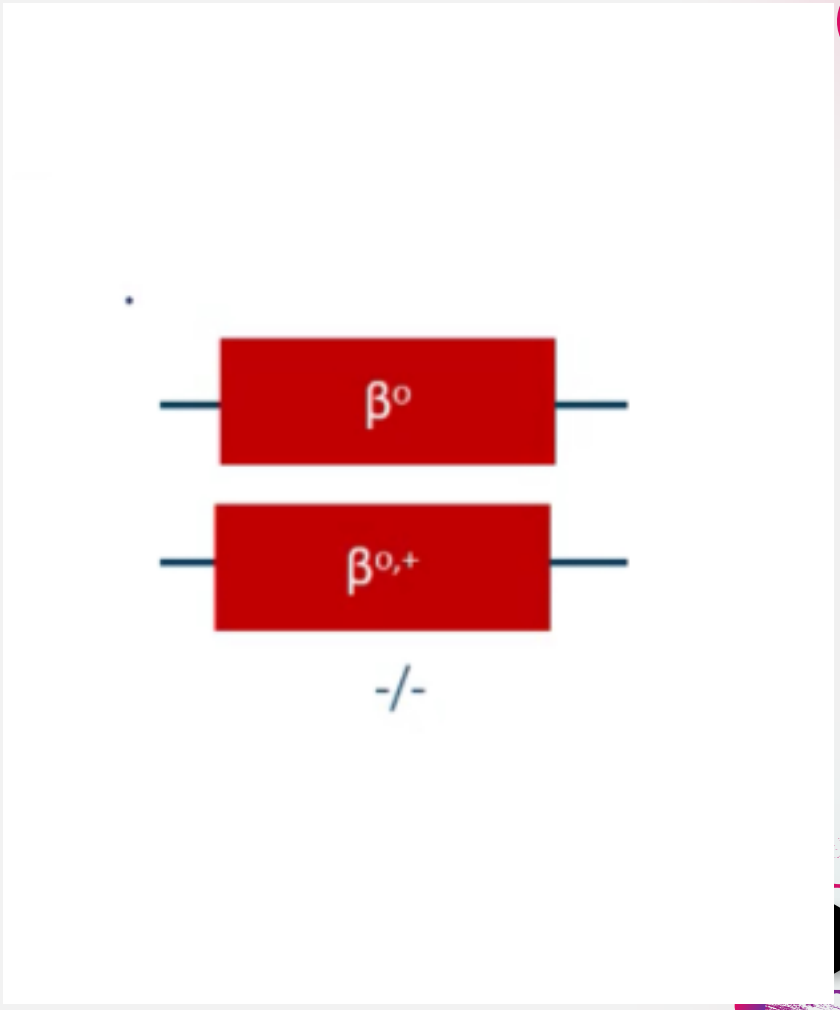
- Reduced β globin synthesis
- Asymptomatic
- Possible microcytosis with ↑ RBC
- Diagnosed by electrophoresis
- ↑HgbA2: α2δ2 – no beta chains
- normal ~3%



Transfusion – dependent beta thalassemia

beta thalassemia major

- Cooley's Anemia
- No or severely limited β globin production
- Anemia beginning 1st year of life
  - Usually begins 6 to 12 months
  - Occurs when HgbF (α2 γ2) production wanes
- Ineffective erythropoiesis
  - Alpha chains form tetramers
  - Precipitate → RBCs damage
  - Failure to produce RBCs
- Life long transfusion dependent anemia



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Transfusion – dependent beta thalassemia clinical features

- Hypochromic, microcytic anemia
- Bone changes "Chipmunk faces"
- Iron overload
  - Ineffective erythropoiesis → ↑ intestinal iron uptake
  - Also from transfusions
- Splenomegaly
  - Spleen clears abnormal RBCs
- Bizarre red cell morphology
  - Abnormal size and shapes
  - Many abnormalities possible

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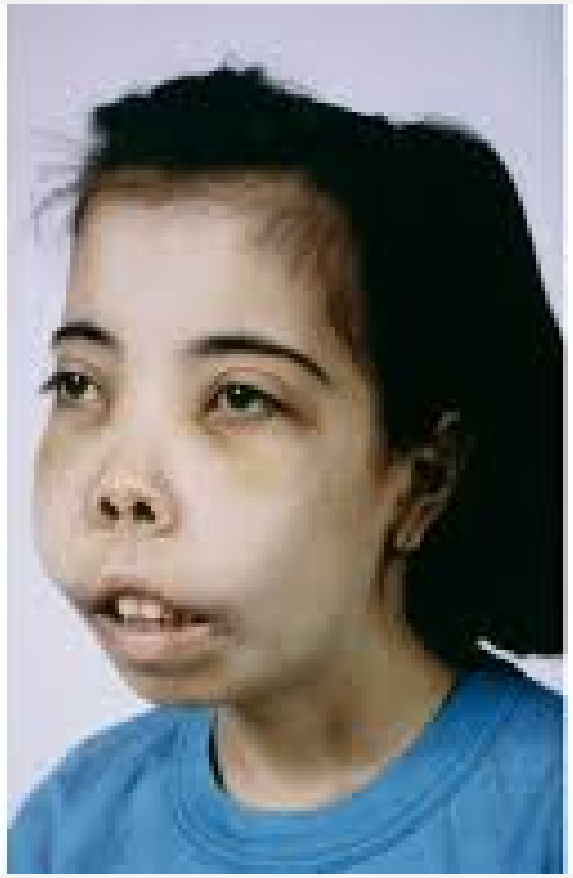
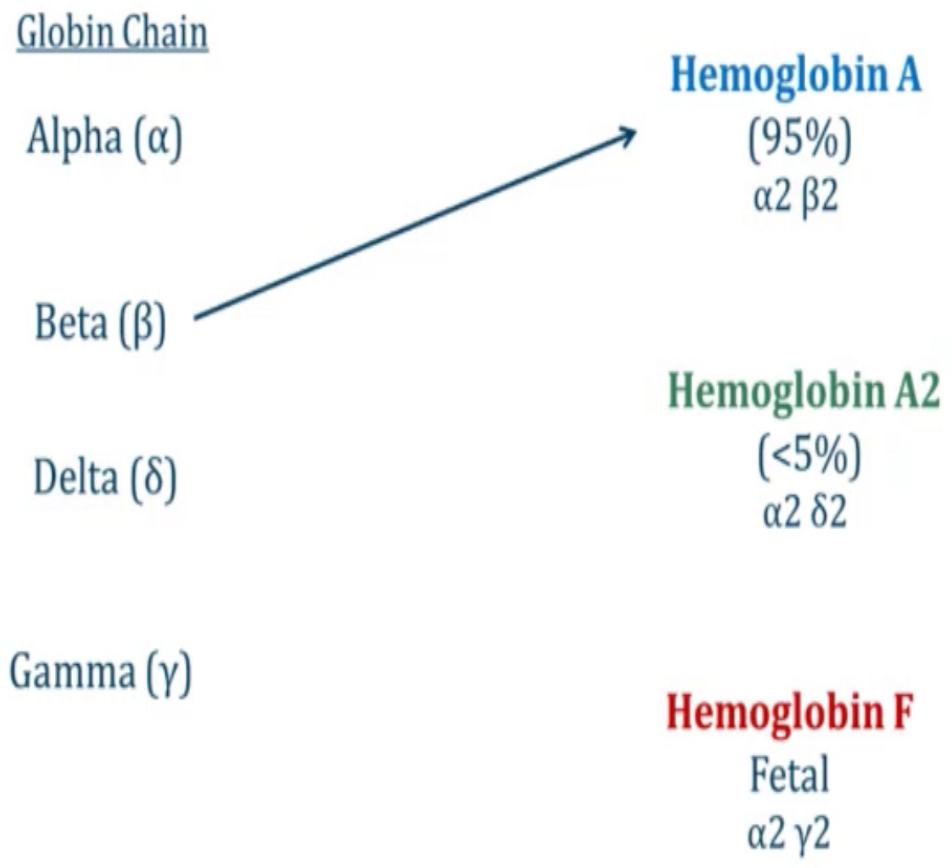
Transfusion – dependent beta thalassemia bone changes

- ↑↑ EPO without normal response
- Erythroid hyperplasia
- Massive expansion of bone marrow
- Abnormalities of skull & facial bones
- “Chipmunk faces”
- Delayed skeletal maturation
- Widening of marrow spaces → osteoporosis



Diagnosis & treatment

- **Diagnosis**
  - **Electrophoresis**
    - Or absent HbA (α2β2)
    - HbA2 (α2δ2)
    - HbF (α2γ2)
  - **Genetic testing**
- **Treatment**
  - Blood transfusions
  - Splenectomy
  - Bone marrow transplantation
  - Long term risk: iron overload
  - Iron chelating therapy usually required



BETA thalassemia intermedia

- Symptomatic beta thalassemia
- Doesn’t require transfusions
- Chronic hemolytic anemia
- Bone marrow expansion
- hepatosplenomegaly

