THE THALASSEMIAS

DEFINITION

The thalassemias, or more comprehensively the thalassemia syndromes, are a heterogeneous group of inherited hemolytic anemias characterized by deficient or absent production of one of the globin chains of hemoglobin. This leads to imbalanced globin chain synthesis that is the hallmark of all the thalassemia syndromes.

EPIDEMIOLOGY

- Taken together, the thalassemias are the most common single-gene disorder in the world population, with estimated carrier numbers of more than 270 million, and more than 300,000 children are born each year with one of the thalassemia syndromes or one of the structural hemoglobin variants.
- The extremely high frequency of the hemoglobin disorders compared with other monogenic diseases reflects natural selection mediated by the relative resistance of carriers against Plasmodium falciparum malaria.
- Other factors that may be involved include the widespread practice of consanguineous marriage, increased maternal age in the poorer countries, and gene drift and founder effects. For these reasons, the thalassemias are most frequent in southeastern and southern Asia, in the Middle East, in the Mediterranean countries, and in northern and central Africa. However, as the result of mass migrations of African populations from high-prevalence areas, thalassemias are now encountered worldwide

PATHOBIOLOGY

- Normal adult red cells contain 97% adult hemoglobin (HbA: α2β2), with approximately 2.5% of the minor component HbA2 (α2δ2) and a small amount of fetal hemoglobin (HbF: α2γ2). Because the stable tetramer α2β2is the major component of hemoglobin after birth, there are two main forms of thalassemia: α-thalassemias and β-thalassemias.
- Because β-chain synthesis is fully activated only after birth, it follows that the β-thalassemias are not expressed as a disease in intrauterine life; they are manifested as γ-chain synthesis declines during the first year of life. In contrast, because α chains are shared by both fetal and adult hemoglobin, α-thalassemias are manifested in both fetal and adult life.

GENETIC AND CLINICAL CLASSIFICATIONS OF THE THALASSEMIAS

	GENETIC	CLINICAL
α-Talassemias	α^0 α^+ Deletion ($-\alpha$) Nondeletion (α^T)	α-Minor HbH disease Hydrops fetalis
β-Talassemias	β^0 β^+ Variant with high HbA_2 Normal HbA_2 Silent Dominant Unlinked to β-gene cluster	β-Minor Talassemia intermedia Talassemia major
δβ-Talassemia	$(\delta\beta)^0$ $(\delta\beta)^+$ $(^A\gamma\delta\beta)^0$	δβ-Minor Talassemia intermedia
HPFH	Deletion Nondeletion	Silent increase HbF

α thalassaemia

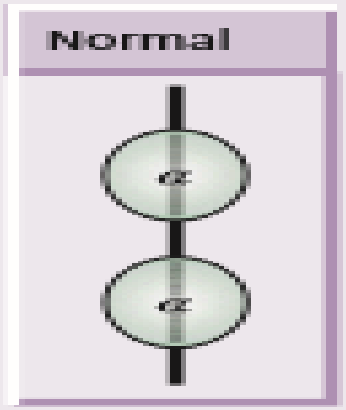
Two α globin genes on each chromosome 16, with total of 4 α globin genes per cell (normal person is designated αα/αα) making α thalassaemia more heterogeneous than β thalassaemia. Like sickle cell anaemia, patients can either have mild α thalassaemia (α thalassaemia trait, − −/αα or −α/−α or −α/αα) where 1 or 2 α globin genes are affected or they may have severe α thalassaemia if 3 or 4 of the genes are affected.

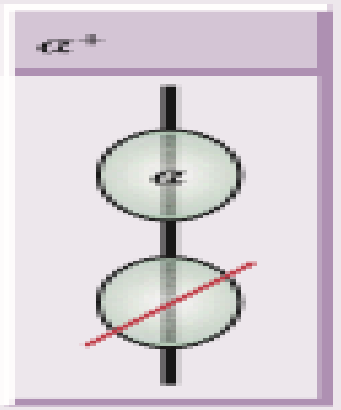
α thalassaemia is generally the result of large deletions within α globin complex. High prevalence of α thalassaemia in Africa, Afro-Caribbeans, South and SE Asia (−α/−α or −α/αα). αo thalassaemia (i.e. − −/αα) found most commonly in Mediterranean and SE Asian ethnic groups. α thalassaemia occurs from loss of linked α globin genes on 1 chromosome (i.e. − −/αα). Deletions in α gene HS40 region (upstream regulatory region) account for most αo thalassaemia mutations. α+ results from deletion of 1 of the linked α genes (−α/αα) or inactivation due to point mutation (αTα/αα).

