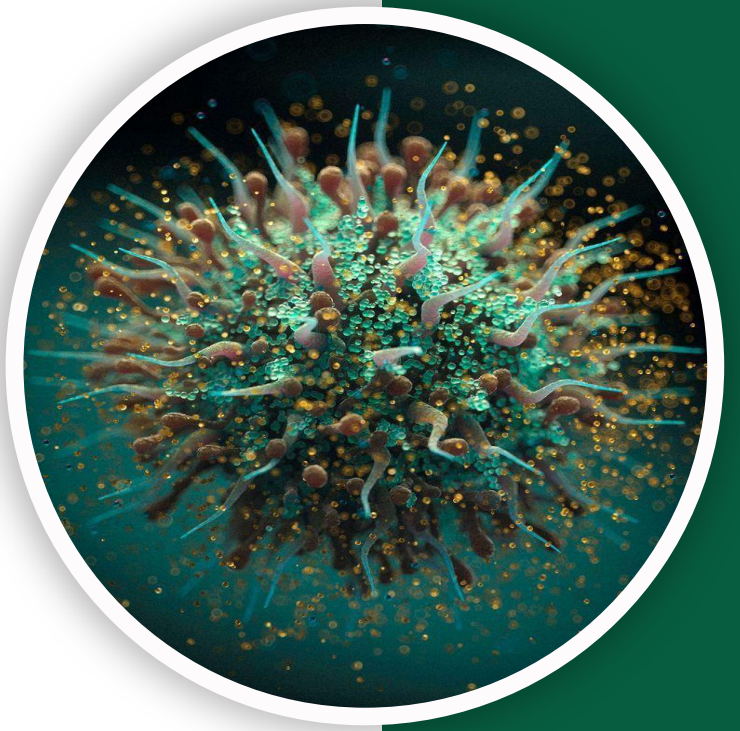
بسم الله الرحمـٰن الرحيم

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Pathology | FINAL 5

Hemoglobin-opathies

Written by : DST

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Hemoglobinopathies

- **Inherited diseases** related to the **synthesis** of **hemoglobin**.

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Thalassemia

- Group of inherited disorders that result in decreased production of either α/β chains.
- Amount of synthesized adult Hg is below normal resulting in microcytic hypochromic anemia.
- The deficiency in one of globin chains results in a relative increase in the other one, excessive unpaired chains will cause instability and hemolysis.
- It can be classified as a special type of hemolytic anemia.
- Mode of inheritance: autosomal recessive — this means there can be silent carriers with no symptoms.
- Common in Middle East, Africa and South East Asia.
- Resistant to infection by malaria falciparum by an unknown mechanism.
- Patients with thalassemia have protection against severe symptoms of infection with *Malaria falciparum*.
- Normal Hg types in adults: HgA (≈95%), HgA2 (≈2.5%-3.5%), HgF (≈1%)
- Hemoglobin structure: HbA ($2\alpha + 2\beta$), HbA_2 ($2\alpha + 2\delta$), HbF ($2\alpha + 2\gamma$).

genetics

- α-chain is encoded by 2 genes on each copy of chromosome 16, therefore we have **4 α-chain genes** .
- Most mutations in α-thalassemia are deletion.
- Deletion in 1, or 2 gene(s) results in a silent carrier, **asymptomatic**.
- Deletion of 4 genes results in hydrops fetalis — it's incompatible with life due to **complete absence** of **HbA**, **HbF** and **HbA2**, because there are **no alpha chains**.
- Deletion of 3 genes results in Hemoglobin H disease (extra β- chains binds each other to a tetramer called Hg-H, extra γ- chains form Hg-Barts). Both have high affinity to oxygen.
- In the case of **deletion** of **three alpha genes**, alpha chains are still produced but in **low amount**, leading to an **excess amount** of **beta** and **gamma**, which results in **HbH** and **Hb Barts** formation. Patients with this condition show **symptoms** and **hypoxia**.

