HEMATOPOIETIC & LYMPHATIC SYSTEM

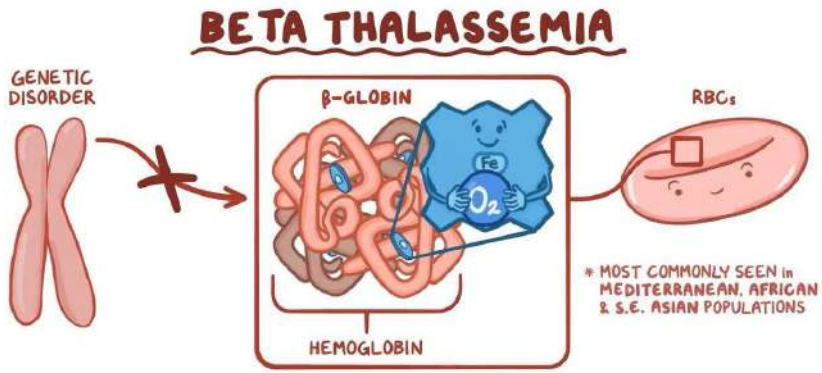
SUBJECT : _____

LEC NO. : Lec 3

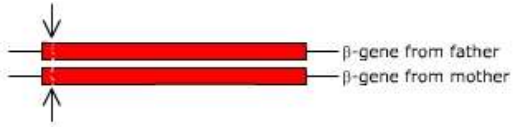
DONE BY : Raneem Azzam

وَقُل رَّبِّ زِدْنِي عِلْمًا

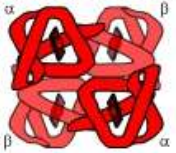
للتذكير : احنا عنا نقص في تصنيع الغلوبين بالتالي ال HB رح تكون قليلة ورح تأدي ل Michael



With a mutation on one of the two β-globin genes, a carrier is formed with lower protein production, but enough hemoglobin



Without a mutation enough Hemoglobin



No thalassemia carrier

With one mutation less Hemoglobin

β-thalassemia carrier without illness, but less hemoglobin (slight aneamia)

With two mutations no β-globin

β-thalassemia major patient with severe aneamia

β-Thalassemia

	β	α
present on chromosome	11	16
	2 beta alleles are present	4

β-Thalassemia

زي الفا

- Inherited in an **autosomal recessive manner**
- Beta thalassemia is caused due to **gene mutation of beta chain of hemoglobin**. Mutations result in absent (aka **B0**) or diminished (aka **B+**) production of B-globin chain.

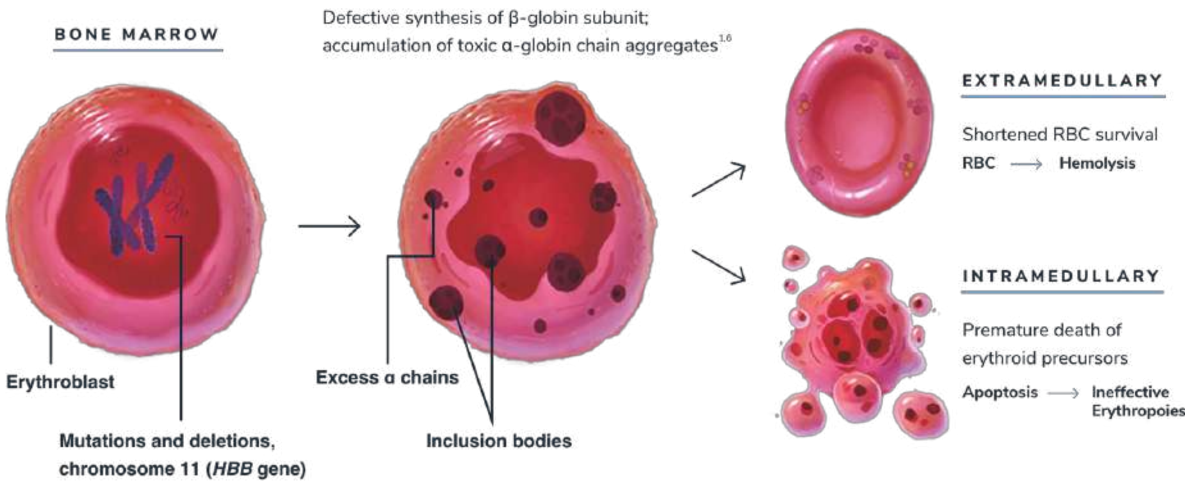
Total absent (1) (2)

Hb ال synthieses في شوية

انواع ال mutations

- Normally, 2 beta alleles are present on chromosome 11 (1 allele per chromosome)

من الام
2 < من الاب



Heterozygous refers to having twodifferent alleles for a particular gene, one inherited from each parent.
Homozygous refers to having two identical alleles for a particular gene, inherited from both parents

للتذكير

β-Thalassemia; types

هسا هون المريض مارح تكون عندو symptoms لانو تقريبا انتاج البيتا موجود بس ممكن نلاقي عندو شوية microcytic anemia

هاد الكروموسوم الي فيه mutations و فيه احتمالين possible يا β0/ β+

Types	Alleles	Description
Thalassemia minor ال minors بكون heterozygous وحدة من هدول (β+ /β)و(βo /β)	β^+/β β^o/β ماخذ كروموسوم نورمال من أهلو	Only one of β globin alleles has a mutation. Patients will have microcytic anemia (MCV <80 fL)
Thalassemia intermedia Homozygous	β^+/β^+ β^o/β^+ الاثنين فيهم ميوت بس diminish فيه	Patients can have a normal life, but may need occasional transfusions, example at times of increase demand (illness or pregnancy)
Thalassemia major Homozygous	β^o/β^o هون زيرو انتاج ل بيتا	Severe microcytic, hypochromic anemia. Untreated, causes anemia, splenomegaly and severe bone deformities, and death before age 20. Treatment is blood transfusion; splenectomy for splenomegaly and chelation for iron overload

+ عند هاد المريض رح نتوقع انو انتاج ال HbA شوي نازلة بس ستيل امور تمام ورح يعوض عنها وجود ال HbA2 (الفا ٢ ودلتا ٢)

نلاقيها شوي مرتفعة حتى تعوض النقص الي هناك

هسا هون فيه ميوت بس لسا في بيتا تنتج شوي ممشي حالو فيها ، وبترفع كمية ال HbA2 بعيش فيهم ،، بس مرات بحتاج ل transfusion بسبب increase of demand (حامل ، عندو عملية ...)

