Hemoglobinopathies

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Hemoglobinopathies

**Definition:**

- Hemoglobinopathies are **hereditary diseases of the globin synthesis** that compromise oxygen transport to the organs.

- They fall into 2 broad categories:
  - Sickle cell disease (drepanocytosis)
  - Thalassemias
Hemoglobin is a protein whose primary function is the transport of oxygen in the human body.

The hemoglobin is essentially located within the red blood cells, which gives them their red color.
Human hemoglobin is a tetramer protein composed of four units:
- Two $\alpha$ chains
- Two $\beta$ chains

Each chain is associated with a prosthetic group: the heme.

The name hemoglobin comes from two words: heme and globine. Its symbol is « Hb ». 
The heme

- **Heme** is a cofactor consisting of an $\text{Fe}^{2+}$ (ferrous) ion contained in the centre of a large heterocyclic organic ring called a porphyrin.

- Iron is the **oxygen binding site**.
Hemoglobinopathies

Alpha and Beta globin genes are encoded on chromosomes 16 and 11, respectively.
Like many other proteins, hemoglobin chains may present multiple mutations which are usually not clinically relevant.

More than 500 abnormal hemoglobins have been identified.
Hemoglobinopathies

Mutations on the β-globin coding gene (chromosome 11)

- Substitution of glutamic acid for valine

HbS

Responsible for sickle cell disease
Drepanocytosis (also called sickle cell anemia), is an inherited autosomal recessive disorder that is characterized by an alteration of hemoglobin.
DREPANOCYTOSIS

There are several sickle cell syndromes depending on the type of mutation.

<table>
<thead>
<tr>
<th>Association</th>
<th>Sévérité</th>
<th>Fréquence relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/S</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>S/S ( /\alpha \text{ thal}_1 \text{ ou } \alpha \text{ thal}_2 )</td>
<td>+ à ++</td>
<td>+</td>
</tr>
<tr>
<td>S/(\beta^0) thal</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>S/(\beta^+) thal</td>
<td>+ à ++</td>
<td>+</td>
</tr>
<tr>
<td>S/C</td>
<td>+ à ++</td>
<td>++</td>
</tr>
<tr>
<td>S/D Punjab</td>
<td>+++</td>
<td>rare</td>
</tr>
<tr>
<td>S/O Arab</td>
<td>+++</td>
<td>rare</td>
</tr>
<tr>
<td>S/C Harlem</td>
<td>+++</td>
<td>rare</td>
</tr>
<tr>
<td>S/PHHF</td>
<td>0 à +</td>
<td>rare à +</td>
</tr>
<tr>
<td>A/S Antilles</td>
<td>+</td>
<td>rare</td>
</tr>
</tbody>
</table>

\(HbS/S:\) properties of hemoglobin modified

**Qualitative hemoglobin disease**
DREapanocytosis

Epidemiology:
- > 50 million people affected worldwide
- > 250,000 children with a severe form are born each year
- Sub-sahara Africa, Middle-east, India, Brasil
The sickle cell trait appears to protect against severe forms of malaria
DREPANOCYTOSIS

Pathophysiology

- The red blood cells of homozygous persons (Hb S/S) are almost completely composed of HbS.

- HBS has the property of polymerizing when deoxygenated, resulting in the formation of fibers that distort the red blood cell and give it an sickle shape.
DRE Pancytosis

**Stress**
- Hypoxia
- Cold
- Dehydration
- Infection

HbS → polymerisation → Sickling

HUG Hôpitaux Universitaires de Genève
Pathophysiology

- Sickling

  Decrease of the mechanical strength and elasticity of Red Cells

  - Hemolytic anemia
  - Painful vaso-occlusive crisis
  - Damage to organs
DREPNOCYTOSIS

Signs and symptoms

- **Acute painful episodes due to vaso-occlusive crisis**

Vaso-occlusive crisis is caused by sickle-shaped red blood cells that obstruct capillaries and restrict blood flow to an organ resulting in ischaemia, pain, necrosis and often organ damage (e.g. spleen).

Pain can occur in any part of the body

- Back
- Thorax
- Extremities
- Abdomen

are most commonly affected.