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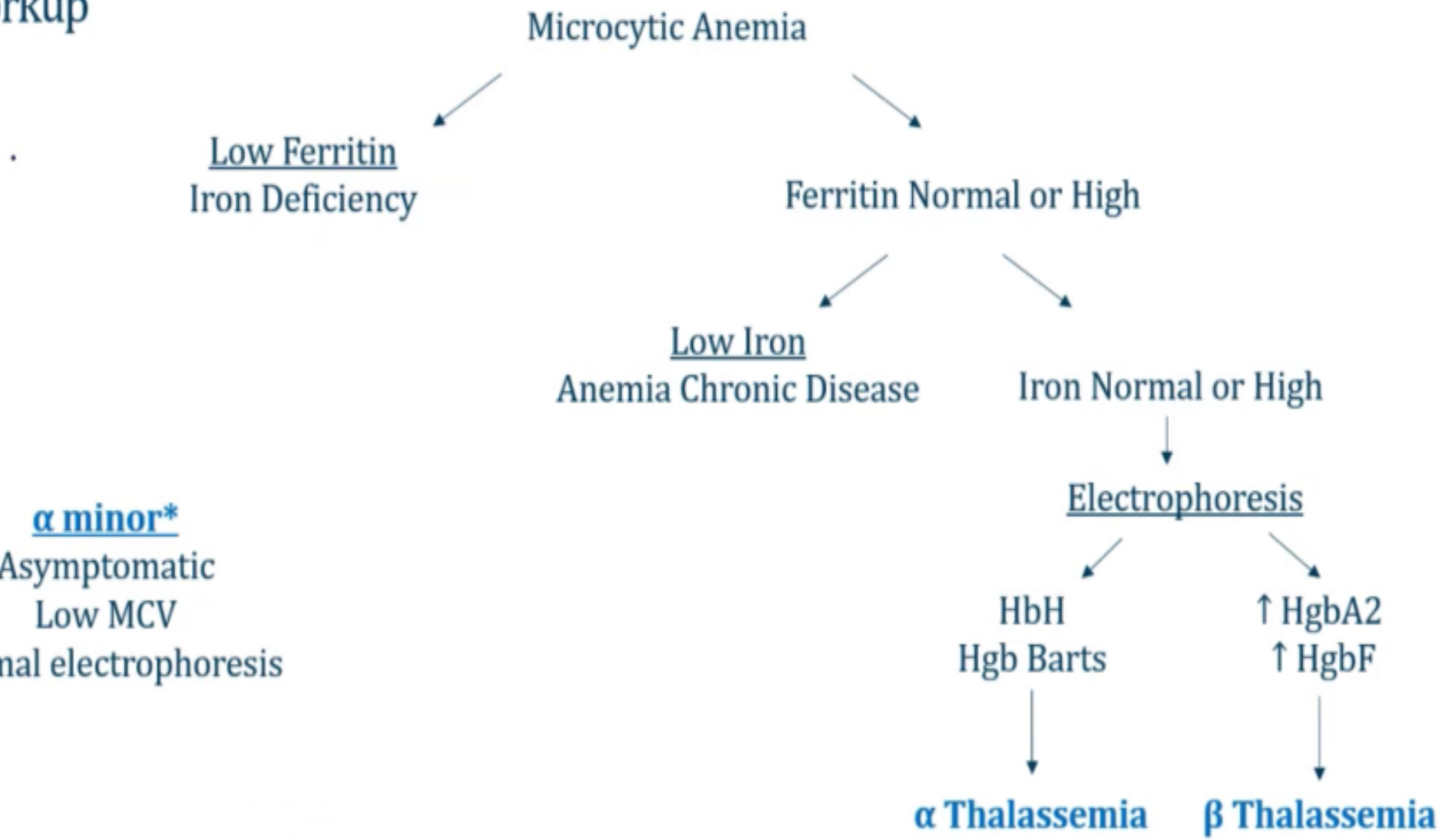
Microcytic Anemias

Workup



α minor*
Asymptomatic
Low MCV
Normal electrophoresis

Thank You

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Cystic Fibrosis

Usra Sobuh

Introduction

- Cystic Fibrosis (CF) is an **Autosomal Recessive** genetic disorder.
- It is caused by a genetic mutation in the CFTR gene on chromosome **7**.
- Over a thousand mutations of this gene have now been identified.

- The most common mutation is **DeltaF508** (Delta for Deletion, F for Phenylalanine, and 508 for the number of the affected amino acid).

Epidemiology

- More common in people with European Decent.
- The most common fatal genetic disorder in Caucasian population.
- An incidence of about 1 in 2500 live births.

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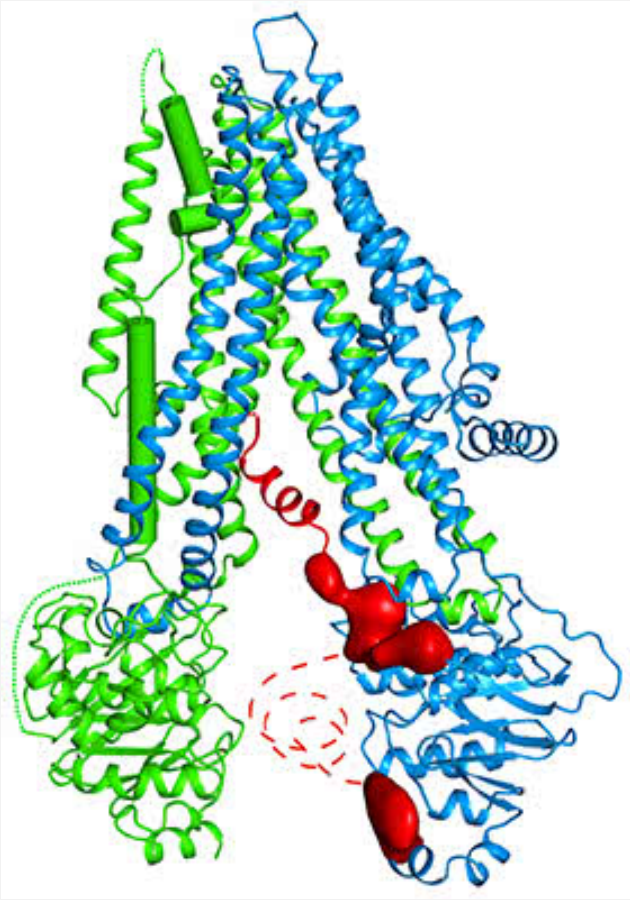
CFTR Protein

- Cystic Fibrosis Transmembrane conductance Regulator.
- It is basically a Chloride ion channel.
- ATP dependent.
- It is found on the epithelial cells of the lungs, intestine, pancreas, reproductive system and sweat glands

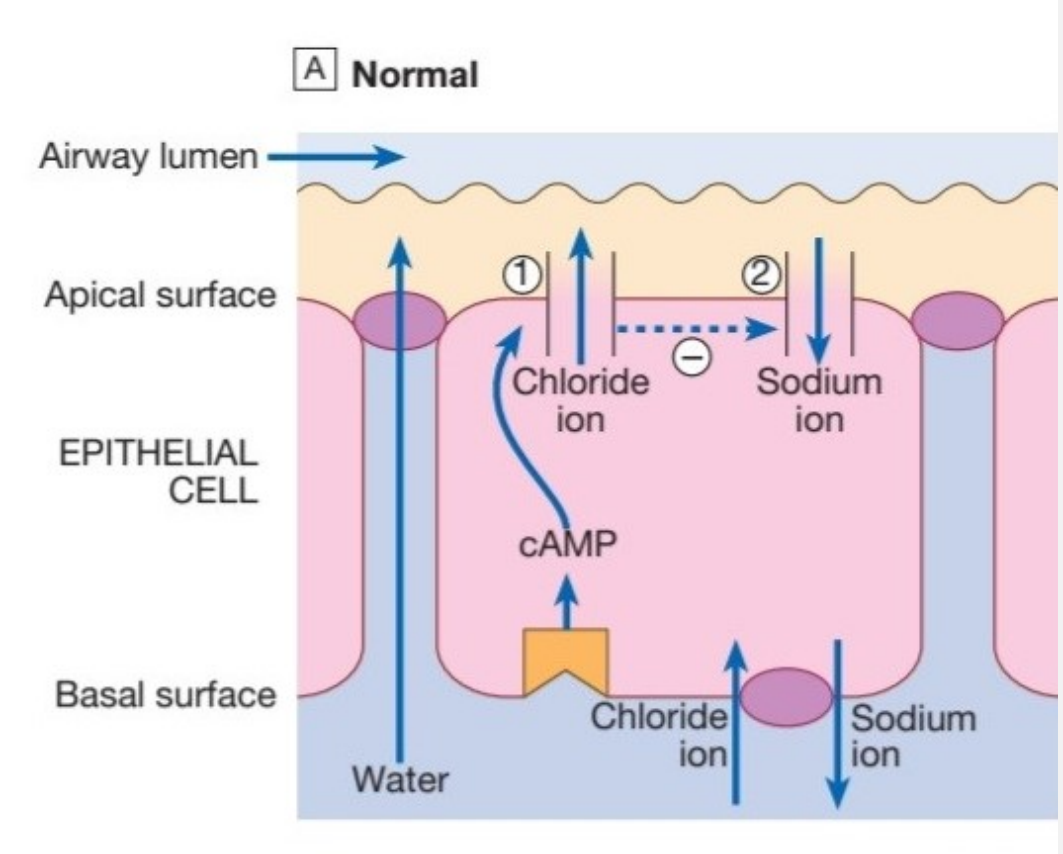
Etiology

- The absence of Phenylalanine from the 508th position causes the CFTR protein to become misfolded.
- This causes failure of the CFTR protein migration from the Endoplasmic reticulum (where it was translated) to the Plasma Membrane (where it should go).
- Absence of the CFTR protein from the Plasma Membrane is the underlying issue in CF.



CFTR function in the respiratory and GI tracts

- Chloride excretion
- Inhibits sodium reabsorption
- Accumulation of NaCl in the lumen
- NaCl will attract water molecules by Osmosis..
- Normal CFTR Chloride channel will indirectly increase the secretions water content, and decrease its thickness in different parts of human body.



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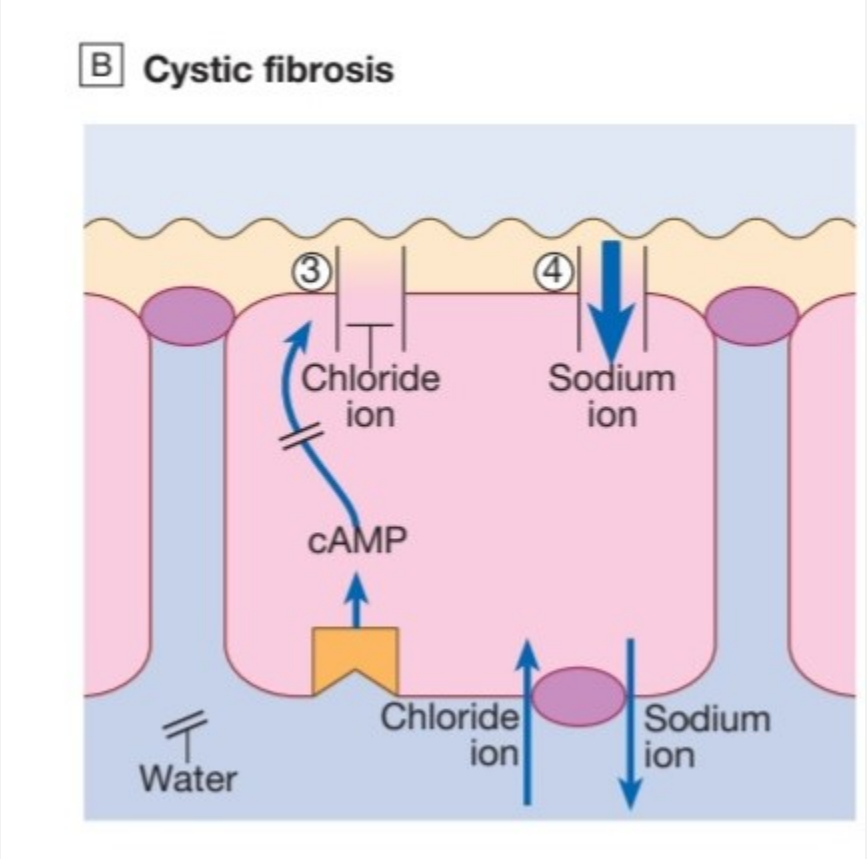
In case of CF

- Absent or unfunctional CFTR protein.
- No chloride excretion.
- Increased sodium reabsorption.
- Trapping of NaCl and subsequently H2O inside the ECs.
- Thick, sticky respiratory secretions that are difficult to remove.