هون المهببة

الاخطر

Mutations as (βo) means no formation of β globin - mutations (β+) means some β globin chain is formed

(βo) مافي إنتاج بالمرة

(β+) عنا شوية انتاج

Thalassemia major Homozygous	β^0/β^0	Severe microcytic, hypochromic anemia. Untreated, causes anemia, splenomegaly and severe bone deformities, and death before age 20. Treatment is blood transfusion; splenectomy for splenomegaly and chelation for iron overload

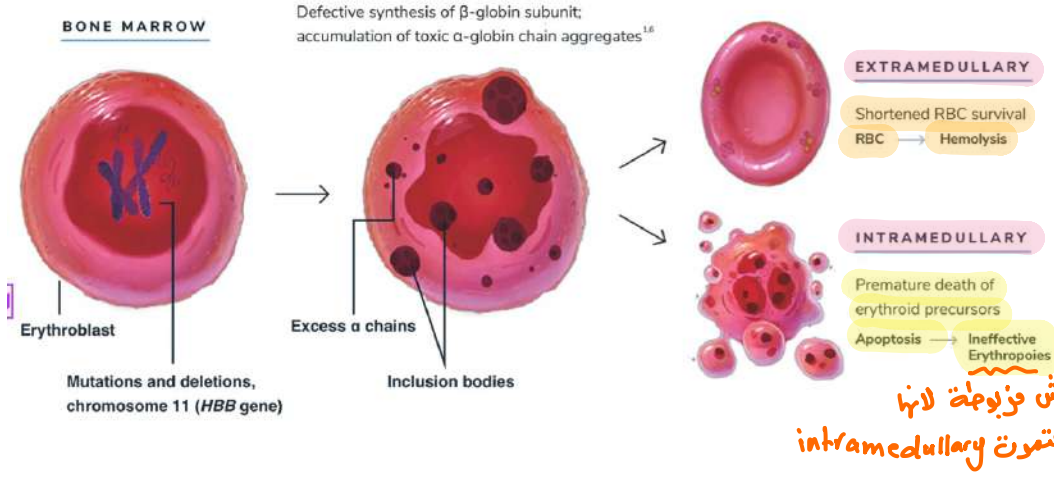
هون المصيبة

هون زيرو انتاج ل بيتا

بشيل الـ spleen حتى تبطل تكسر الدم عندي

طايعيشو اكتر من ٢٠ سنة

اشيل الـ fe إلي عم يدخل مع transfusion



حش مزبوطة لانها intramedullary عم بتموت

نتخيل الصورة لمريض عندو thalassemia major معناتو ما عندو بيتا بالمرة ،،اعراضو بتبلش بعد عمر ٦ل٩ شهور ليه؟ لانو البيبي لهاد العمر بكون عندو HbF وبدو يعمل سويتش ل HbA فهون المصيبة انوما عندي بيتا غلوبين فشو بتعمل الفا؟؟ بتصير تتجمع على حالها وتعمل tetramer of alpha 4 وهاي toxic
بتعمل inclusion bodies و toxic of RBC،فهاد ال RBC وهو جوا ال bone marrow وبصير apoptosis (زي ما مكتوب بالصورة) ← بتموت داخل الـ BM يعني .

في حالة اتسربت لبرا بنحكي extramedullary بشوفها ال spleen وبعملها hemolysis وهون المريض بفوت ب hemolysis

β Thalassemia Minor

The most common

- ✓ Is much more common form of thalassemia , also affects most commonly individuals in Mediterranean countries and parts of Southeast Asia & Africa .
- ✓ The patients are heterozygous therefore asymptomatic & anemia is mild if it is present .
- ✓ The abnormalities are confined to peripheral blood and CBC.
- ✓ Peripheral blood smear show hypochromic microcytic anemia.
- ✓ There is increased Hb A2, while Hb F may be normal or increased .

