GENETIC DEFECTS OF HAEMOGLOBIN

(Other than thalassaemia)

These result from the synthesis of abnormal haemoglobin due to amino acid substitutions in the β-globin chains. In many cases, however, the abnormality is completely silent, as the underlying mutation causes no alteration in the function, solubility or stability of the haemoglobin molecule.

The common haemoglobin variants include Hb C, D, E and S. Some of the first syndromes which arise include haemolysis (HbS,C,D,E), familial polycythaemia and methaemoglobinaemia (HbM). The clinically most important abnormality is homozygous sickle cell anaemia (HbSS).

Pathophysiology of sickle cell anaemia

The abnormality is due to substitution of valine for glutamic acid in position 6 in the β chain. HbS is insoluble and forms crystals when exposed to low oxygen tension. Deoxygenated sickle haemoglobin polymerises into long fibres consisting of intertwined double strands with cross-links. The red cells sickle and may block different areas of the microcirculation causing infarcts of various organs.

Laboratory findings of homozygous HbSS

- Severe anaemia (Hb 6 - 9 g/dl)
- Sickle cells and target cells on the blood film
- Howell-Jolly bodies may be present due to splenic atrophy
- Screening tests for sickling are positive when the blood is deoxygenated
- No normal HbA is detected and the amount of HbF is variable (5-15%)

Findings of HbS with other genetic defects

S/β-thalassaemia: MCV and MCH lower than HbSS; clinically present as sickle cell anaemia, splenomegaly usual

S/Hb C,D,E disease: Tendency for thrombosis and pulmonary embolism (especially in pregnancy); high incidence of retinal abnormalities; mild anaemia and splenomegaly usual

Findings in other homozygous variants

HbC: Mild haemolytic anaemia; marked target cells; rhomboidal shaped cells; microspherocytes; enlarged spleen
HbD: Mild haemolytic anaemia
HbE: Mild hypochromic, microcytic anaemia
No treatment is required for these variants
Clinical features of HbS:

The symptoms of anaemia are often mild in relation to the severity of the anaemia since HbS gives up oxygen to tissues relatively easy.

Sickle cell trait (HbS) is a benign condition with no anaemia and normal appearance of red cells on a blood film but crises can be caused by extreme stress, e.g. anoxia and severe infections. Haematuria is the most common symptom. HbS varies from 25% to 45% of the total haemoglobin. Care must be taken with anaesthesia and in pregnancy.

The clinical expression of homozygous sickle cell disease (HbSS) varies from patients having an almost normal life, free of crises, but others develop severe crises, even as infants, and may die in early childhood or as young adults. Crises may be:

- **Painful vascular-occlusive crises**
  Precipitated by factors such as infection, acidosis, dehydration or deoxygenation (e.g. altitude, operations). Infarcts may occur in organs such as bones, lungs, spleen, brain and spinal cord. In children the “hand-foot” syndrome is frequent and may lead to digits of varying lengths.

- **Visceral sequestration crises**
  Due to sickling within organs and pooling of blood, often with a severe exacerbation of anaemia.

- **Aplastic crises**
  Occur due to infection with parvovirus and/or folate deficiency. Characterised by a sudden fall in haemoglobin and reticulocytes (requiring transfusion).

- **Haemolytic crises**
  Characterised by an increased rate of haemolysis with a fall in haemoglobin but a rise in reticulocytes.

- **Other clinical features**
  - Ulcers of the lower legs are common due to vascular stasis and local ischaemia
  - Enlarged spleen in infancy and early childhood but later reduce in size due to infarcts
  - Proliferative retinopathy and priapism
  - Chronic damage to the liver due to micro-infarcts may occur
  - Pigment gallstones are frequent

Kidneys are vulnerable to infarction resulting in failure to concentrate urine, aggravating the tendency to dehydration.

Specimen
One 5ml EDTA specimen. Hb electrophoresis can be done on a specimen up to 14 days after collection.
**Treatment of homozygous HbSS**

- Avoid factors known to precipitate crises, especially dehydration, anoxia, infections and stasis of the circulation.
- Folic acid supplement.
- Good general nutrition and hygiene.
- Pneumococcal vaccination and regular oral penicillin to reduce the frequency of crises precipitated by infection.
- Crises - rest, rehydrate, antibiotics if infection is present and bicarbonate only if the patient is acidotic.
- Particular care is needed in pregnancy and anaesthesia. Transfuse repeatedly with normal blood to reduce the amount of HbS prior to these procedures.
- Transfusions to suppress HbS production completely over several months. Iron overload may become a problem and iron chelation therapy should be included.
- Bone marrow transplantation, but the risks generally outweigh the benefits.

**References**


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