genetics

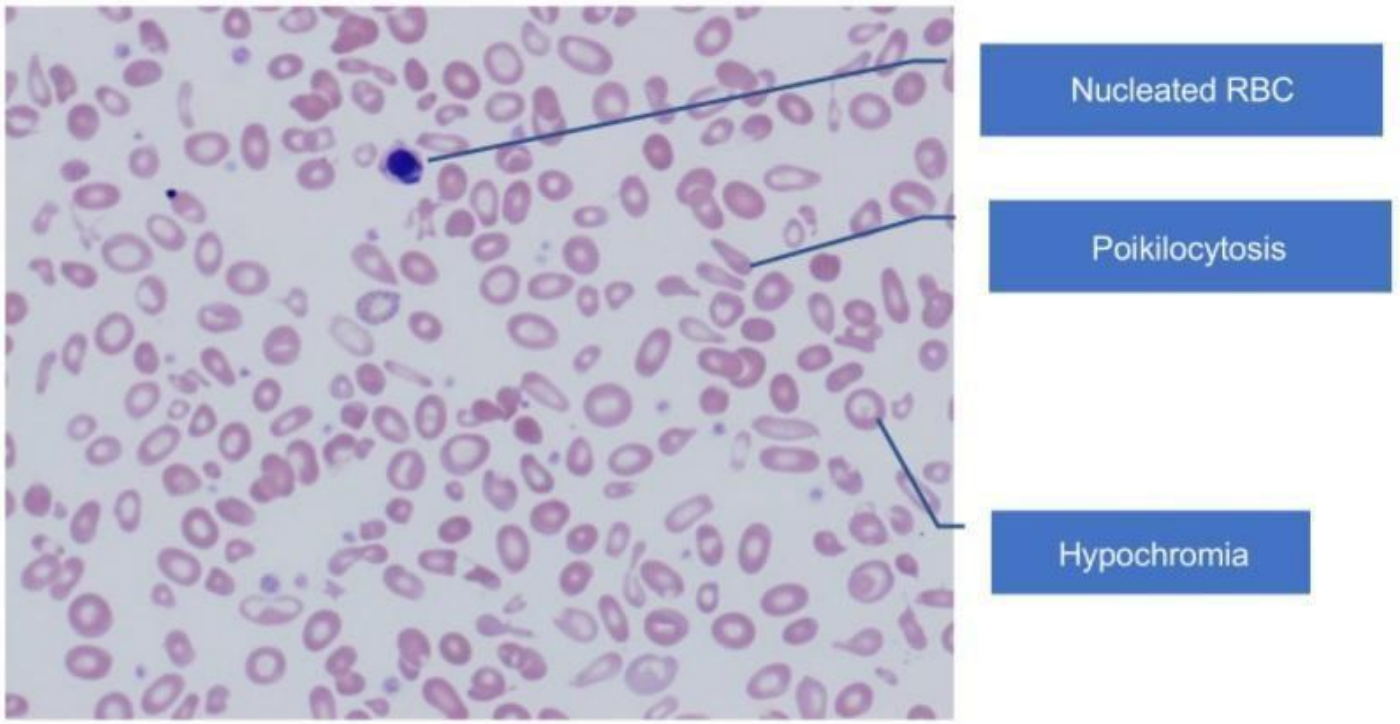
- B-chain is encoded by a single gene on each copy of chromosome 11, therefore we have **2 β-chain genes**, which means **higher probability** for **symptoms**.
- Most mutations in β-thalassemia are point mutations -> produces **heterogeneity.**
- β^0: no production of β-chain, no HbA.
- β^+: decreased production of β-chain, less HbA.
- β/β^+:silent carrier or mild anemia (thalassemia -minor) — RBCs are **slightly smaller** and **paler** than normal, usually with **no symptoms**.
- β^+/β^+: thalassemia intermedia, more deficiency, **symptoms start** to appear.
- β^0/β^0 or β^0/β^+: thalassemia major (Cooley anemia) — **Complete absence** of **HbA** with **higher** amounts of **HbA2** and **HbF**, the latter being the dominant form.
- β^0/β^+ has **less than 5%** of **HbA**.
- **Thalassemia major** is a **lifelong anemia** requiring regular **transfusions**, in contrast to **thalassemia intermedia** which presents with a **tolerable anemia**.
- Extra α-chains remain uncoupled, causing hemolysis (more than α-thalassemia) of RBCs in spleen and erythroid precursors in bone marrow (ineffective erythropoiesis)

Morphology

- Hypochromic microcytic anemia
- Target cells — RBC with a **red dot in** the **center pallor area**. it's not specific to thalassemia, we can see it in any disease involving **abnormal hemoglobin** such as **iron deficiency** anemia and **sickle cell** anemia.
- Basophilic stippling — **blue small dots**, which are **residual ribosomes**.
- In thalassemia major:
- Peripheral blood: + poikilocytosis, nucleated RBCs
- Bone marrow: ↑↑ normoblasts, filling BM spaces and expanding into bone, hemosiderosis
- In **normal** cases the **dominant** cell type in the **bone marrow** is the **myeloid stem cell**, but due to **high levels of EPO** we see a **large number of normoblasts**.
- In addition, 1) **repetitive transfusions** and 2) **low levels** of **hepcidin** increase iron absorption in the gut, leading to **hemosiderosis**.