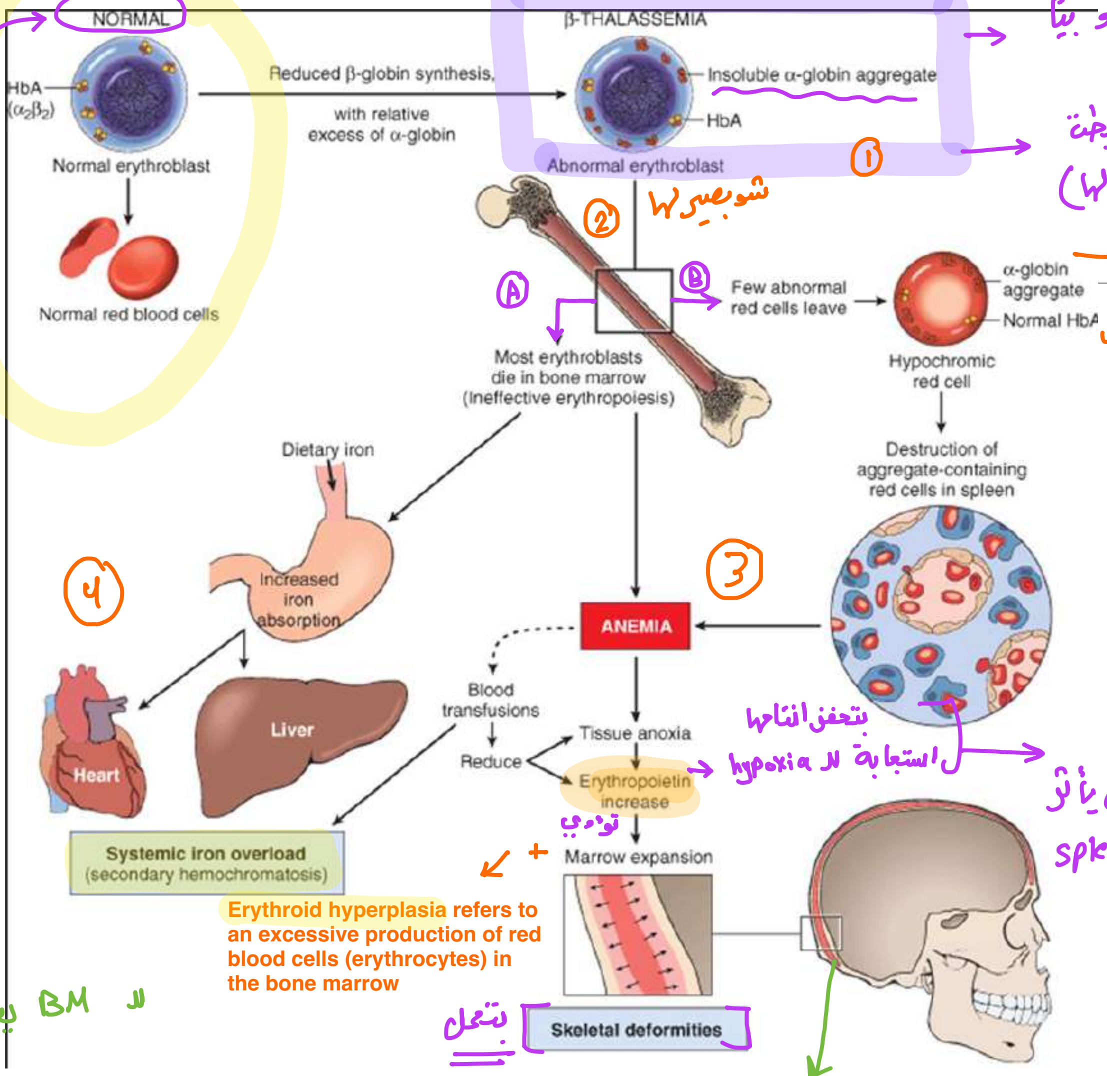
الاسود

β-Thalassemia Major

- ✓ Affects individuals in Mediterranean countries and parts of Southeast Asia & Africa .
- ✓ Most individuals inheriting any two βo have β-thalassemia major .
- ✓ The patients are homozygous .
- ✓ The anemia manifests at 6th-9th months after birth as Hb synthesis switches from HbF to HbA

هون بتصير المشكلة

- ✓ Affected children fail to develop normally and their growth is retarded .
- ✓ With transfusions alone the survival into the second & third decades is possible, but gradually they develop iron overload , hemochromatosis & heart failure .



splenomegaly,hemolysis, Jaundice

Hematopoiesis.

*هسا افرزنا ال erythropoietin طب بدنا نزيد ال RBC ف بدنا مواد و وحدة من المواد الي بنحتاجها ال iron ف بصير عندي increase of iron absorption، ف أنا رفعت نسبة ال iron في الجسم + اني كمان بعطي blood transfusion كل ما اعطي blood في iron كثير فهاي كمان بترفع نسبتو في الجسم فهاد المريض عرضة انو يصيرلو iron overload ف مدخل في haemochromatosis

Pathogenesis of β thalassemia

هي نفسها

Normoblasts, also known as erythroblasts, are a type of erythroid precursor.

- β chains not produced →α chains accumulate in normoblasts → destruction of normoblasts in bone marrow → ineffective erythropoiesis ↓
- Anemia → → Hypoxia in tissues
- ↓
- ↓ →↑erythropoietin production by renal cells .
- ↓ ↓
- Extramedullary hematopoiesis
- ↓ ↓
- Bone changes + cardiac failure & ↓ death.
- Repeated blood transfusions.
- ↓
- Iron overload “Secondary Hemochromatosis”

For 2 reasons —> تجمع ال الحديد داخل القلب
—> بتعب القلب بسبب ضخ الدم لانو بعرف عندو hypoxia

β-Thalassemia Major

كيف رح اشوف شكلهم في الفحصين

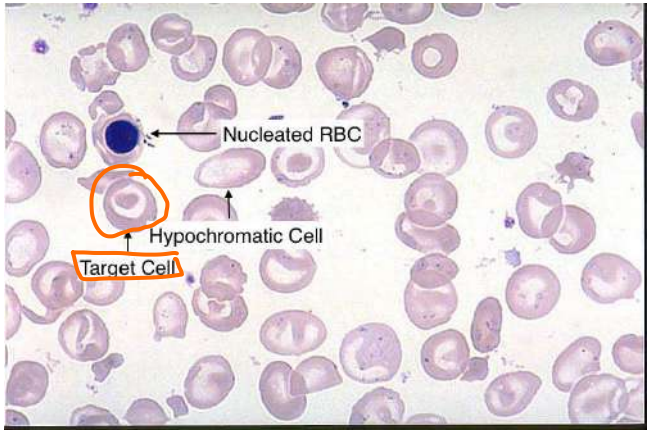
Morphology :

خلايا صغيرة و very pale

- **Peripheral blood** shows microcytic hypochromic red blood cells with variation in shape of RBCs called (poikylocytosis) & variation in size of cells called (anisocytosis) with **target cells**

لو اخذت خزعة من ال

- **Bone marrow** is hypercellular with erythroid hyperplasia .