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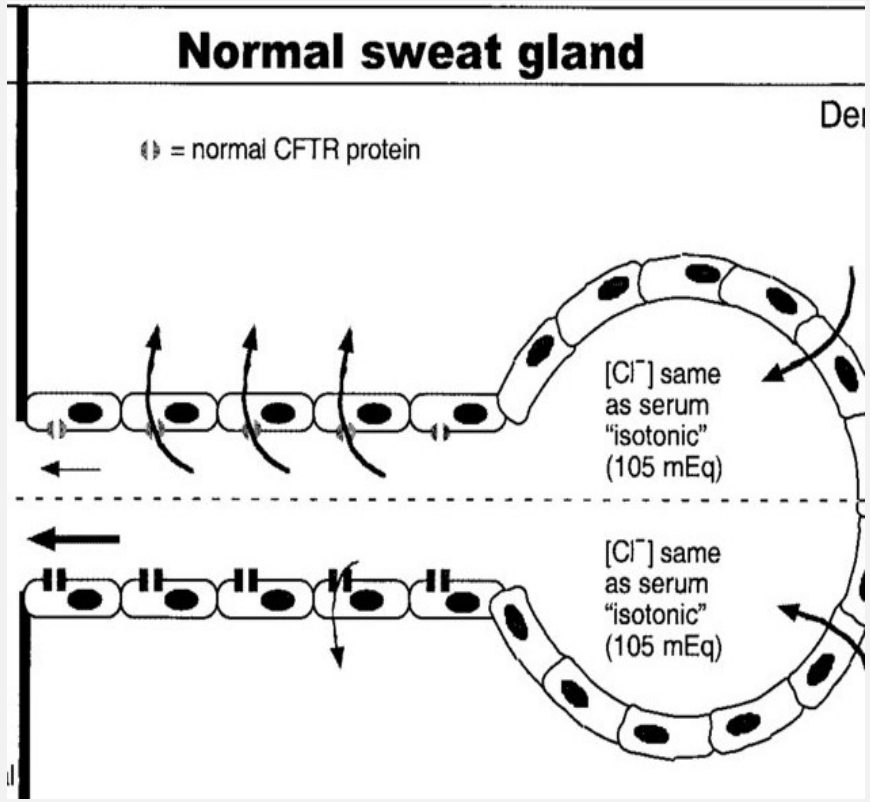
CFTR function in sweat glands

- In the sweat glands the CFTR membrane protein performs the opposite,
- it pumps chloride ions from sweat back into the gland.

- **In case of CF**

Increased chloride content in the sweat.

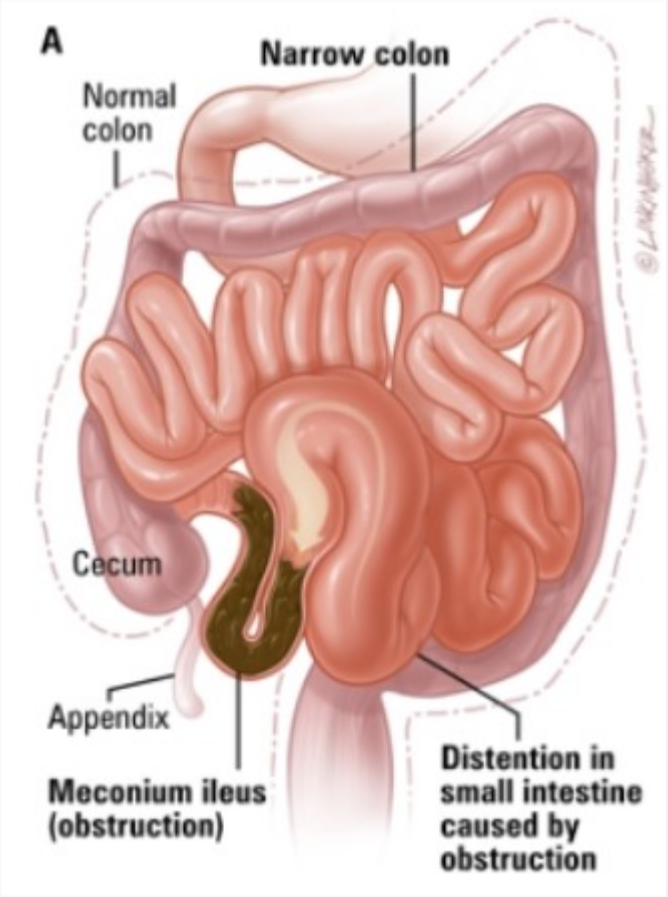
Used in diagnosis of CF.



Clinical Picture of CF (Newborn)

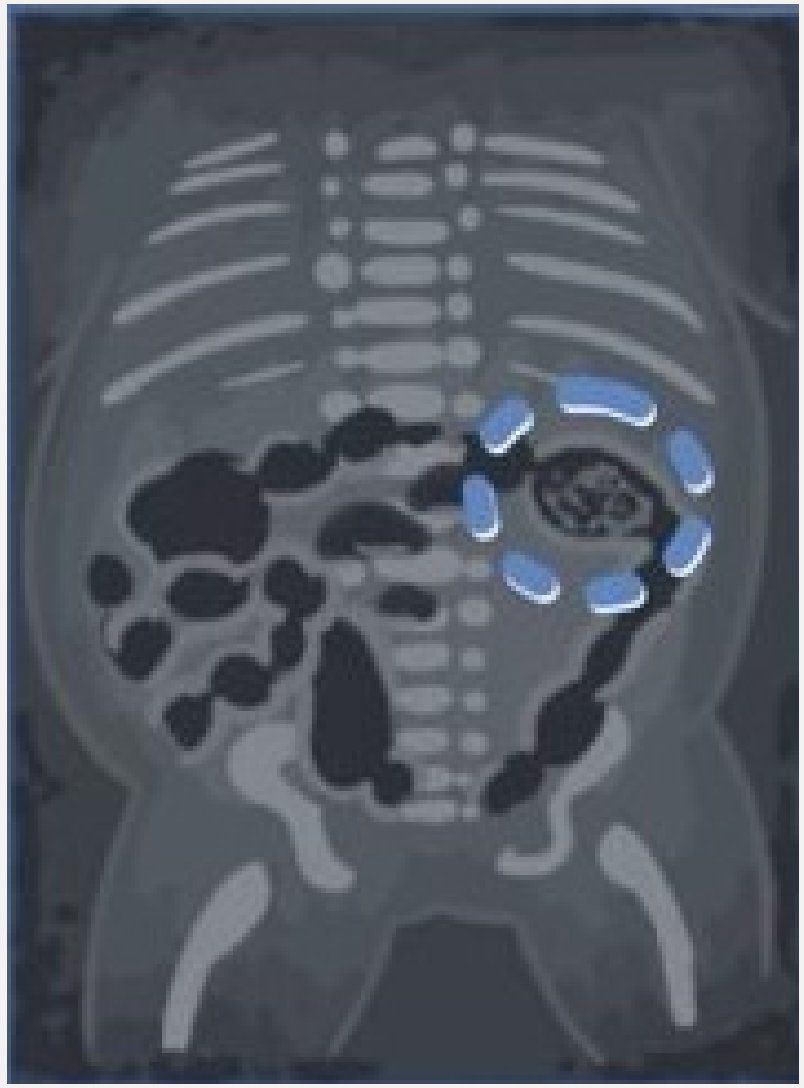
Meconium ileus

- Meconium is the newborn’s first stool.
- Meconium Ileus is a condition where the baby's first stool gets very thick and sticky that it gets stuck in the baby's small intestines and it doesn't pass normally.
- Meconium ileus can cause small bowel obstruction.
- Affect 20% of newborns with CF.



