**Normocytic Normochromic Anaemia**

**Objectives:**

1-Define normochromic normocytic anaemia and enumerate its causes(differential diagnosis)

2-Define compensated haemolysis and haemolyic anaemia.

3-Classify haemolytic anaemia.

4-Mention the general laboratory features of haemolytic anaemia.

5-Define sickle haemoglobin and its underlying genetic lesion.

6-Know the features of sickle cell disease.

-Know the main defect underlying hereditary spherocytosis ,clinical features and lab. diagnosis.

In **normochromic normocytic anaemia** both MCV and MCH are normal

**Causes of normochromic normocytic anaemia:**

1-Many haemolytic anaemia

2-Anaemia of chronic disease (some cases)

3-After acute blood loss.

4-Renal disease

5-Mixed deficiencies

6- Bone marrow failure

**Haemolytic anaemias**

Red cell destruction usually occurs after a mean lifespan of 120 days when the cells are removed extravascularly by the macrophages of the reticuloendothelial (RE) system, **especially in the marrow** , also in the liver and spleen.

Intravascular haemolysis (breakdown of red cells within blood vessels) plays little or no part in normal red cell destruction.

 **Because of erythropoietic hyperplasia and anatomical extension of bone marrow, red cell destruction may be increased several-fold before the patient becomes anaemic, this is called compensated haemolytic** **disease**.

 The normal adult marrow, after full expansion, is able to produce red cells at 6-8 times the normal rate provided this is 'effective'.

Therefore, haemolytic anaemia may not be seen until the red cell lifespan is less than 30 days.

1. **Extravascular** **b) Intravascular**



(a) Normal red blood cell (RBC) breakdown. This takes place extravascularly in the macrophages of the reticuloendothelial system. (b) Intravascular haemolysis occurs in some pathological disorders .

* ***Haemolytic anaemias*** are defined as those anaemias that result from an increase in the rate of red cell destruction.

**Classification of haemolytic anaemias:**

|  |  |
| --- | --- |
|  **Hereditory** |  **Acquired** |
| **1.Defect in the metabolism of RBCs** e.g.Glucose 6 phosphate dehydrogenase deficiency(G6PD) 2.**Defect in the membrane of RBCs**e.g.hereditary spherocytosis,hereditary elliptocytosis **3. Defect in haemoglobin** Sickle cell anaemia,thalassemia | **1.Mechanical damage:** Red cell fragmentation syndrome **2.Antibody damage:** autoimmune haemolytic anaemia,alloimmune haemolytic anaemia**3.Oxidant damage**Exposure to oxidant drugs or chemicals.**4.Enzymatic damage**Certain snakes.**5.Heat damage.** Sever burns |

***Laboratory findings (Diagnosis of haemolysis):***

1. ***Evidence that there is increased red cells breakdowm (*** *increased billirubin-particularly unconjugated bilirubin-,lactate dehydrogenase, free haemoglobin in plasma or urine,reduced serum haptoglobin, incraesed urinary urobilinogen* .)
2. ***Evidence of increased bone marrow activity***  *(retculocytosis, nucleated red cells in the blood film)* .
3. ***Abnormal red cells of a type that is found in hae*molytic anaemia** (spherocytes or sickle cells or red cell fragments …… )
4. ***Evidence of specific type of haemolytic anaemia***

*( positive direct antiglobulin test or*  reduced G6PD ).

**Hereditoy** **Haemolytic Anaemia**

**Sickle cell anaemia**

Sickle cell disease is a group of haemoglobin disorders in which the sickle –**globin** gene is inherited.

- Hb S (Hb **α2β2s)**

-The sickle –**globin** abnormality is caused by substitution of **valine** for **glutamic acid** in **position 6 in the β** chain .

It is very widespread and is found in up to one in four West Africans, maintained at this level because of the protection against malaria that is afforded by the carrier state.



- Hb S (Hb **α2β2s**) is insoluble and forms crystals when exposed to low oxygen tension. Deoxygenated sickle haemoglobin polymerizes.