Peripheral blood

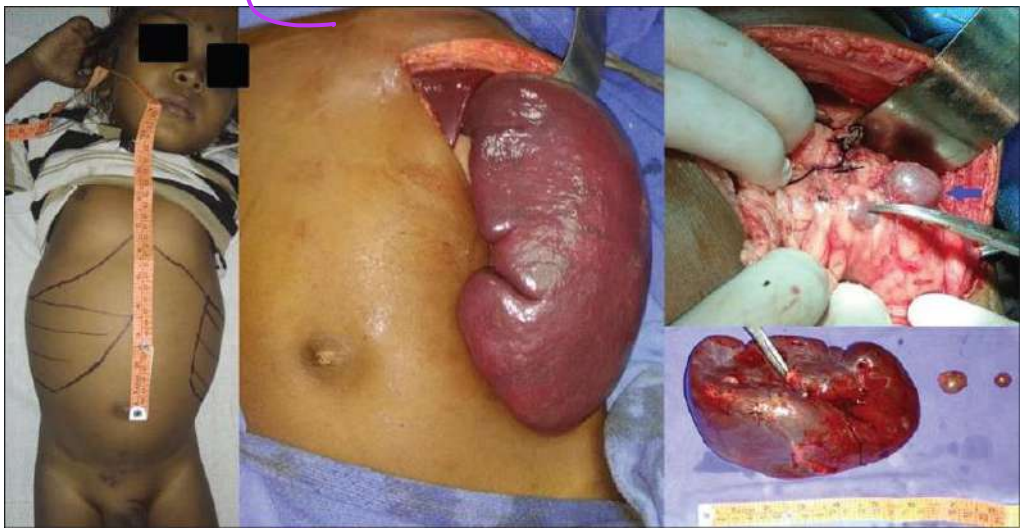
محكلن تلافيفها في α / β و الـ iron حتى

انا عندي في النورمال تجمع Hb بكون بالأطراف والوسط لونو فاتح بس لما الاقي لون غامق بالنص بعرف صار hb بالنص معناتو ال biconcave خربت ورح يصير عندي نتوءات على سطحها

لانو عدد ال hb قل بسبب التيترامر ،بتبطل تحافظ على شكلها ال concave +السبب الاخر انو عندي Erythroid hyperplasia. بحاول يصنع كثير RBC جزء منها بتسرب وبتكون ال(nucleated RBCs)

β thalassemia major “splenomegaly”

Extramedullary hematopoiesis occurs in the liver & spleen causing prominent splenomegaly (up to 1500 grams) & hepatomegaly.

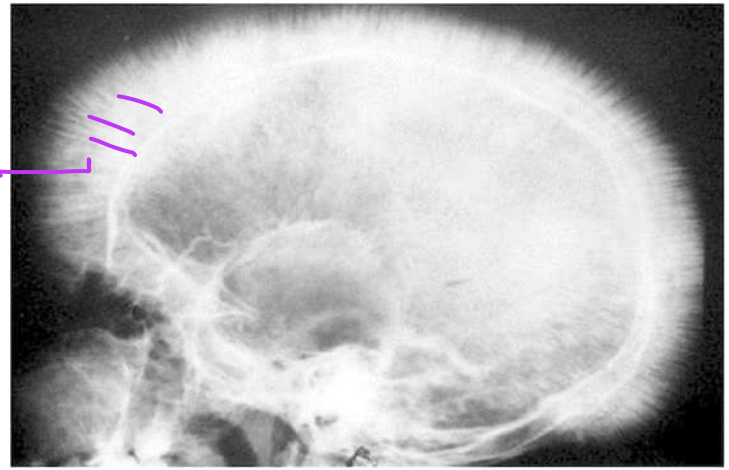


β thalassemia

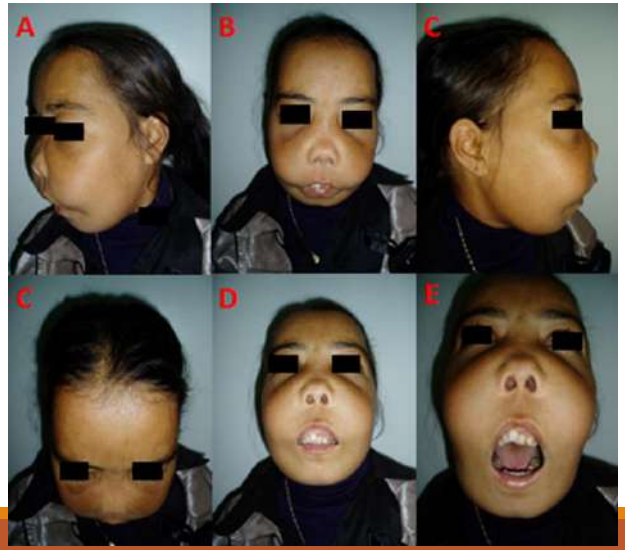
Major ال

The ineffective erythropoiesis & red cell hemolysis stimulates erythropoietin secretion.

This causes severe erythroid hyperplasia and skeletal deformities due to expanded hyperplastic marrow invading the bone cortex giving an appearance of what is called "hair on end" as in the skull also there is a delay of bone growth.