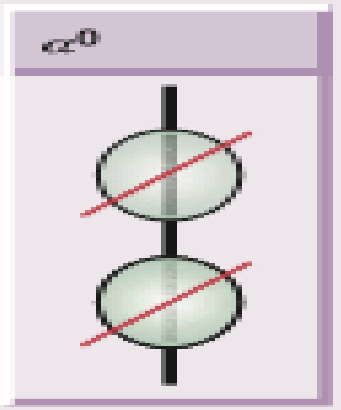
α thalassaemia trait (− **α/αα**, or **αα**/− − or −**α**/−**α**) 1 gene deleted. Asymptomatic. d MCV and MCH in minority.

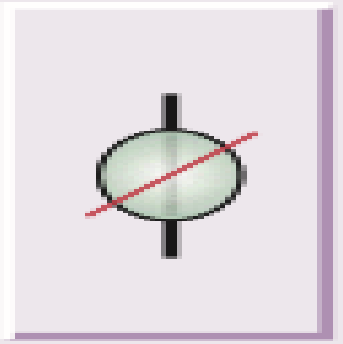
- **α** thalassaemia trait (**αα**/− − or −**α**/−**α**) 2 common α+ deletions and Asymptomatic carrier—recognized once other causes of microcytic anaemia are excluded (e.g. Fe deficiency). Hb may be n or minimally d. MCV and MCH are d. Absence of splenomegaly or other clinical findings. Requires no therapy