On examination:

- Rigid distended abdomen.
- Bilious vomiting.
- Mottled & lethargic baby



X-RAY

- Air- fluid level
- Dilated bowel loops
- Soap bubble

Meconium ileum surgical emergency

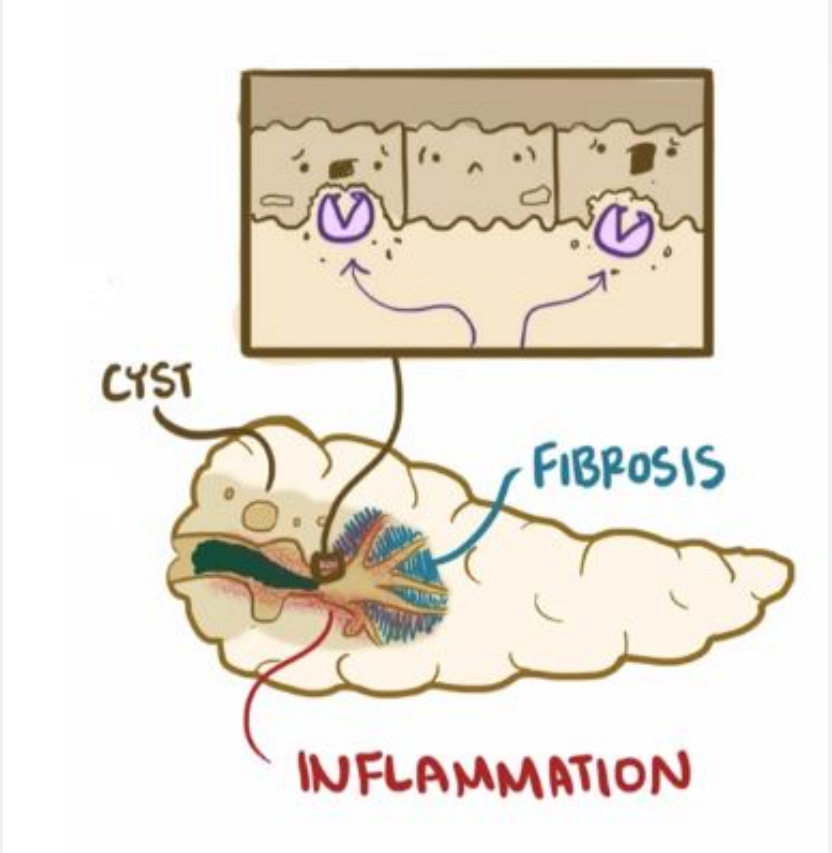
Intestinal obstruction → intestinal perforation → septic shock

So, the baby presents with:
Hypovolemia
Hypotension
Tachycardia
Tachypnea
Temperature instability

Without proper management will likely die of cardiorespiratory complications like pneumonia, bronchiectasis (> 80% of CF death)

Clinical Picture of CF (Early Childhood)

- -At this stage the **pancreas is the most affected** organ.
- Pancreatic Secretions are thicker than normal which block the pancreatic ducts. This leads to:
- 1- Pancreatic Insufficiency
- 2- Pancreatitis
- 3- Endocrine Dysfunction

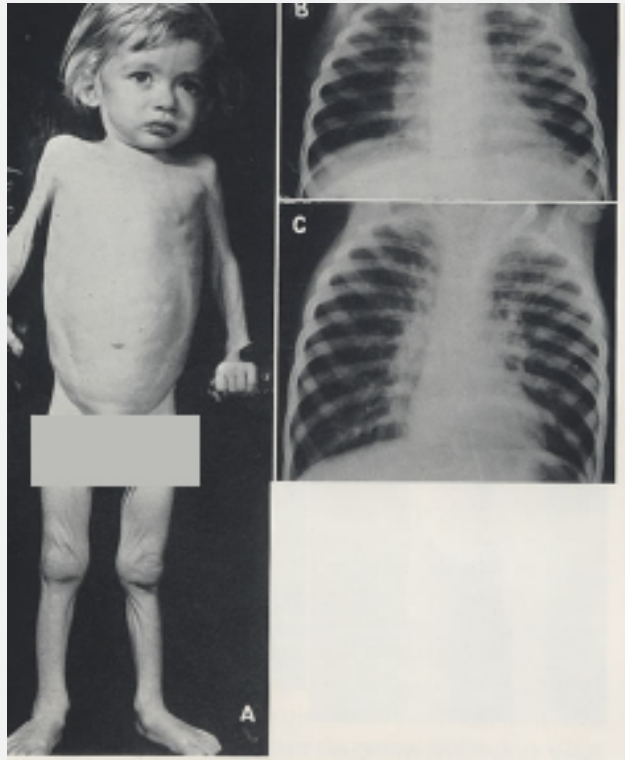


Clinical Picture of CF (Early Childhood)

- 1- Pancreatic Insufficiency :

because of blocked pancreatic ducts, the digestive enzymes can not pass to the intestine lead to food indigestion

- The lack of Protein, Lipid and Carbohydrate digestion will cause:
- A- Failure to thrive due to malabsorption of these nutrients << poor weight gain >>
- B- Steatorrhea due to fat being passed down in the stool.



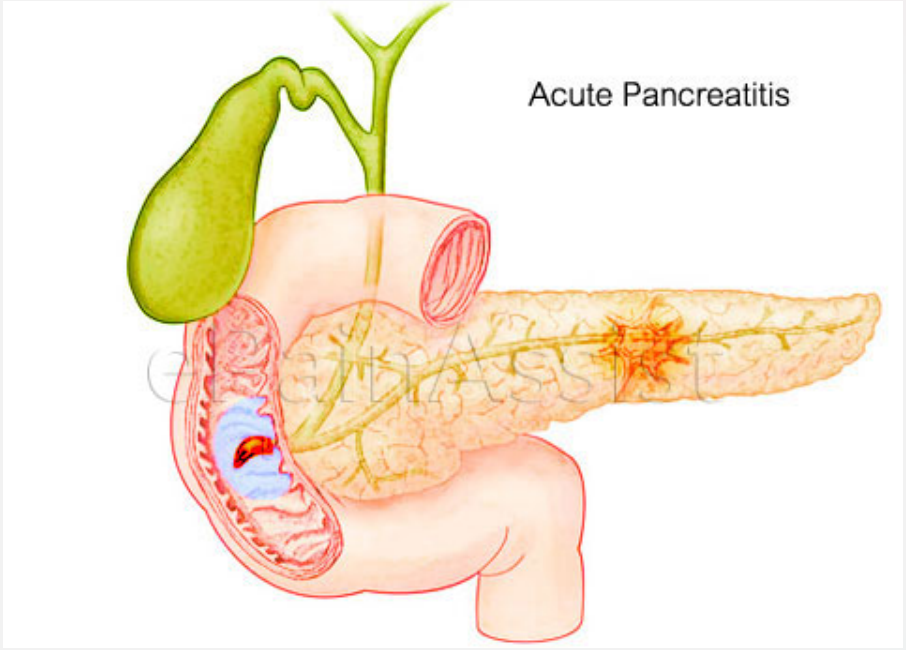
igure 7. A. Patient with Cystic Fibrosis of the Pancreas at two years, ve months. B. Lungs at one year, two months. C. Lungs at two years, ve months. When infection becomes established in the viscid secretion the bronchioles at an early age, and persists, the lungs show progres- ve development of peribronchial infiltration and emphysema. The atritional state deteriorates with advance of the infection. (Repro- uced from Plate V, May, C. D. and Lowe, C. U., Fibrosis of the ancreas in Infants and Children, *J. Pediat., 34*:663 (1949) with per- mission of C. V. Mosby, St. Louis.)

C- fat soluble vitamins deficiencies (A , D , E , K)

- Vit K : coagulopathy
- Vit D : rickets
- Vit A : night blindness
- Vit E : ataxia, hemolysis

Clinical Picture of CF (Early Childhood)

- <u>2- Pancreatitis:</u>
- This is caused by the backed up proteolytic and fat digesting enzymes which start digesting the pancreas.
- The damage to the Pancreas starts as Acute Pancreatitis and then turns into Chronic Pancreatitis after multiple attacks.



Clinical Picture of CF (Early Childhood)

- In Acute Pancreatitis the pt. will suffer from:
- 1- Upper abdominal pain that radiates to the back and is worse after eating.
- 2- Fever
- 3- Tachycardia
- 4- Tender Abdomen
- 5- Nausea
- 6- Vomiting

Clinical Picture of CF (Early Childhood)

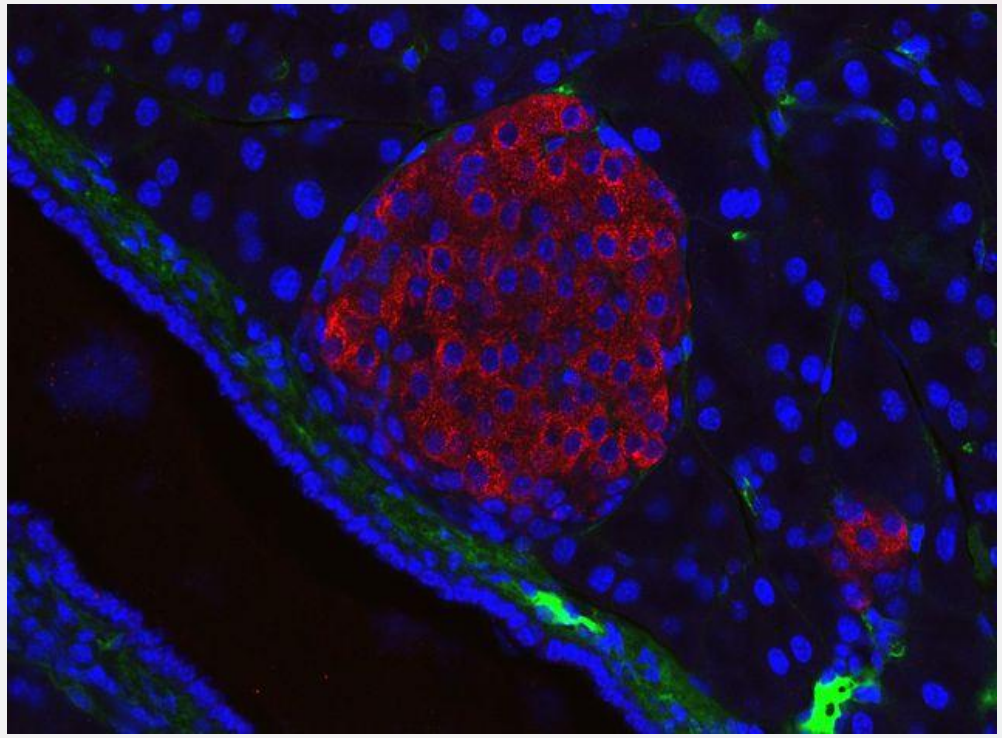
- **B- Chronic Pancreatitis:** In cases where Pancreatitis becomes long standing chronic pancreatitis will ensue.
- The pancreatic ducts will undergo fibrosis due to persistent inflammation. and the Pancreatic parenchyma will contain multiple cysts. hence the name cystic fibrosis.