  Iron-chelating agents such as **Exjade** help reduce iron absorption in the gut and control hemosiderosis caused by frequent blood transfusions.
- EPO suppresses hepcidin.

Basophilic stippling of RBCs



Thalassemia major blood film

Clinicalsymptoms

- Thalassemia traits are asymptomatic, but RBCs have **slightly smaller size** and **less Hb**, **MCV ≈ 75**, normal life span, premarital test is important.
- When conducting premarital test and observing microcytic hypochromic RBCs**, iron deficiency anemia** should be **suspected first**, as it is much **more common**.
- Thalassemia major: symptoms begin after age of 6 months due to **decline** in **HbF** , patient present with persistent symptoms of anemia, growth retardation, skeletal abnormalities, hepatosplenomegaly, these symptoms are ameliorated by regular blood transfusion.
- Systemic hemochromatosis and related organ damage — such as cardiac complications and endocrine diseases — occurs in 2nd or 3rd decade of life.
- Thalassemia intermedia and HgH disease have moderate anemia, do not require regular blood transfusion.

Diagnosis

- Hemoglobin electrophoresis test shows what **type** of **Hb** in **RBCs** and their **percentages.**
- In all types of β-thal, there is increase in HgA2 (**more than 3.5%** in **all** forms of the disease — **carrier**, **intermedia** and **major**) and HgF percentages
- In β-thal major, HgA is absent or markedly decreased
- In HgH disease, HgH and Hg Barts bands appear along with **decreased HbA.**
- In α-thal carrier and minor, no abnormality is found on electrophoresis because of **decreased production** of **alpha chains** in **all types** of **hemoglobin** . Genetic testing is available.
- In **hypochromic microcytic anemia** with **low MCV**, we **first examine iron** levels:
  - If **iron** is **decreased**, it is **iron deficiency anemia**.
  - If **iron** is **increased**, perform **hemoglobin electrophoresis**:
    - If **HbA2 increased**, it suggests **beta thalassemia**.
    - If **HbA2** is **normal**, it suggests **alpha thalassemia** (potentially).

Sickle cell anemia

- Most common familial hemolytic anemia worldwide
- Common in Africa, Middle East, Saudi Arabia, African Americans
- Resistant to malaria falciparum infection by an unknown mechanism.
- Mode of inheritance: autosomal co-dominance — each allele contributes to the phenotype, so the RBC contain **both HbS** and **HbA** in **heterozygous**.
- Caused by single amino acid substitution - glutamic acid (hydrophilic) → valine (hydrophobic) in β-chain at 6^{th} amino acid position.
- In sickle cell disease (homozygous), Hg electrophoresis shows HgS and absent HgA
- In sickle cell carrier (heterozygous), Hg electrophoresis shows both HgA and HgS bands with **no symptoms.**

Pathogenesis

- In deoxygentated case, HgS tends to polymerize in a longitudinal pattern, distorting cell shape and creating sickle shape
- The change is reversible by re-oxygenation, however, with repeated sicklings, cell membrane is damaged and the RBC is shrunken permanently with a sickle shape
- The presence of normal HgA (carrier) and increased HgF (newborn) inhibits HgS polymerization (**inhibitors** of sickling)
- Increased HgS concentration inside RBC promotes sickling (dehydration, acidosis due to **infection**), while decreased HgS concentration prevents sickling (the presence of additional α-thalassemia) this is mainly because of the **lower level** of **alpha chains** and thus **less HbS** formation, **decreasing sickling.**

Pathogenesis

- Sickle-shaped RBCs take a longer time to pass through capillaries, non deformable.
- Removed by macrophages in spleen (extravascular hemolysis).
- Also adhere to endothelial cells, may create a thrombus which is the **most dangerous complication** of the disease.