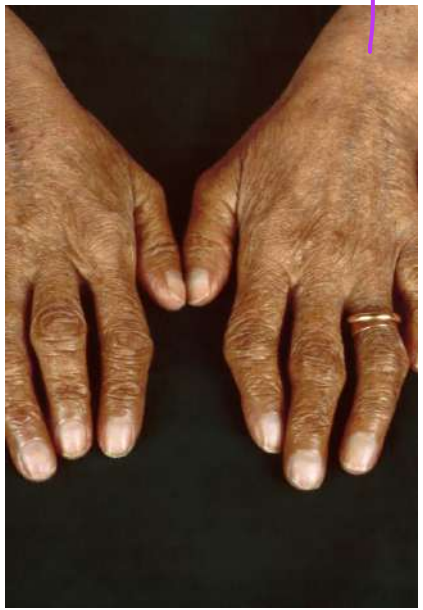
X-ray على زي الشعر الواقف من البرد



β thalassemia

* كل هاي ياد بسبب effect ترسب الـ iron

لونو جلدو كتير غامق بسبب ترسب الـ iron على الجلد



بأثر على البنكرياس فبعمل سكري

Another disastrous effect is the excessive absorption of iron together with frequent blood transfusions given to the patients will lead to **secondary hemochromatosis due to increased iron overload.**

Progressive hemochromatosis is an important cause of death.

لـ الـ iron كتير toxic على الـ Tissue ويسبلش يتراكم فيها زي (.. skin / spleen / liver)

Diagnosis of **β thalassemia**

ما عندهم اعراض

- The diagnosis of β-thalassemia minor is made by **Hb electrophoresis**.

اذا لقيت حميد بعرف انو Minor

- In addition to reduced amounts of HbA (α2β2), the level of HbA2 (α2δ2) is increased.
- The diagnosis of β-thalassemia major can generally be made on clinical grounds.

Treatment: chronic blood transfusion; splenectomy and iron chelation to prevent secondary hemochromatosis

Thalassemia – extra notes

- **Parvovirus B19** is a virus that affects erythrocyte precursors and shuts down RBC production. In a normal person, shutting down RBC production for a week would not affect the person. → الانسان الطبيعي بتحملها

However, patients with β-thalassemia major cannot tolerate RBC production loss. So, they have a high risk of developing an aplastic crisis. → characterized by a sudden and severe decrease in the production of red blood cells

- It was found that patients with thalassemia are **protected against malaria infection by plasmodium falciparum.**

معروفة في دول افريقيا منها مصر في الدراسة هما بي

Iron panel for microcytic anemias

جدول بطلبهم في البيشنت

	Iron Deficiency	AOCD	Thalassemia Minor
Serum iron	↓	↓	Normal
TIBC	↑	↓	Normal
% saturation	↓	↓	Normal
Serum ferritin	↓	↑	Normal

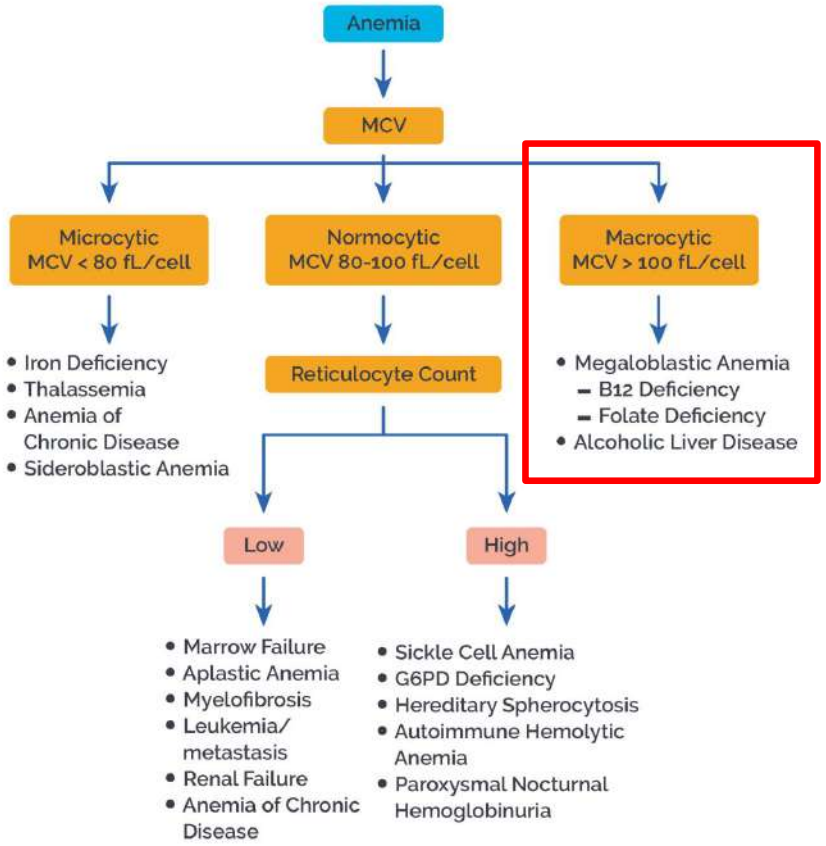
ليه مش Major ؟

لانو بيبين على المريض اول حياتو

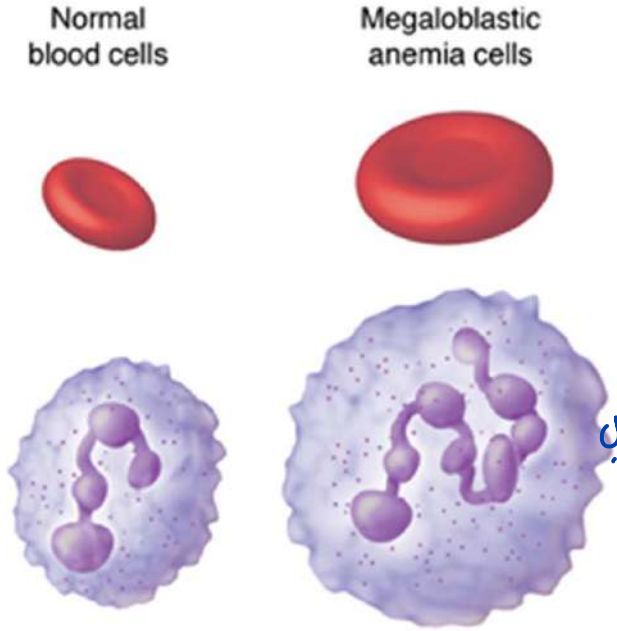
هون بعمل

Hb electrophoresis

CLASSIFICATION OF ANEMIAS



Macrocytic anemia



MACROCYTIC ANAEMIA

MCV > 100

الاثنين كبار

MEGALOBLAST (immature cell)