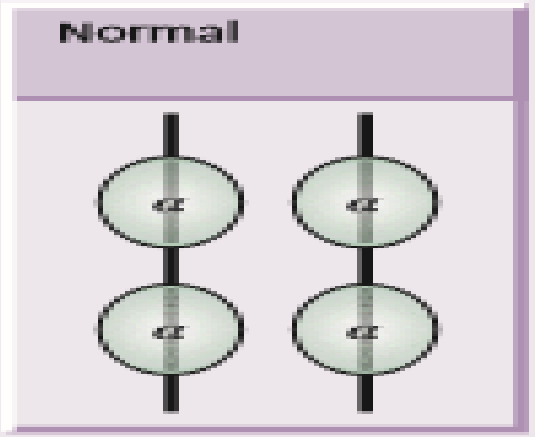
Chromosome 16

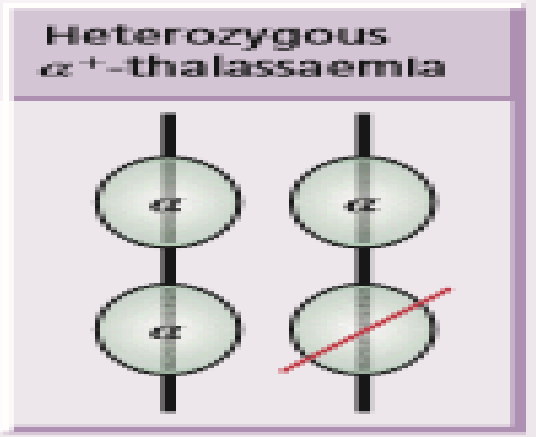


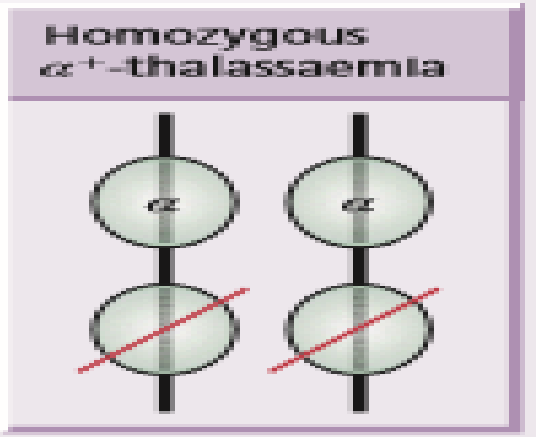


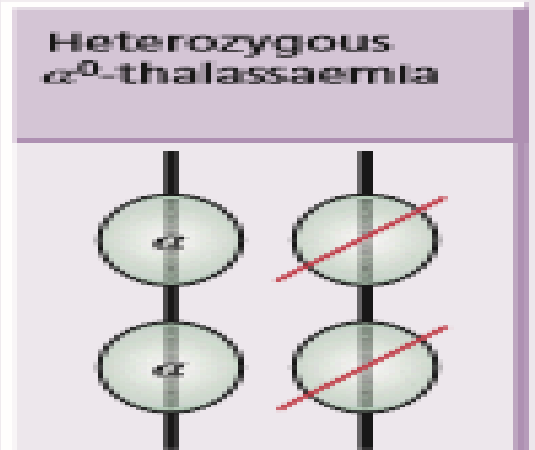


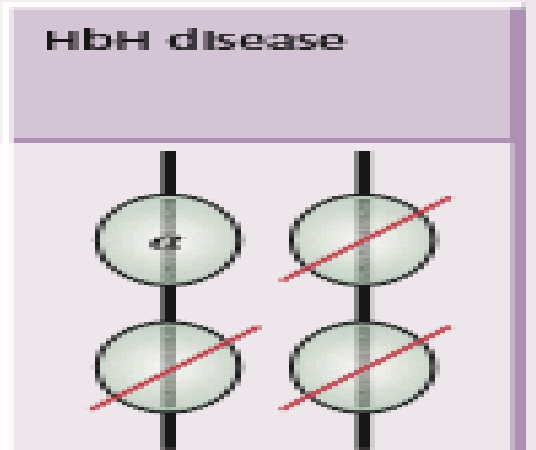

= Deleted gene

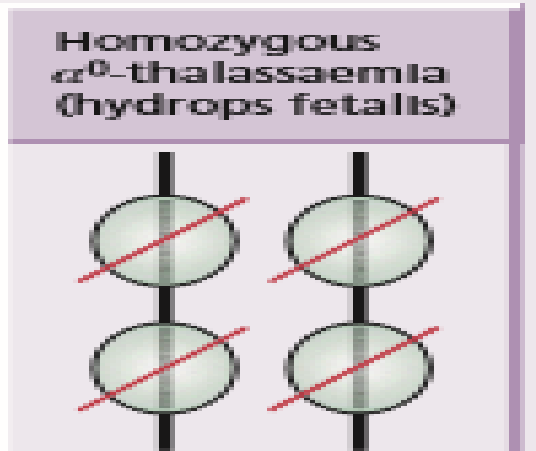












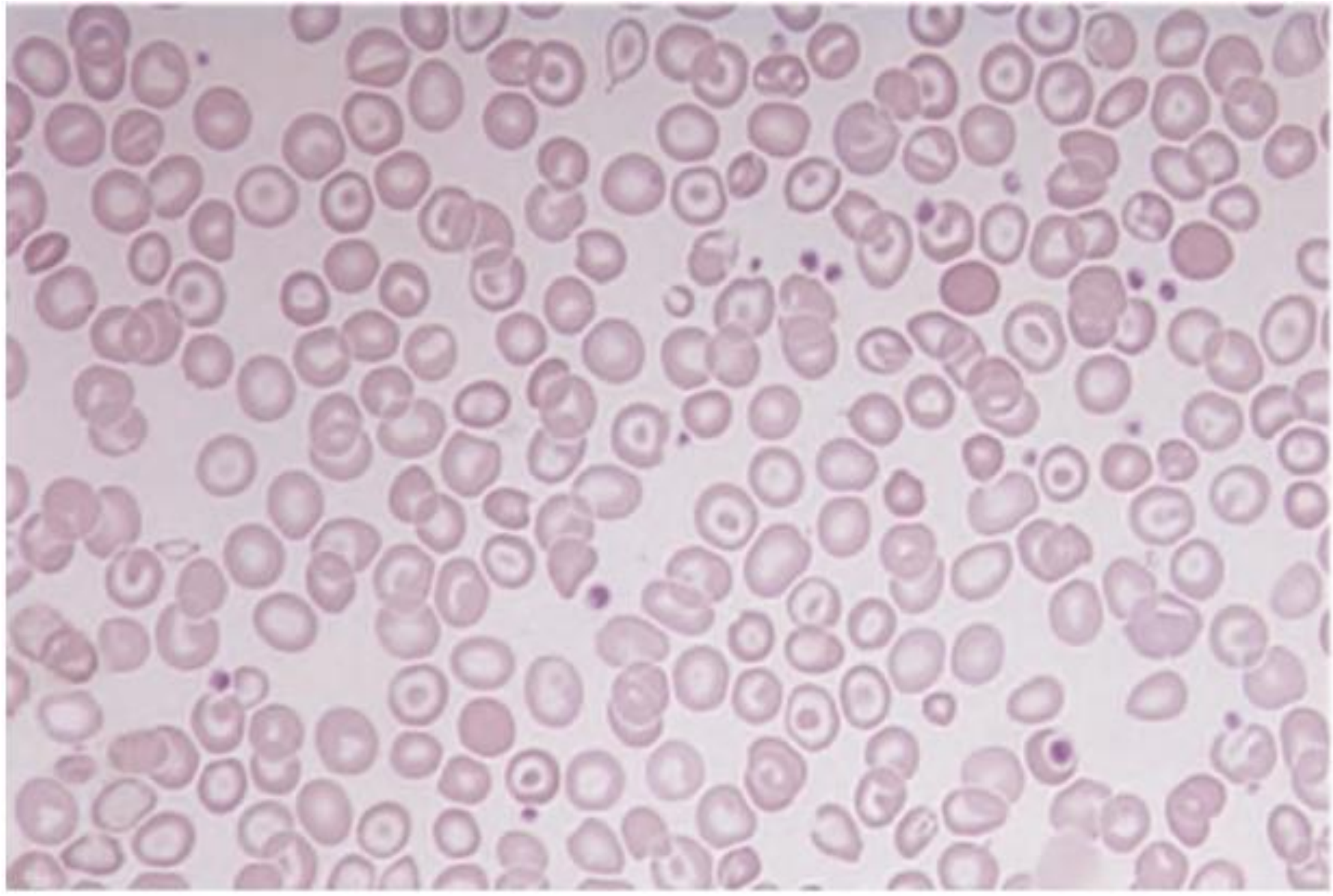
Haemoglobin H disease

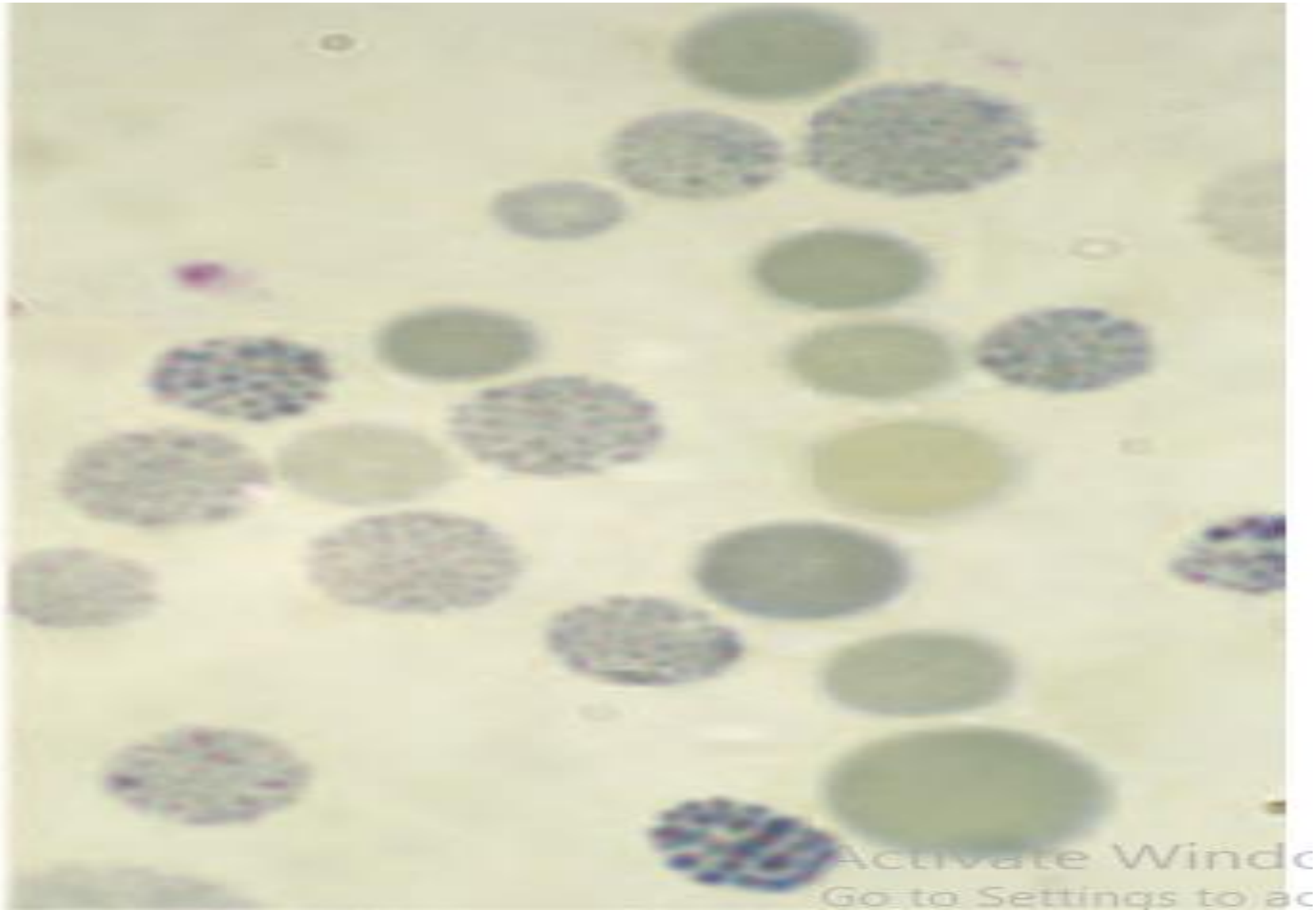
- (– –/–α) Three α genes deleted; only 1 functioning copy of the α globin gene/ cell. Clinical features variable. May be moderate anaemia with Hb 8.0– 9.0g/dL. MCV and MCH are decreased. Hepatosplenomegaly, chronic leg ulceration, and jaundice (reflecting underlying haemolysis).
- Infection, drug treatment, and pregnancy may worsen anaemia. Blood film shows hypochromia, target cells, NRBC and increased reticulocytes. Brilliant cresyl blue stain