Clinical features

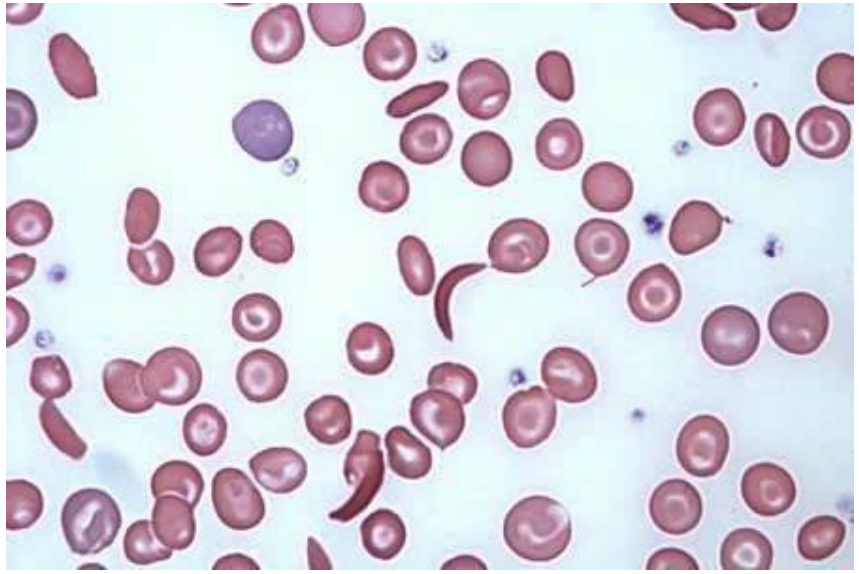
- Chronic moderate-severe hemolytic anemia, manifesting as hepatosplenomegaly, short stature, abnormal faces after the age of 6-months (dependent on fraction of sickled cells). The chronic course is interrupted by repeated sudden attacks of worsening anemia, often due to **infection**.
- Vaso-occlusive crisis (independent on fraction of sickled cells), results in organ infarction. Commonly associated with systemic infection, inflammation, dehydration and acidosis.
- Hand-foot syndrome: Repeated infarctions in the **small bones** of the **hands** and **feet** cause **painful** swelling and **deformities** of the digits. It is **very common**.
- acute chest syndrome involves infarction in the **heart**, **lungs** and **bones** in the **chest** with **severe pain**, and is the **main cause of death** between sickle patients.
- Other complications include stroke, myocardial infarction, retinopathy, autosplenectomy due to **repeated splenic infarction** leading to **fibrosis**.

Clinical features

- Aplastic-crisis: shutdown of the BM due to infarction, infection by Parvovirus B19, causing worsening anemia, self-limited
- Paravovirus B19 is a mild virus in healthy individuals, but in patients with sickle cell disease and thalassemia major, it infects normoblasts in the bone marrow, causing temporary cessation of erythropoiesis. The condition resolves on its own, but blood transfusion may be required.
- Susceptibility for encapsulated bacteria due to functional asplenia: pneumococcus, salmonella (causing osteomyelitis).
- Sickle cell carrier: asymptomatic

Laboratoryfindings

- Routine blood smear: presence of sickle cells, target cells
- Sickling test: adding hypoxic agent to RBCs promote sickling
- Hemoglobin electrophoresis is the **definitive diagnostic test**. It can detect both carriers and patients with HbS disease.
  - In **carriers (sickle cell trait)**, two bands are seen —**HbA** and **HbS**.
  - In **HbS disease (sickle cell anemia)**, only the **HbS band** is present, with small amounts of **HbA_2** and **HbF**.
- In sickle cell trait, Blood smear is normal



Pathology Quiz 5



رسالة من الفريق العلمي:

عَنْ أَبِي هُرَيْرَةَ رَضِيَ اللهُ عَنْهُ قَالَ: قَالَ رَسُولُ اللهِ ﷺ:

«اِحْرِصْ عَلَى مَا يَنْفَعُكَ، وَاسْتَعِنْ بِاللهِ، وَلَا تَعْجَزْ».

أَخْرَجَهُ مُسْلِمٌ فِي «صَحِيحِهِ» (٢٦٦٤).

كلنا بنسمع إنه **سيستم الهيماتو هو سيستم الباثو**، وعشان هيك مهم يكون عندك مصدر موثوق يساعدك تفهم **مادة الباثولوجي** وتتعامل معها بطريقة صحيحة.

بهذا القروب على التليجرام، زميلتنا **حنين البنا** بتوفّر نصائح وإرشادات لكيفية التعامل مع كل مادة في السيستم، بالإضافة إلى **شرح لمادة الباثو بسعر مميّز مع امكانية تجربة الشرح قبل الإشتراك.**

إذا بدك تفهم المادة بشكل أفضل وتدخل مادة الفاينل وأنت مستعد، هاي فرصتك، هذا رابط القروب ::

HLS Pathology By Haneen

For any feedback, scan the code or click on it

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			