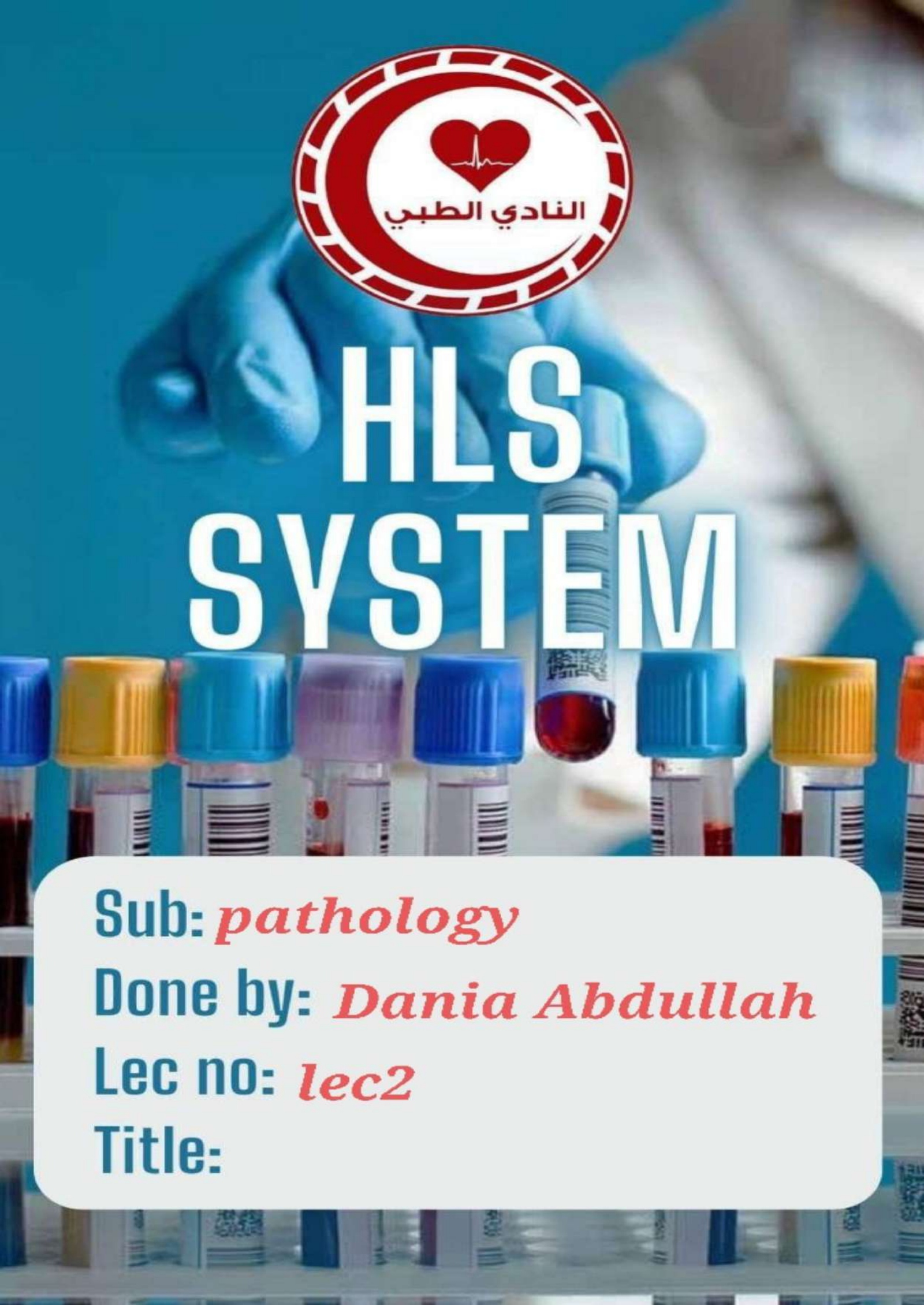


Sub: *pathology*

Done by: *Dania Abdullah*

Lec no: *lec2*

Title:

LECTURE(2) SUMMARY

Thalassemia

- In adults, HbA is the major hemoglobin (97%), composed of (α2β2) with minor amount of HbA2 (1.5 - 3.5%; α2δ2) and HbF(< 1%; α2γ2).
- Thalassemia: A heterogeneous group of inherited disorders caused by mutations that decrease the rate of synthesis of α- or β-globin chains.

can be of two types:

• α-thalassemia : characterized by deficient synthesis of α-globin chains.
• β-thalassemia : caused by deficient synthesis of β-globin chains.

So, there is a deficiency of hemoglobin, with additional secondary red cell abnormalities caused by the relative excess of the other unaffected globin chain.

α-thalassemia

* Alpha thalassemia is an inherited disorder characterized by reduced or absent production of α-globin subunits
*It results in low levels of hemoglobin, decreased (MCV) and decreased (MCH)
*α-thalassemia is usually inherited in an autosomal recessive manner.