Clinical Picture of CF (Early Childhood)

- In Chronic Pancreatitis the patient will suffer from:
- 1- Upper abdominal pain
- 2- Weight loss
- 3- Steatorrhea

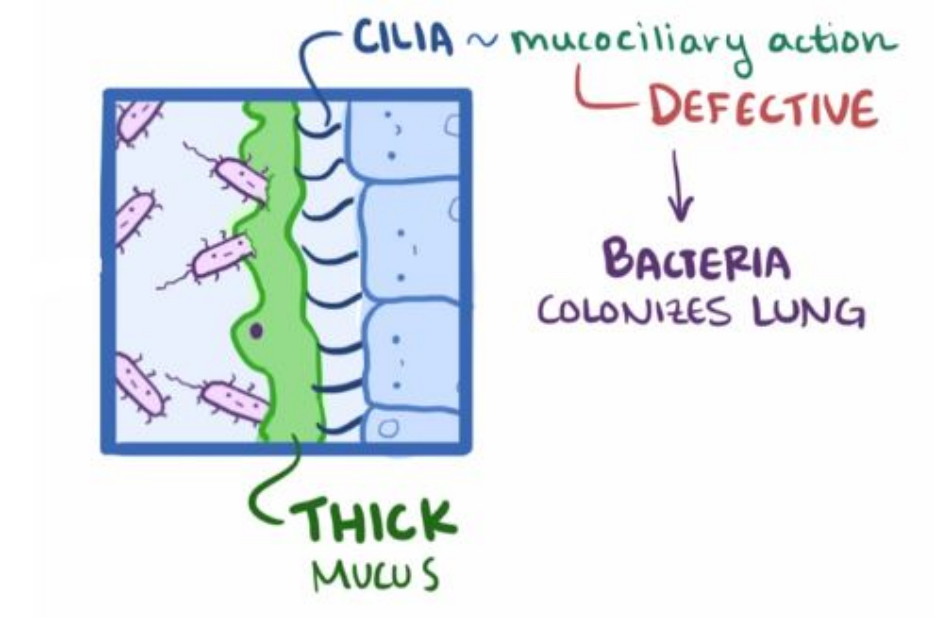
Clinical Picture of CF (Early Childhood)

- 3- Endocrine Dysfunction:
- Damage to the pancreas might extend to the endocrine part of the pancreas and cause insulin - dependent diabetes due to the destruction of beta islets cells in the Langerhans Islets.



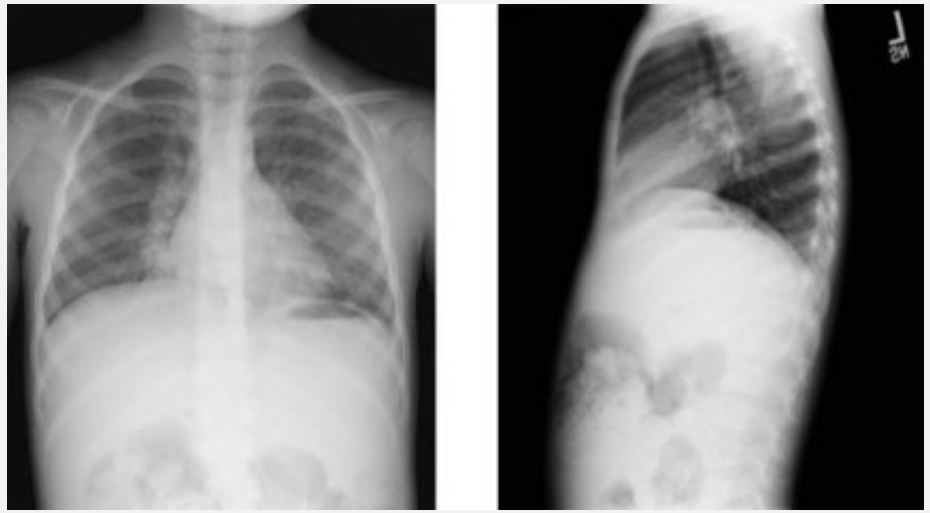
Clinical Picture of CF (Late Childhood)

- Lung problems start to appear in this phase of life.
- Mucociliary action of the lung fails due to the sticky and thick nature of the mucus.
- This leads to mucus getting stuck in the airway and the bacteria inside of it are not getting expelled outwards, this leads to bacterial colonization of the lungs.



Clinical Picture of CF (Late Childhood)

- **CF Exacerbation :**
- Basically it is a lung infection brought on by CF.
- Signs and symptoms of a CF exacerbation are the same as a chest infection. (Cough + Fever + CXR changes).
- Treatment of a CF exacerbation is done via the administration of antibiotics.
- Some difficult bacterias that can be involved in a CF exacerbation are Staphylococcus Aureus (G +ve) and Pseudomonas Aeruginosa (G -ve). They are hard to treat because they can be antibiotic resistant and they can also create a biofilm that can protect them from the immune system and antibiotics.



Clinical Picture of CF (Late Childhood)

- **Consequences of repeated CF Exacerbations:**
- 1- Bronchiectasis: this is a condition where airways are damaged and lose their elasticity due to chronic inflammation. The Elastin in the walls of the airways gets broken down and replaced by Collagen, rendering the airways dilated and non elastic. Sometimes when the damage to the wall is severe Hemoptysis, due to blood vessel rupture, can be seen.
- 2- Respiratory failure: due to repeated attacks. This is the most common cause of death in CF patients.

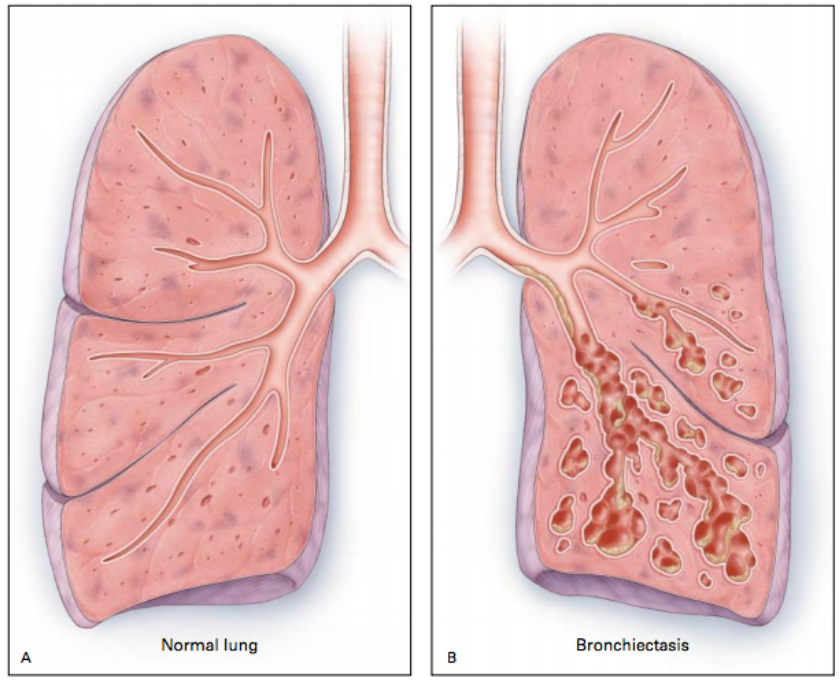
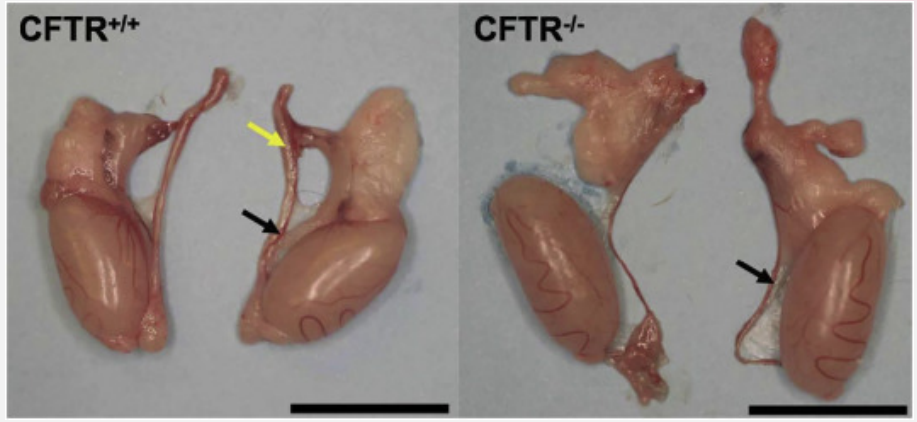
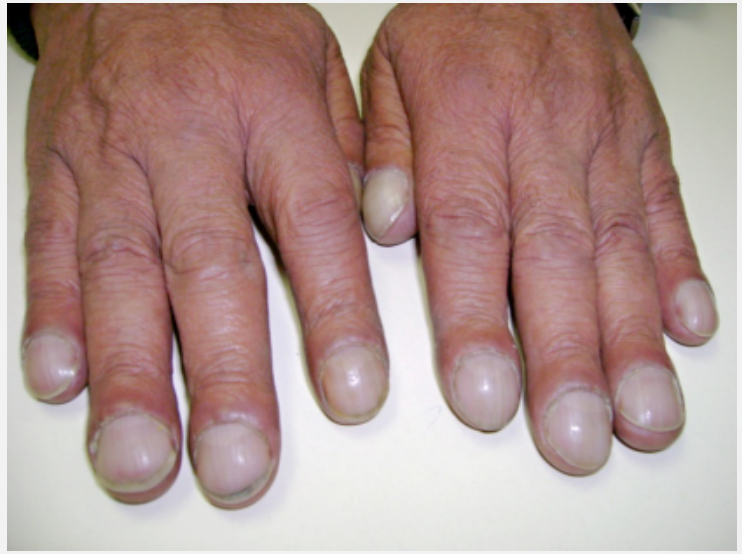


Figure 2. Normal Lung and Airways (Panel A) and the Lung of a Patient with Bronchiectasis (Panel B).
In Panel B, bronchiectasis is primarily in the lower lobe, which is the most common distribution. The saccular dilatations and grape-like clusters with pools of mucus are signs of severe bronchiectasis.

Other issues in CF

- 1- Male infertility : Males with CF lack the Vas deferens. It will be congenitally stenosed. The Vas deferens is responsible for transferring Sperms from the testicles to the urethra.
- 2- Digital Clubbing
- 3- Allergic Bronchopulmonary Aspergillosis: Allergic reaction to Aspergillus Fumigatus. A type of fungi that can live in the lungs.





Newborn Screening for CF

- 1- Newborns are screened for Immunoreactive Trypsinogen (IRT), a pancreatic enzyme released when there is damage to the pancreas.
- 2- Newborns are also screened for Cl- levels in sweat. High levels support a CF diagnosis. In fact parents of CF patients report salty taste when kissing their children due to high Cl- levels on their skin.