The red cells sickle and may block different areas of the microcirculation or large vessels causing infarcts of various organs.

* **Homozygous disease :(** ***βsβs*)**

- The symptoms of anaemia are often mild in relation to the severity of the anaemia because Hb S gives up oxygen *(O2)* to tissues relatively easily compared with Hb A,

- *Patients suffer from recurrent painful crises as a result of tissue infarction in the chest,abdomen,spine and limbs* precipitated by such factors as infection, acidosis, dehydration or deoxygenation (e.g. altitude, operations, obstetric delivery, cold, violent exercise).

*-In children and to alesser extent adult, stoke due to cerebral infarction.*

*-Pulmonary infarction can lead to hypoxia .*

*-Infarction of the kidneys causing haematuria.*

The 'hand-foot' syndrome (painful dactylitis caused by infarcts of the small bones) is frequently the first presentation of the disease and may -lead to digits of varying lengths.

- Splenic sequestration (sickling within organ and pooling of blood, often with a severe exacerbation of anaemia) is typically seen in infants and presents with an enlarging spleen, falling haemoglobin and abdominal pain.

- The spleen is enlarged in infancy and early childhood but later is often reduced in size as a result of infarcts (autosplenectomy).

***-*** *Aplastic crises*

These occur as a result of infection with parvovirus or from folate deficiency and are characterized by a sudden fall in haemoglobin, and by a fall in reticulocytes .

*-Haemolytic crises*

These are characterized by an increased rate of haemolysis with a fall in haemoglobin but rise in reticulocytes.

- Ulcers of the lower legs are common, as a result of vascular stasis and local ischaemia.

**Laboratory findings**

1. The haemoglobin is usually low in comparison to symptoms of anaemia.

2. **Blood film**: Sickle cells and target cells features of splenic atrophy (e.g. Howell Jolly bodies) may also be present.

3. **Sickling tests** are positive when the blood is deoxygenated (sealing a drop of blood under a coverslip to exclude oxygen or by adding 2% sodium metabisulphite.) .

4. **The solubility test** for HbS utilizes a reducing

agent such as sodium dithionite, which is added to the haemolysate. Deoxy - HbS is insoluble and renders the solution turbid

5. **Haemoglobin electrophoresis**

**Shows Hb S, A2 ,F ,and total absence of Hb A**

**Sickle cell trait(*βsβ*): Heterozygous**

**-**It is a carrier state.

-This is a benign condition with no anaemia and normal appearance of red cells on a blood film.

-Haematuria is the most common symptom and is thought to be caused by minor infarcts of the renal papillae.

-Haemoglobin electrophoresis:

 Hb S , Hb A ,Hb A2

- Care must be taken with anaesthesia, pregnancy and at high altitudes.

**Hereditary spherocytosis**

There is defects in the proteins involved in the vertical interactions between the membrane skeleton and the lipid bilayer of the red cell, therefore leave part of the membrane unsupported .

 The marrow produces red cells of normal biconcave shape but these lose membrane and become increasingly spherical (loss of surface area relative to volume) as they circulate through the spleen and the rest of the RE system. Ultimately, the spherocytes are unable to pass through the splenic microcirculation where they die prematurely.

-The **inheritance is autosomal dominant** with variable expression; rarely it may be autosomal recessive.

-The anaemia can present at any age from infancy to old age.

- Jaundice

-splenomegaly occurs in most patients.

 -Pigmented gallstones

 -aplastic crises, usually precipitated by parvovirus infection.

-***Haematological findings:***

 -Anaemia .

 - Reticulocyte increased .

 -The blood film shows microspherocytes(which are densely

 staining with smaller diameters than normal red cells).

 - An osmotic fragility test is abnormal (The curve is shifted to the

 right of the normal range) ..

 - **Diagnosis confirmed by showing reduced binding of a dye**

 **,eosin -5-maleamide ,to red cells(detected by measuring**

 **fluorescence on flow cytometry).**