α-thalassemia;4 types

1. Bart's hydrops fetalis syndrome
complete absence of all 4 α chains (--/--)
2. HbH disease
absence of 3 α chains (--/-α)
3. α-thalassemia trait
absence of 2 α chains either (--/αα)/(-α/-α)
4. α-thalassemia silent carrier
absence of 1 α chain (αα/-α)

pathophysiology:

*Two α-globin genes are located on each chromosome 16, resulting in 4 α-gene loci (αα/αα)
*Severity of α-thalassemia depends on th number of inactivated or deleted alpha loci.

****

(1)Bart's hydrops fetalis syndrome

* complete aosence or ail a cnains (-/-)
*Because of the absence of a chains, no HbA or HbF is present.
*There is excess production of gamma globin of the HbF which is called Hb Bart's (y4) .

*Hb Bart's have an extremely high oxygen affnity and are incapable of effective oxygen delivery.
*Incompatible with life, fetuses are still born with severe anemia, marked edema and hepatosplenomegaly.

(2) HbH disease:

absence of 3 α chains (–/-α)

- There is excessive HbH (β4) hence called HbH disease .
- This HbH has a high affinity to oxygen (10 X the affinity of HbA) but it cannot transfer oxygen to the cells properly.
- RBC have precipitated HbH and damaged walls, so they are phagocytosed in the spleen.
- Chronic hemolytic anemia, mild jaundice and hepatosplenomegaly.
- Most individuals clinically do well and survive;transfusion is rarely needed.

(3) α-thalassemia trait:

absence of 2 α chains either (–/αα) or (-α/-α)

- Benign condition with most patients diagnosed on routine screening
- Does not require treatment.

4. α-thalassemia silent carrier :

absence of 1 α chain (αα/-α)

- No clinical abnormalities

*Diagnosis of thalassemia is done by CBC,electrophoresis, blood smear, family hx

α-thalassemia; lab findings :

•Hb Bart's hydrops fetalis syndrome:

CBC: severe microcytic hypochromic anemia and reticulocytosis
Hb Bart's > 80%

•HbH disease:

CBC: decreased MCV and MCH, and reticulocytosis

•α-thalassemia trait:

CBC: may show mild hypochromic (low MCH), microcytic (low MCV) anemia

•α-thalassemia silent carrier:

CBC: either normal or mild reduction of MCV and MCH

β-Thalassemia :

- Inherited in an autosomal recessive manner.
- Beta thalassemia is caused due to gene mutation of beta chain of hemoglobin. Mutations result in absent (aka BO) or diminished (aka B+) production of B-globin chain.
- Normally, 2 beta alleles are present on chromosome 11 (1 allele per chromosome).

β-Thalassemia types:

Types	Alleles	Description
Thalassemia minor 2 genes واحد من الـ طبيعي, والثاني mutated	β^+/β β^o/β	Only one of β globin alleles has a mutation. Patients will have microcytic anemia (MCV <80 fL) (MCH is normal)
Thalassemia intermedia Both genes are mutated, with at least one β^+	β^+/β^+ β^o/β^+	Patients can have a normal life, but may need occasional transfusions, example at times of increase demand (illness or pregnancy)
Thalassemia major No beta-globin producing في الاشهر الأولى من حياة الطفل يكون معتمد عال HbF, لكن بعد ما يصير يعتمد عال HbA بتبلش الاعراض تظهر	β^o/β^o	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

β-Thalassemia Minor

- 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 HbA2, while HbF may be normal or increased .

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
- 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 .

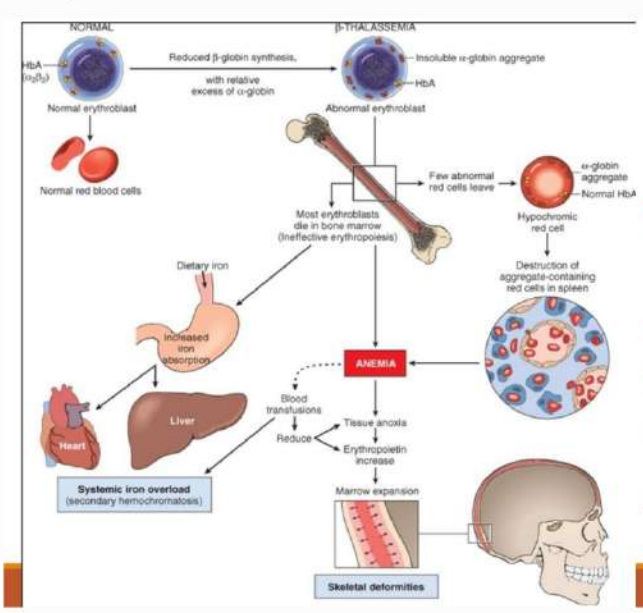
Pathogenesis of β thalassemia

• β chains not produced →α chains accumulate in normoblasts → destruction of normoblasts in bone marrow → ineffective erythropoiesis ↓ → ANEMIA

• Anemia → Hypoxia in tissues→ ↑ erythropoietin production by renal cells → Extramedullary hematopoiesis →

• Bone changes + cardiac failure & ↓ death.

• Repeated blood transfusions → Iron overload "Secondary Hemochromatosis".