The painful episodes usually last for 3 to 10 days and are difficult to predict.
Foot and hand syndrome or DACTYLITIS

This syndrome only occurs in children before the age of 2 years.

Feet and hands become hot, swollen, and movements are painful.

This may be the first manifestation of the disease in young children, with or without fever.
○ **Haemolytic anemia**

- Anemia refers to a lack of hemoglobin (or red blood cells) and results in excessive fatigue and a feeling of weakness.

- When anemia is severe enough, the patient may have difficulty breathing (shortness of breath) and faster heart beats (tachycardia).

- People with SCD are constantly anemic but usually adapt to it quite well. Sometimes the only visible signs are fatigue and yellow eyes or skin (jaundice), and dark urine.
Worsening anemia (SPLENIC SEQUESTRATION)

- Splenic sequestration crises are acute, painful enlargement of the spleen, caused by intrasplenic trapping of red cells and resulting in a precipitous fall in hemoglobin levels with the potential for hypovolemic shock.

- Sequestration crises are considered an emergency. If not treated, patients may die within 1–2 hours due to circulatory failure. Management is supportive, sometimes with blood transfusion.

- These crises are transient, they continue for 3–4 hours and may last for one day.

- If sequestration crises occur bring the child urgently to the hospital.
Worsening anemia  **(APLASTIC CRISIS)**

- Aplastic crises are acute worsenings of the patient's baseline anemia, producing pale appearance, fast heart rate, and fatigue.

- Anemia is non-regenerative (**no reticulocytosis**)

- This crisis is normally triggered by parvovirus B19, which directly affects production of red blood cells by invading the red cell precursors and multiplying in and destroying them.

- This crisis takes 4 days to one week to disappear. Most patients can be managed supportively; some need blood transfusion.
DREPANOCYTOSIS

ACUTE CHEST SYNDROME

- This syndrome is characterized by fever, discomfort or difficulty breathing (dyspnea), rapid breathing, cough, and chest pain.
- It is the second-most common complication and it accounts for about 25% of deaths in patients with SCD.
- In children acute chest syndrome is often associated with a pulmonary infection.
The clinical manifestations are highly variable, and may be transient (known as transient ischemic attacks or TIA's): loss of sensitivity or strength in one arm, one leg, half of the face, paralysis on one side of the body or a member (hemiplegia), headache, sudden speaking difficulty (aphasia), balance disorders, convulsions, sometimes coma.

Severe headache or sudden learning difficulties can be warning signs in children.
STROKE

- Stroke concerns especially children between four and six years.
- Often the symptoms appear and disappear suddenly but the risk of recurrence is high.
- The child can escape safely, but in many cases, stroke causes brain damage leaving motor and/or intellectual sequelae.

DREPANOCYTOSIS

- **INCREASED SUSCEPTIBILITY TO INFECTION**

  - Children (sometimes as young as three months), and to a lesser extent adults, are very susceptible to bacterial infections that can be fulminant, and therefore must be treated promptly.

  - Increased susceptibility to infection is due to *splenic dysfunction*.

  - SCD people are especially susceptible to pneumonia, flu, but also hepatitis, meningitis, urinary tract infections, septicemia and bone and joint infections.

  - Bacteria: *S. pneumoniae, H. influenzae* type B, *M. pneumoniae, Salmonella* sp ...
The risk of infection is highest among children less than 5 years, but it continues throughout life.

In children, it is very important to prevent chronic infectious foci (at the teeth, tonsils, bone, bladder), ensuring good hygiene (brushing teeth, etc.), maintaining their vaccinations updated, and making sure they take penicillin every day until the age of 5 years.
DREPNOCYTOSIS

○ Chronic complications of SCD
  ○ Cardiac, kidney & skin involvement
  ○ Pulmonary Arterial HT
  ○ Retinopathy
  ○ Priapism
  ○ Gallstones
  ○ ...etc
FIG 2. Sickle-cell disease complications by age.
The diagnosis is made on:

- Blood smear and the shape of RC
- Electrophoresis of hemoglobin
- Genetic tests
DREPSANOCYTOSIS

**TREATMENT**

There is no cure for this genetic disease, except for a transplantation of hematopoietic stem cells.