Treatment of Cystic Fibrosis

- 1- Nutrition and weight gain
- 2- Lung treatment:

Treatment of Cystic Fibrosis (Nutrition)

- **1- Nutrition and weight gain**
- A- Fat soluble vitamins (ADEK) supplements:

  This is done in order to correct the deficiency in these enzymes due to low fat absorption. Recall that these enzymes are absorbed just like fat is in the intestines, in fact they are absorbed while dissolved in the fat micelles.

- B- Extra Calories:

  - Patients with CF have a problem digesting food and therefore absorbing it due to pancreatic enzyme deficiency.

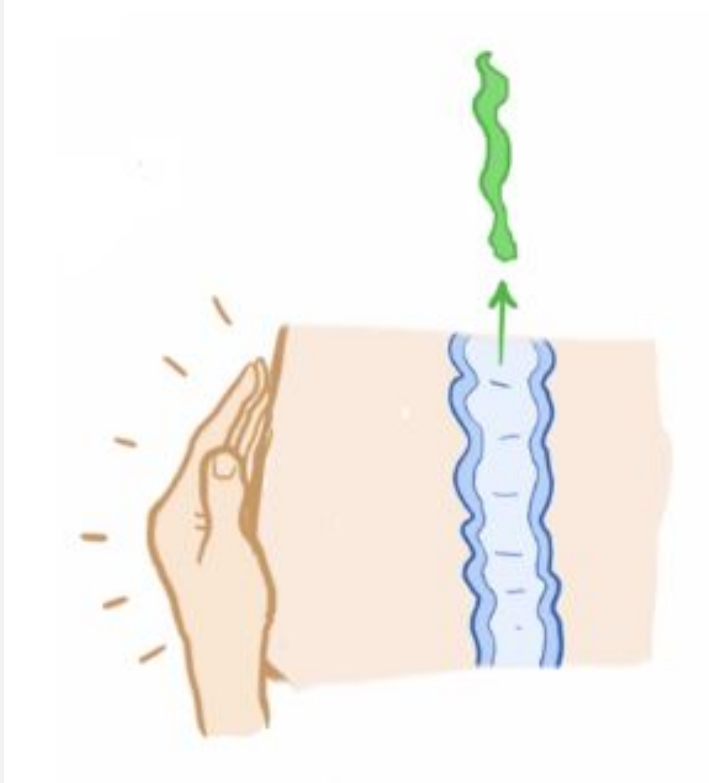
- C- Replacement pancreatic enzymes.

Treatment of Cystic Fibrosis (Lung Tt.)

- **A- Chest Physiotherapy**
- **B- Medications:**
- 1- Inhaled bronchodilators
- 2- N-Acetyl Cysteine
- 3- Dornase Alfa
- 4- Novel treatments
- 5- Lung transplant can eventually be needed

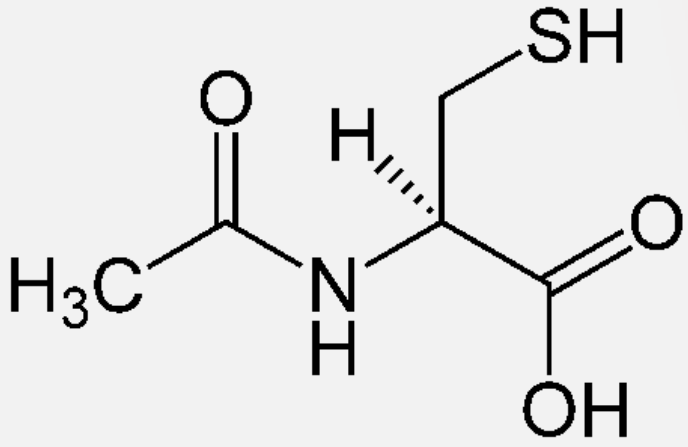
Treatment of Cystic Fibrosis (Lung Tt.)

- **A- Chest Physiotherapy:**
- In order to relieve the clogged up mucus, tapping on the chest is used in order to move mucus around in the lungs and make it easier to expectorate.



Treatment of Cystic Fibrosis (Lung Tt.)

- **B- Medications:**
- 1- Inhaled bronchodilators.
- 2- N-Acetyl cysteine: This is used as a mucolytic. It is inhaled. It breaks down thick mucus and makes it easier to expectorate. This is done using N-Acetyl Cysteine's free Sulfhydril Group (-SH) to break down Disulfide bonds in the mucus matrix rendering it less viscous.



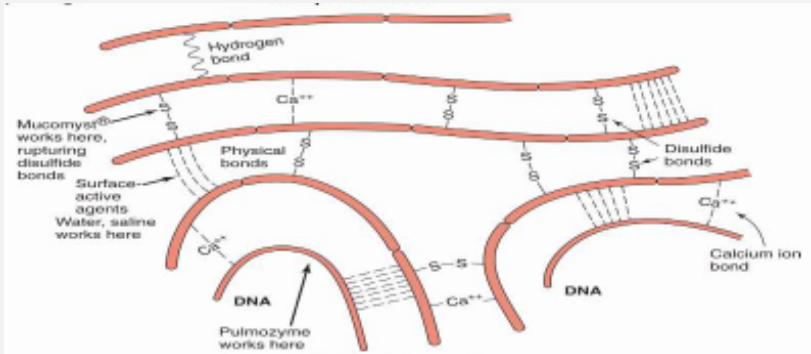


Figure 6–2: The Mucus Structure

Treatment of Cystic Fibrosis (Lung Tt.)

- 3- Dornase Alfa: This is a purified form of the enzyme Deoxyribonuclease I, an enzyme that breaks down DNA. It is used in CF as a mucolytic to break down DNA molecules in mucus. The DNA found in CF mucus is attached to the Glycoproteins.

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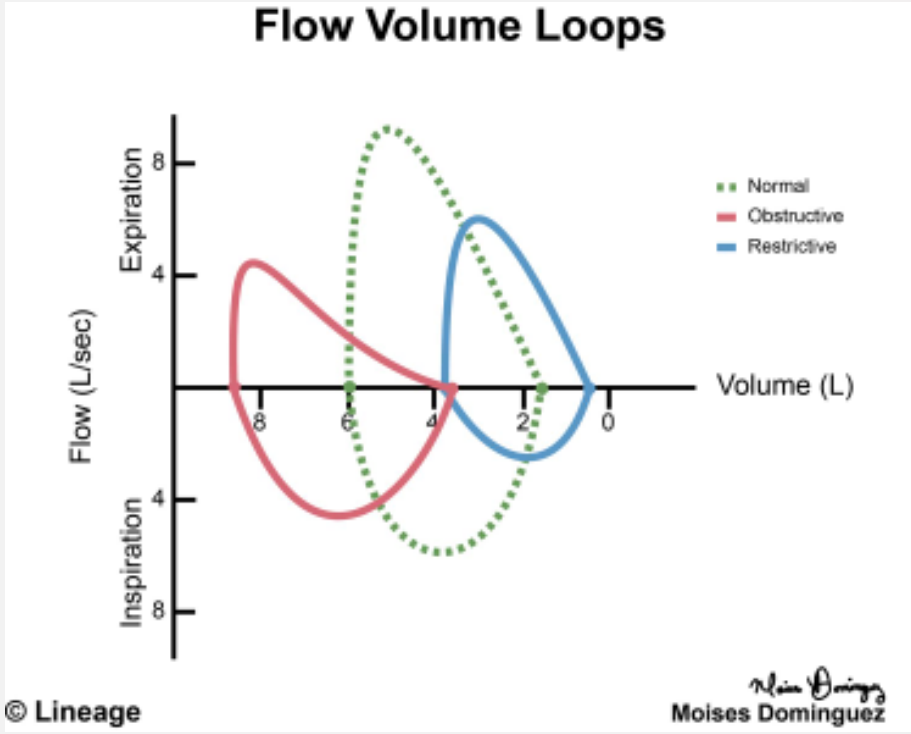
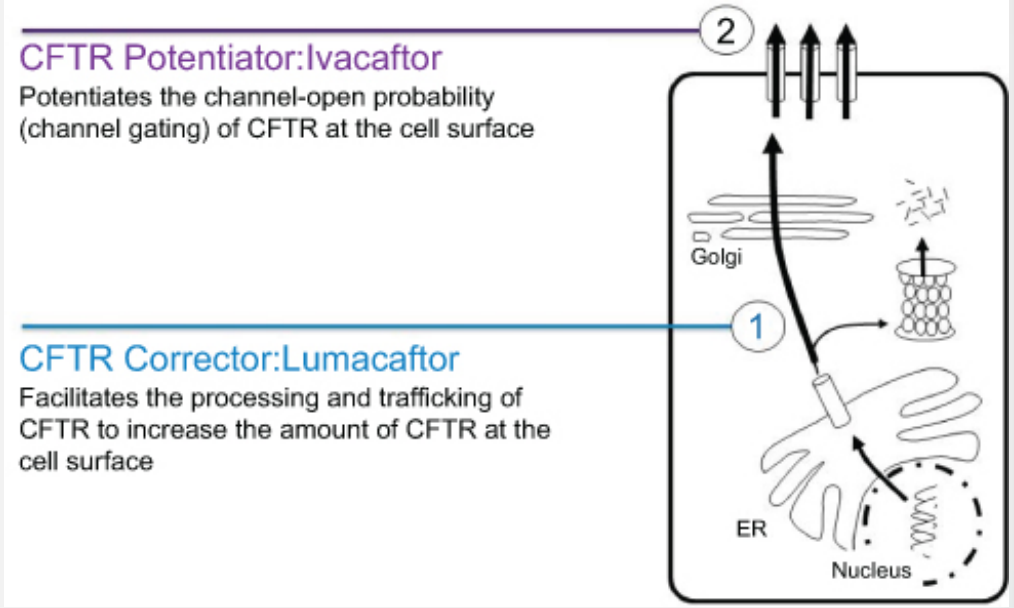