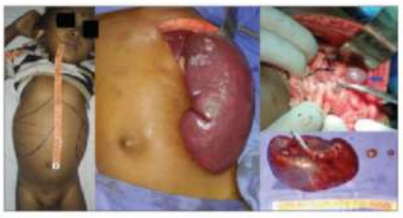
β-Thalassemia Pathogenesis

**نلخص الحكي اللي بالصورة :

- اول اشي يصير في تكوين لـabnormal erythroblasts
- الـerythroblasts هاي رح تتجمع بالـbone marrow عشان هيك لازم يخلص منها
- معظمها رح يصيرله apoptosis داخل الـBM, وجزء منها رح يطلع عالدم ويوصل الـspleen ويتم تكسيره
- الأن بالنهاية رح يصير عنا anemia, اللي رح تزيد من إفراز الـerythropoietin
- زيادة إفراز الـerythropoietin ممكن تأدي لـ skeletal deformities
- هنا كل هاض الحكي, الجسم رح يحاول يعمل حاله يطل ويعالجه بزيادة امتصاص الـiron, ومع عمليات الـtransfusion رح ترتفع كمية الـiron بالجسم كثير
- ارتفاع الـiron بالشكل هاض رح يأدي لـiron overload, أو ما يُعرف بـSecondary Hemochromatosis

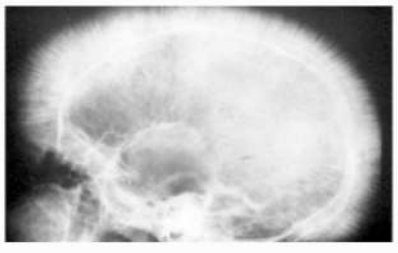
β thalassemia major "splenomegaly"

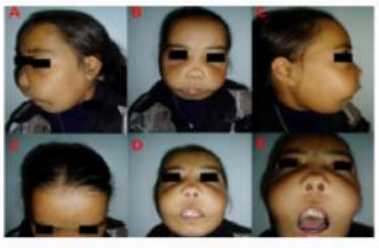
Extramedullary hematopoiesis occurs in the liver & spleen causing prominent splenomegaly (up to 1500 grams) & hepatomegaly.



β thalassemia

*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.





*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.

Diagnosis of β thalassemia

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

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

**➢Parvovirus B19 is a virus that affects erythrocyte precursors and shuts down RBC production.

**➢It was found that patients with thalassemia are protected against malariainfection by plasmodium falciparum.

Both folate and Vit B12 are involved in DNA
precursor synthesis, so their deficiency leads to DNA synthesis problems.

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

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

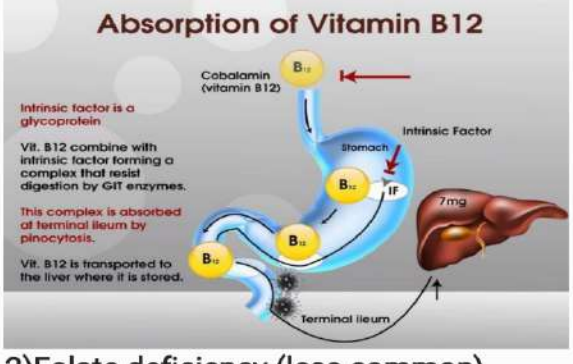
Megaloblastic anemia Etiology

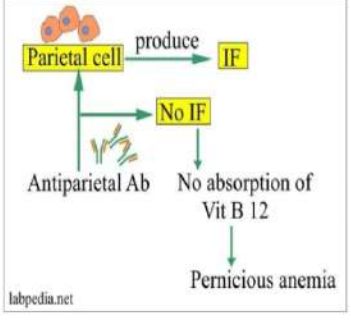
1)Vitamin B12 deficiency:

- Dietary deficiency "especially in vegans"
- Pernicious anemia (autoimmune)
- Increased demand "ex: pregnancy"

What is pernicious anemia?

*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.





Anti-parietal Ab
Ani-IF Ab

2)Folate deficiency (less common)

- Dietary deficiency
- Increased demand "ex: pregnancy"

Megaloblastic anemia clinical features

Presentation depends on the underlying cause of megaloblastic anemia;

- General anemia symptoms: weakness, shortness of breath, impaired concentration and exercise ability,.....
- Anemia (Macrocytic RBCs and hypersegmented neutrophils)
- Glossitis
- Serum low folate OR low Vitamin B12
  *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.
- Increased serum homocysteine (causes an increased risk for thrombosis)
- **Subacute combined degeneration of the spinal cord** (only in Vit B12 deficiency); with neurological manifestations, such as paresthesia, balance disorders, peripheral 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.

Pathogenesis

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

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

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

Diagnosis and morphology

CBC: anemia with high MCV and normochromic. Also, might have leukopenia, and thrombocytopenia (pancytopenia). Low retic count

Peripheral smear: Macrocytes. anisocytosis, poikilocytosis, Nucleated red cells are seen with immature nucleus. Neutrophils show hypersegmentation. Pancytopenia

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