- B12 deficiency (e.g. pernicious anaemia)
- Folate deficiency (e.g. dietary insufficiency)

NON-MEGALOBLAST (Mature)

- Alcohol
- Reticulocytosis (e.g. haemolysis)
- Liver disease
- Hypothyroidism

*جهون ع نحكي بالتفصيل

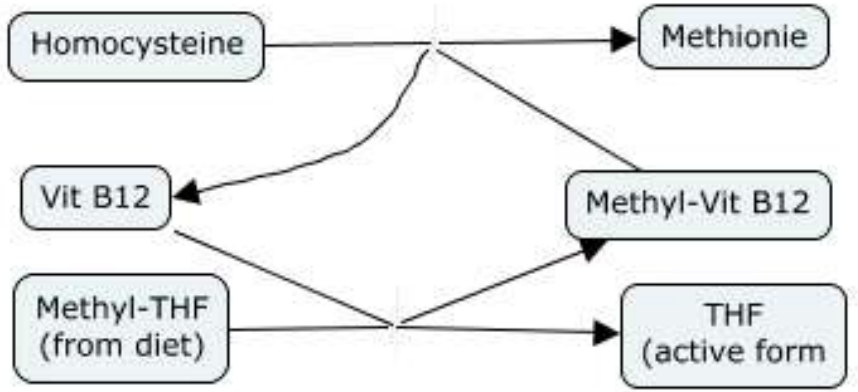
+جهون ع نفس اسبابهم

حجمها كبير

+ الفهم / مش مطلوب حفظ

Folate and Vitamin B12

- Both **folate** and **Vit B12** are involved in DNA precursor synthesis
- Folate comes to body as methylated tetrahydrofolate (**M-THF**).
- **THF** is the active form. M-THF donates its methyl group to Vit B12. Vit B12 then gives methyl group to homocysteine.
- **Homocysteine** now becomes **methionine**.



اللي عندهم نقص B12 + فوليك بيرتفع عندهم

فيه risk لل thrombosis

حكمت عهم نفوت هاي المعلومة

Megaloblastic anemia

Megaloblast: abnormal erythroid precursors showing nuclear: cytoplasmic dyssynchrony (more immature nucleus for the degree of maturity of the cytoplasm)

Macrocyte: mature red blood cell with increased MCV (100 - 110 fL)

Megaloblastic anemia is a disorder of impaired DNA synthesis (with normal RNA synthesis).

Manifests with the presence of megaloblasts in the bone marrow resulting in **ineffective erythropoiesis**, and macrocytes in the peripheral blood and hypersegmented neutrophils

* **Disorder of impaired DNA synthesis → delayed nuclear maturation → nuclear: cytoplasmic dyssynchrony**

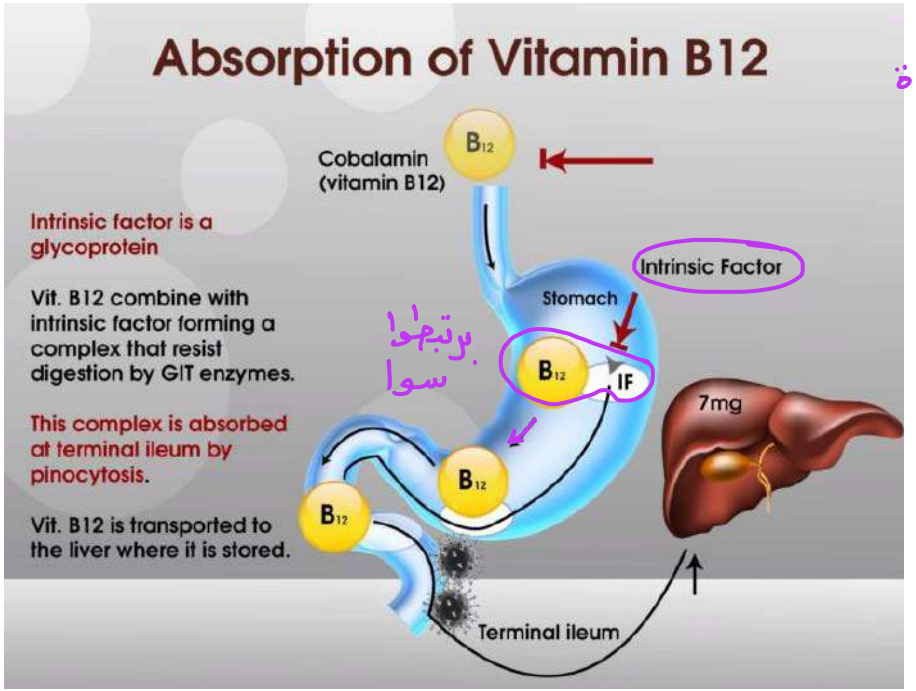
Vitamin B12

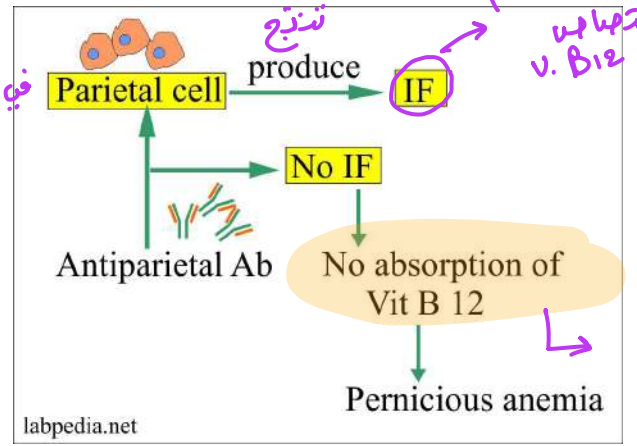
- Source of Vit b12 is mainly animal derived proteins
- Vitamin B12 is mainly absorbed in ileum
- Vitamin B12 deficiency takes years to develop due to large hepatic storage

Examples of vitamin B12 deficiency include:

- ✓ Dietary deficiency "especially in vegans"
- ✓ Pernicious anemia (autoimmune)
- ✓ Damage to terminal ileum (mainly in Crohn's disease)

What is pernicious anemia?