**Symptomatic treatment:**

- **Vaso-occlusive crisis:** Pain reliever (paracetamol, AINS, morphin)
- **Acute anemia:** Transfusion, Folic acid
- **Infection:** Antibiotics
  - Prevention: Immunization, Daily penicillin (min 5 years)
Along with medical treatment, simple measures must be taken to ease the patient in a crisis:

- Rest in a warm place
- Drink a lot to stay hydrated
- Quiet (the family must try as much as possible to maintain a calm atmosphere around the patient)

Oxygen therapy is often required during hospitalization.
DREPTANOCYTOSIS

- **Background treatment**

Hydroxyurea

- Increase of the fetal hemoglobin (HbF) production
- Decreased adherence to endothelium
- Modulation of inflammation

![Graph showing changes in hemoglobin levels](image-url)
The production of the fetal hemoglobin (HbF) reduces the aggregation of hemoglobin S.

In people who respond well to HU, the frequency of painful crises and hospitalizations decrease.

The need for transfusion and the risk of onset of acute chest syndrome are also reduced.

This treatment has significantly improved the quality of life of people with severe or moderately severe form (with more than three painful crises per year requiring hospitalization, severe anemia or a history of acute chest syndrome).

However, HU has no effect on lung or bone infections, and does not prevent stroke episode.
References

Diallo DA, Guindo A. “Sickle cell disease in sub-Saharan Africa: stakes and strategies for control of the disease” Curr Opin Hematol. 2014 May;21(3):210-4


www.orpha.net/

Thalassemias

THALASSEMIAS

Genetic defect in the production of the alpha or beta globin chain

Quantitative Hemoglobinopathy
Thalassemias are inherited, autosomal recessive diseases, characterized by a failure to produce hemoglobin.

- Beta-thalassemia
- Alpha-thalassemia
Beta-thalassemia mainly affects people from around the Mediterranean sea, the Middle East, Asia (China, India, Vietnam, Thailand) and sub-Saharan Africa. It reaches as many women than men.
β-thalassemia

Whether the production of beta globin chains is absent or only reduced, we distinguish:

- β-thalassemia major (Cooley’s anemia)
- β-thalassemia intermedia
- β-thalassemia minor
**β- thalassemia major**

The first signs of beta- thalassemia major are revealed after the age of 6 months, because the blood of the newborn still contains many fetal hemoglobin HbF (alpha2 / gamma2), often in a very heterogeneous form.

**Severe hemolytic anemia**

- Pallor
- Irritability
- Hepatomegaly
- Splenomegaly
- Jaundice
- Developmental delay
To compensate a massive hemolysis, erythropoiesis is increased in bone leading to **bone deformities**.

In children **facial bones thicken** (deformation of the jaws, flattening of the root of the nose, excessive spacing of the eyes).
Secondary complications are due to iron overload consecutive to hemolysis / continuous transfusion

- **Endocrine and metabolic disorders**
  - Hypogonadism: 40-55%
  - Stunting: 33%
  - Diabetes: 6-13%
  - Hypothyroidism: 10%

- **Cardiac complications**
  - Heart failure (hemosiderosis)
  - Ahythmias

- **Cholelithiasis**
β-thalassemia major

Diagnosis:

- Clinical suspicion (signs, symptoms, origin…)
- Blood smear (hypochromic, microcytic anemia)
  
  Biochemistry: Hemolysis (free bili↑, LDH↑, Haptoglobin↓)
  Serum iron↑, ferritin↑

- Electrophoresis of hemoglobin (HbA2↑ 3.5-8%, HbF↑ 1-2%)
β - thalassemia

- β-thalassemia major

**Treatment:**

- Blood transfusion
- (Splenectomy)
- Folic acid
- Iron chelator
In the beta-thalassemia intermedia, the transcription of both beta genes are altered, but they still allow the production of hemoglobin in reduced amount. Symptoms are less severe than in Cooley's anemia.