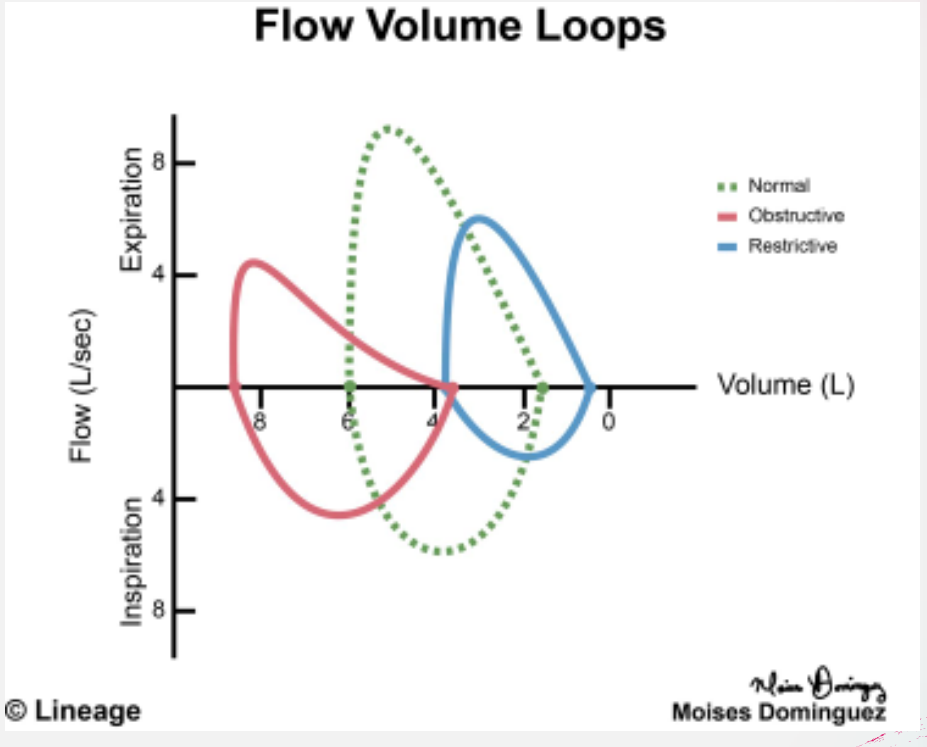
Treatment of Cystic Fibrosis (Lung Tt.)

- 4- Novel treatments:
- a. Lumacaftor (acts as a chaperon during protein folding) is given to accompany the mutated CFTR channel all the way to the cell membrane.
- b. Ivacaftor is also given to improve the function of the mutated CFTR channel, it does that by directly attaching itself to the CFTR channel to induce some changes in its structure so that it can improve its functioning.
- 5- Lung transplant can eventually be needed.



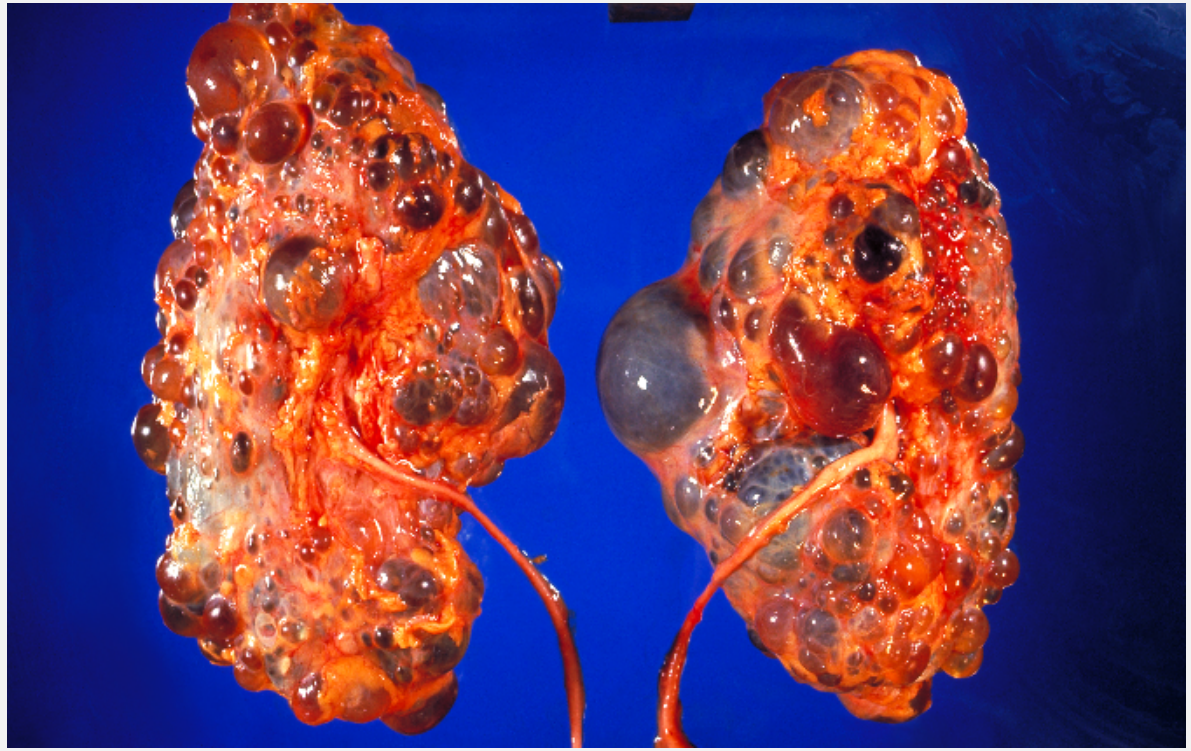
Monitoring

- PFTs:
- These are used to monitor the patient's respiratory status.
- An obstructive pattern (reduced FEV1/FVC ratio) is caused by the presence of mucus in the lung causing obstruction upon expiration.
- A restrictive pattern (reduced FEV1 and FVC but normal FEV1/FVC ratio) indicates Fibrosis in the lungs.



Jens Martensson

Thank You



Polycystic kidney disease

made by .....areej hamdan

pkd

INHERITED DEFECT LEADING TO BILATERAL KIDNEY ENLARGMENT WITH CYSTS

ADPKD	ARPDK
Most common	Most severe
Onset age >30	Infants and children
Half get ESRD by 60	Infant renal failure
Cerebral aneurysm	Liver fibrosis,death

ARPKD

- Occurs in Child-hood
- Defect in PKHD1 gene
- Results in renal failure before birth
- COMPLICATIONS
- 1- Congenital hepatic fibrosis which leads to Portal hypertension
- 2- Systemic hypertension
- 3- Cholestasis & ascending cholangitis due to presence of Fibrocystin in bile ducts

Renal failure

- Oliguric renal failure in utero can lead to Potter Sequence due to Oligohydramnious.
- Potter Sequence:
- 1- Clubbed feet
- 2- Pulmonary hypoplasia
- 3- Cranial anomalies

- Morphology:

1- Enlarged kidneys

2- Smooth external surface

3- Cysts found in the cortex

- Diagnosis:

Ultrasound then biopsy (Radially oriented cysts)

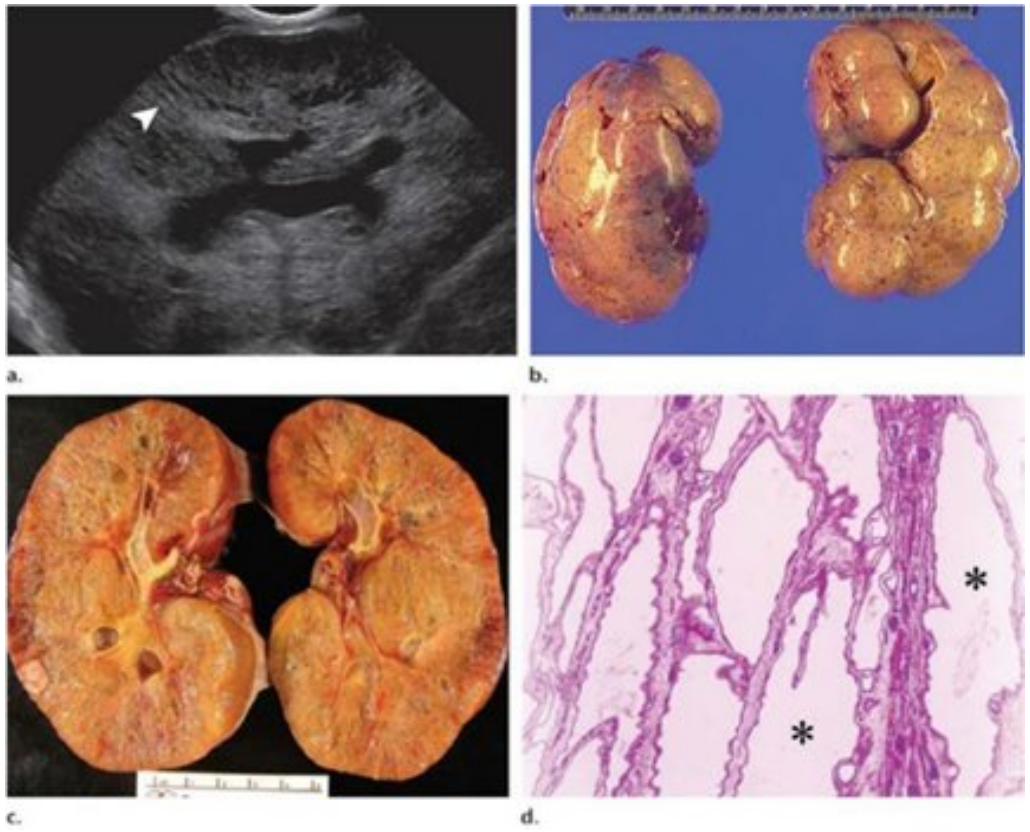
- Presentation:

No urinary output = Anuric

Palpable bilateral mass

- Treatment:

Supportive and transplant



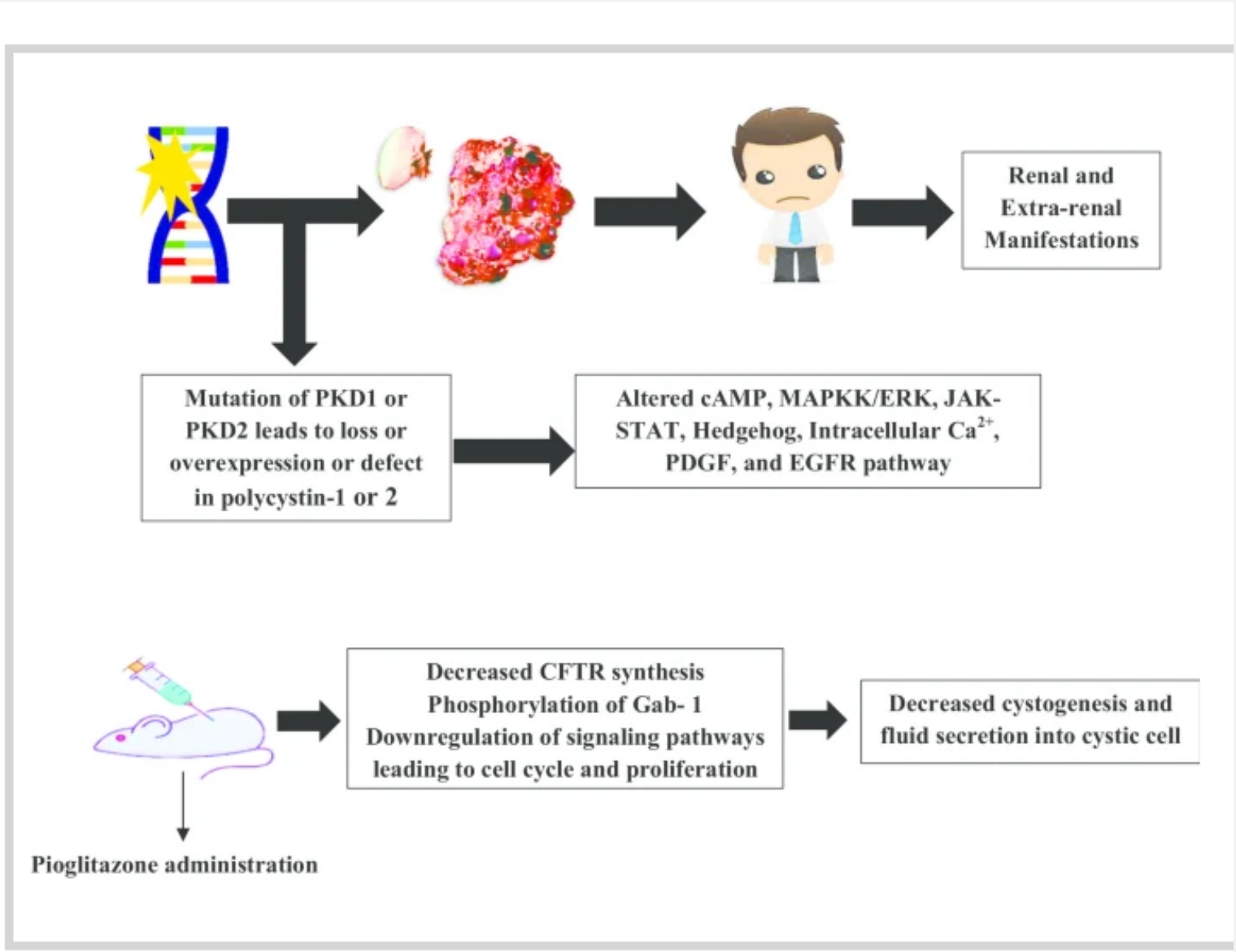
Autosomal dominant (adult) polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common inherited disorders in humans. It is the most frequent genetic cause of renal failure in adults, accounting for 6-8% of patients on dialysis in the United States.

The main feature of ADPKD is a bilateral progressive increase in the number of cysts, which may lead to ESRD. Hepatic cysts, cerebral aneurysms, and cardiac valvular abnormalities also may occur.

etiology

- ADPKD is a hereditary disorder. The pattern of inheritance is autosomal dominant.
- ADPKD is a genetically heterogeneous condition that involves at least 2 genes.
- ***PKD1*** is located on 16p13.3 and accounts for most ADPKD cases.
  PKD2 is located on 4q21-q22 and accounts for 15% of ADPKD cases.
- PKD1 mutation more severe & earlier in onset
- PKD2 mutation less sever &later in onset



Polycystin 1 and 2

Complications

- **Cysts are formed at the cortex of the kidney ,it will press the blood vessels (vasoconstriction like state) leading to activation of RAAS which lead to hypertension**
- **These cysts will press tubules and stasis of the urine**
- **OTHER COMPLICATONS ……..Cysts also will be formed at other places like liver & pancraes & cerebral vessels leading to cerebral hemorrhage**
- **Lastly.....ESRD**

esrd

- An early study estimated that approximately 70% of patients with ADPKD would develop renal insufficiency if they survived to age 65 years. Currently, half of all patients with ADPKD require renal replacement therapy by age 60 years. Risk factors for progression include the following:
- ***PKD1*** genotype
- Large kidneys
- Several episodes of gross hematuria [21]
- Severe and frequent kidney infections
- Hypertension
- Multiple pregnancies
- Black racial background [18]
- Male sex

History

- **Pain—in the abdomen, flank, or back—is the most common initial complaint**
- **Bleeding, which may be confined inside the cyst, or lead to gross hematuria with passage of clots or a perinephric hematoma**
- **Urinary tract infection (eg, acute pyelonephritis, infected cysts, perinephric abscess)**
- **Nephrolithiasis and renal colic**
- **Rarely, a coincidental hypernephroma**

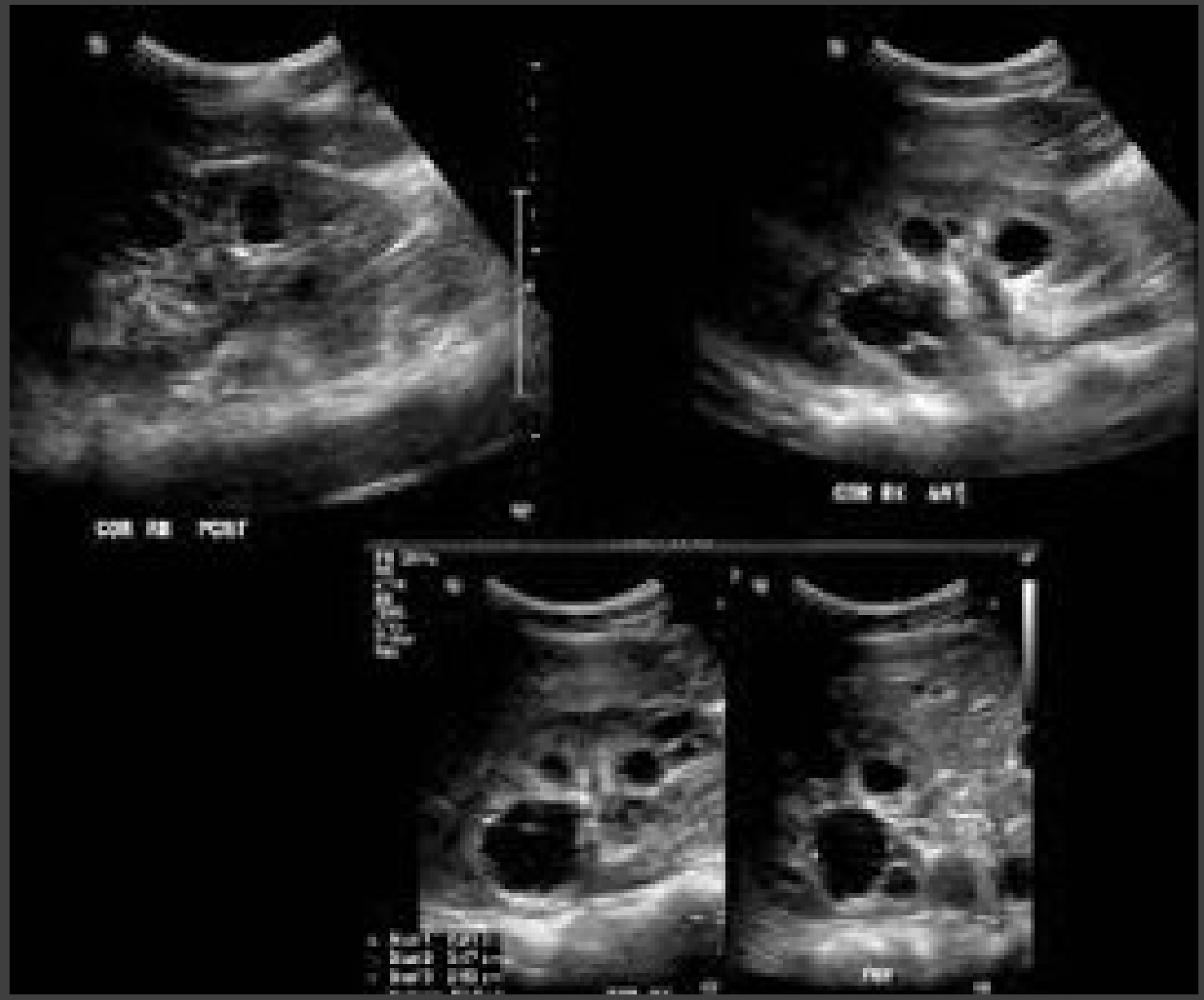
Physical Examination

- **Hypertension is one of the most common early manifestations**
- **Palpable, bilateral flank masses occur in patients with advanced ADPKD. Nodular hepatomegaly occurs in those with severe polycystic liver disease.**

Diagnosis

- **Ultrasonography is the procedure of choice ,crieteria based on:Age , Positive family history,number of cysts**
- **Biopsy**
- **protein in the urine**
- **Hematurea**
- **GFR & creatinine**
- **SECREANING.....Genetic testing**
- **High-risk patients with normal or indeterminate ultrasound scan should have CT scans and MRI.**

ultrasound



management

- controlling blood pressure
- Avoid durgs:
- 1- NSAIDS
- 2- PPIs
- 3- IV contrast in CT scans, angiograms
- 4- MRI with IV contrast
- 5- Herbal OTC products
- Drinking plenty of water (3L)
- Reduce salt intake
- Avoid high protein diet

Treatment

- Tolvaptan
- Targets V2 receptors; decreasing cAMP (Jynarque),
- Supportive:
- Hypertension: ACE/ARBs
- Renal failure: Dialysis/ Transplant
- Portal HTN: Portacaval shunt or liver transplant

Thank You