Anti-parietal Ab
Ani-IF Ab

Vitamin B12 deficiency is caused by pernicious anemia when an **auto-antibody against the parietal cells & intrinsic factor** is seen in autoimmune gastritis. This interferes with vitamin B12 absorption. These autoantibodies can be detected in the patient's serum.

Folic acid

- Source of folic acid is mainly dark green vegetables and food
- Folic acid is mainly absorbed in jejunum
- Folic acid deficiency develops in months as body stores are minimum → مثل زي B12

Examples of vitamin Folic acid deficiency include:

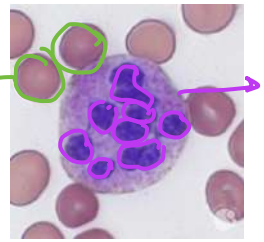
- ✓ Dietary deficiency
- ✓ Increased demand “ex: pregnancy”

مهم لنمو البيبي جدا

Neural tube defect حتى ما يصير

Megaloblastic Anemia
Clinical features

- Anemia (Macrocytic RBCs and hypersegmented neutrophils)
- Glossitis
- Serum low folate OR low Vitamin B12
- Increased serum homocysteine (causes an increased risk for thrombosis)

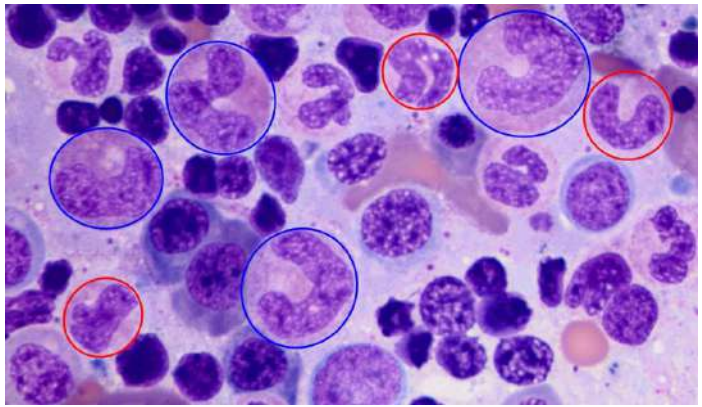


- **Subacute combined degeneration of the spinal cord** (only in Vit B12 deficiency): patients present with neurological manifestations, such as paresthesia, balance disorders, peripheral neuropathy, visual disturbances

Why does Vitamin B12 cause neurological symptoms?

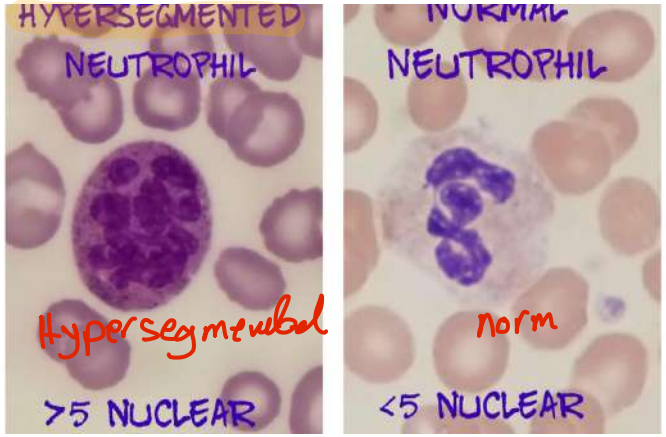
- ✓Because Vit B12 is necessary to convert methylmalonic acid to succinyl Coenzyme A
- ✓Increased methylmalonic acid in myelin cells impairs spinal cord myelinization resulting in subacute combined degeneration of the spinal cord

in BM



Megaloblastic Anemia Pathogenesis

- The morphologic hallmark of megaloblastic anemia is the enlargement of the erythrocytes precursors (**Megaloblasts**)



Blood smer

- The other myeloid lineage are affected; **the granulocytes precursors also enlarged (giant metamyelocytes)** and yield highly characteristic hypersegmented neutrophils

بس يكملو Mature
بدخلوهلن الدورة الدموية بشوف ع

- Eventually, impaired DNA synthesis can lead to ineffective hematopoiesis in all 3 cell lines → **pancytopenia** "anemia , leukopenia & thrombocytopenia"