- Microcytic hypochromic anemia occurring later in life (1-2 y) and less pronounced (>7.5 g/dl)
- Jaundice, splenomegaly
- Bone deformities (+/-)
- No stunting
The minor beta-thalassemia is caused by the mutation of one of the two beta genes. Usually, this form has no impact on health, since the other gene is able to compensate the anomaly and makes enough beta chains to produce normal or near normal levels of hemoglobin.

- Microcytosis
Alpha-thalassemia is prevalent worldwide. It mostly affects people from Asia (Cambodia, Laos, Burma, Thailand in particular), in its intermediate or severe forms, and from equatorial Africa and the Mediterranean basin in its minor forms.
On chromosome 16, two genes encode the alpha chains of the globin
Alpha-thalassemias

**Alpha-thalassemia**

- **Chr 16p**  
  - **αα / αα**  
    - Normal subject

- **Chr 16m**  
  - **αα / −α**  
    - α thalassemia minima

- **−α / −α**  
  - or

- **−− / αα**  
  - α thalassemia minor

- **−− / −α**  
  - α thalassemia major  
    - (Hemoglobin H disease)

- **−− / −−**  
  - Hydrops foetalis
<table>
<thead>
<tr>
<th>Alleles affected</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>None. Silent form</td>
</tr>
<tr>
<td>Two</td>
<td>Few symptoms. Microcytic hypochromic anemia</td>
</tr>
<tr>
<td>Three</td>
<td>Hemoglobin H disease. Can be severe. Microcytic hypochromic anemia, hepatosplenomegaly</td>
</tr>
<tr>
<td>Four</td>
<td>Very severe. The fetus cannot live once outside the uterus and may not survive gestation: most such infants are stillborn with hydrops fetalis, and those who are born alive die shortly after birth.</td>
</tr>
</tbody>
</table>
Hemoglobin H disease

- Anemia (microcytic and hypochromic) is the main symptom

- It is present from birth but is sometimes not diagnosed until adulthood when it is moderate. It varies from one person to another, and over time.
Alpha-thalassemias

- **Hemoglobin H disease**

  **Clinical signs**

  - Pallor
  - Fatigue
  - Jaundice
  - Hepatosplenomegaly
  - Cholelithiasis
**Diagnosis**

- Blood smear
- Electrophoresis of hemoglobin

### The thalassemias: Genetic, clinical, and laboratory findings

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Genotype</th>
<th>MCV</th>
<th>Anemia</th>
<th>Hemoglobin electrophoresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha thalassemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent carrier</td>
<td>$a^a/a^a$</td>
<td>NL</td>
<td>None</td>
<td>$&lt;3%$ Hb Barts at birth</td>
</tr>
<tr>
<td>Minor</td>
<td>$a^a/a^o$ or $a^a/a^-$</td>
<td>Low</td>
<td>Mild</td>
<td>Normal</td>
</tr>
<tr>
<td>Hb H disease (deletional)</td>
<td>$a^-/a^-$</td>
<td>Low</td>
<td>Moderate</td>
<td>5 to 30% HbH present in adults</td>
</tr>
<tr>
<td>Major (fetal hydrops)</td>
<td>$a^-/-$</td>
<td>Low</td>
<td>Fatal</td>
<td>Hb H, Hb Portland, and HbH present</td>
</tr>
<tr>
<td>Beta thalassemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor (trait)</td>
<td>$B^B/B^B$ or $B^B/B^+$</td>
<td>Low</td>
<td>Mild</td>
<td>$HbA_2$ increased (3.5 to 7 percent)</td>
</tr>
<tr>
<td>Intermedia</td>
<td>$g^+ / g^+$ and others*</td>
<td>Low</td>
<td>Moderate</td>
<td>HbF increased in about 50% of patients</td>
</tr>
<tr>
<td>Major</td>
<td>$g^- / g^+$</td>
<td>Low</td>
<td>Severe</td>
<td>$HbA_2$ absent</td>
</tr>
</tbody>
</table>

MCV: mean corpuscular volume; Hb: hemoglobin; NL: normal; $B$: thalasemic gene producing some $\beta$-chain; $B^+$: thalasemic gene producing no $\beta$-chain.

* See text for multiple other genotypes.
Thank you for your attention!