Megaloblastic Anemia
Diagnosis and morphology

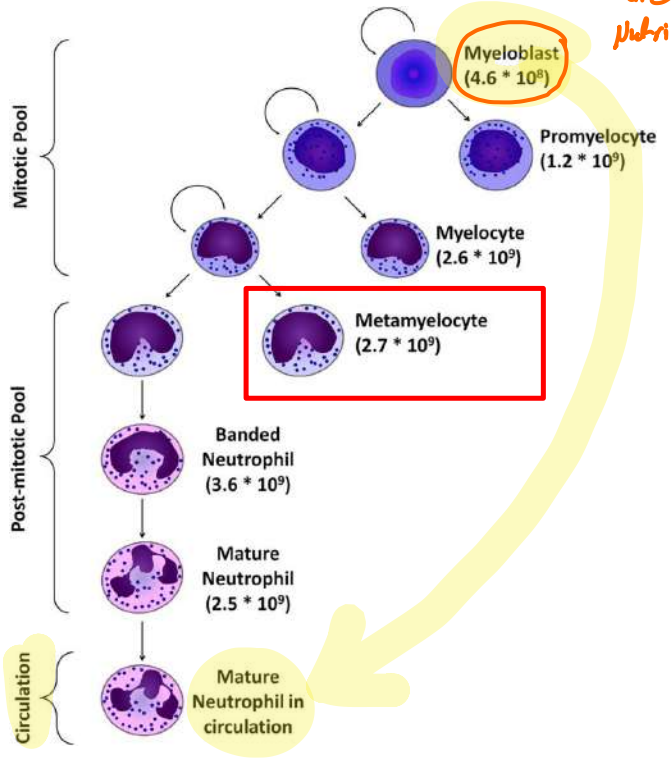
نفس الكلام

CBC: anemia with high MCV. Also, might have leukopenia, and thrombocytopenia (pancytopenia).
Low retic count (ineffective erythropoiesis)
ليه؟ بسبب مشكلة في الانتاج

Peripheral smear: Macrocytes. Anisocytosis (variation in RBC size) and poikilocytosis (variation in RBC shape).
Nucleated red cells are seen with immature nucleus.
Neutrophils show hypersegmentation.

اللي ممكن تتسرب

+ gain Metamyelocytes precursors وحدة من البداية ال تاعت ال Neutrophils

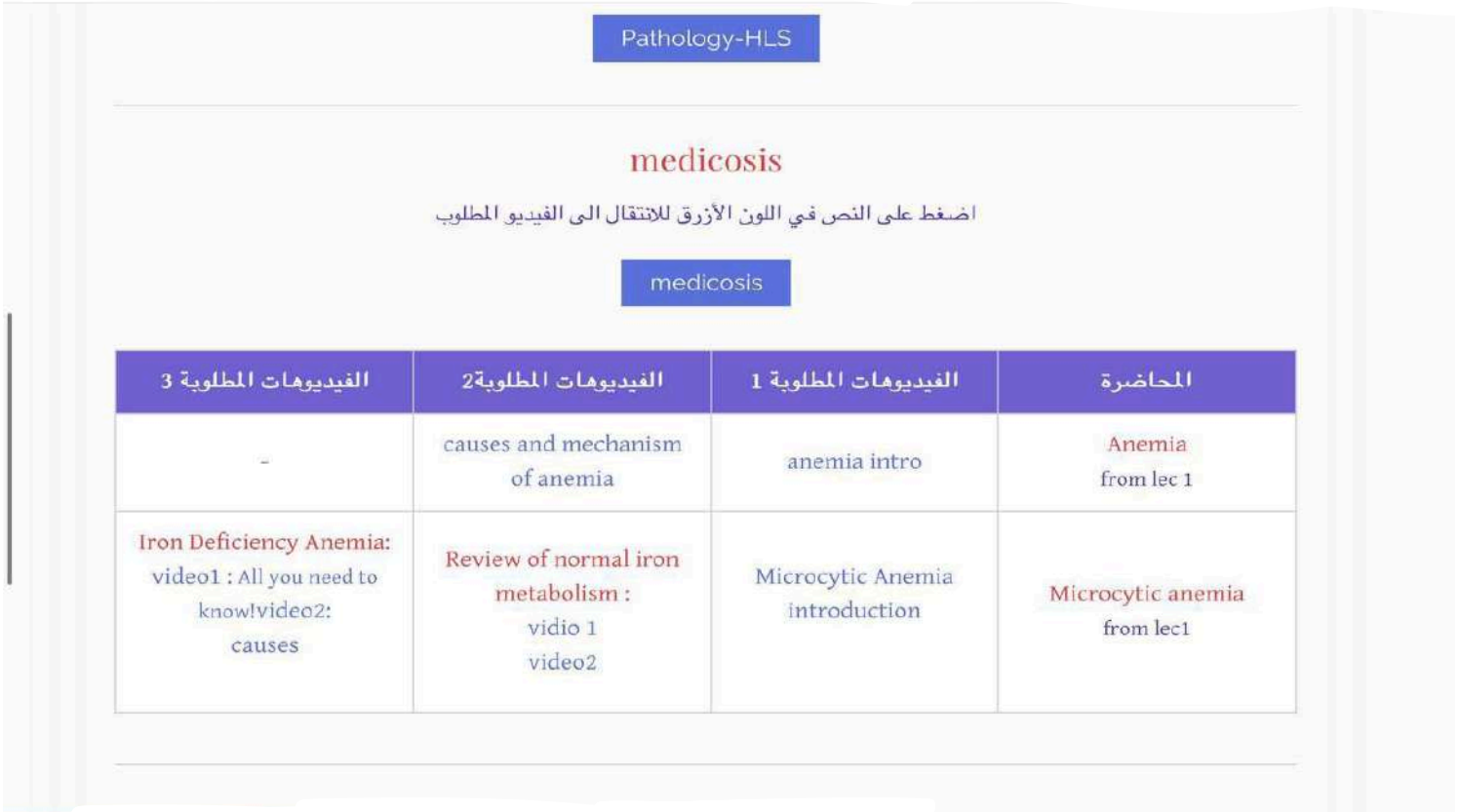


Megaloblastic Anemia

Presentation depends on the underlying cause of megaloblastic anemia;

- **General anemia symptoms:** weakness, shortness of breath, impaired concentration and exercise ability,…..
- **Clinical features specific to cobalamin (vit B12) deficiency**: neurological manifestations
- **Folic acid deficiency is less common**: it is characterized by similar clinical and hematological features but without neurological features**.**

Treatment: Supplementation of B12 and folate with dramatic increase of reticulocytes in blood 2-3 days after vit.B12 injection



وتجدون ع موقع النادي الطبي فيديوهات medicosis لمواضيع محاضراتنا
النادي الطبي من اي متصفح ، دفعة حياة ، Patho ,HLS