will show HbH inclusions (tetramers of β globin, β4, that have polymerized due to lack of α chains). Hb pattern consists of 2–40% HbH (β4) with some HbA, A2 and F.
- Treatment

Not usually required but prompt treatment of infection advisable. Give regular folic acid especially when pregnant. Splenectomy of value in some patients with HbH disease. Needs monitoring and may require blood transfusion.

Haemoglobin Bart’s hydrops fetalis

(− − /− −) Common cause of stillbirth in South East Asia. All 4 α globin genes aff ected. γ chains form tetramers (HbBart’s, γ4) which bind oxygen very tightly, with resultant poor tissue oxygenation. Fetus is either stillborn (at 34–40 weeks’ gestation) or dies soon after birth. They are pale, distended, jaundiced, and have marked hepatosplenomegaly and ascites. Haemoglobin is 76.0g/dL and the film shows hypochromic red cells, target cells, increased reticulocytes and nucleated red cells. Haemoglobin analysis shows mainly HbBart’s (γ4) with a small amount of HbH (β4); HbA, A2, and F are absent. In utero transfusions can aid survival. Long-term transfusions will be required.





β-Thalassaemia syndromes

β-Thalassaemia major This condition occurs on average in one in four offspring if both parents are carriers of the β-thalassaemia trait. Either no β chain (β0) or small amounts (β+) are synthesized. Excess α chains precipitate in erythroblasts and in mature red cells causing severe ineffective erythropoiesis and haemolysis that are typical of this disease. The greater the α-chain excess, the more severe the anaemia. Production of γ chains helps to ‘mop up’ excess α chains and to ameliorate the condition. Over 400 different genetic defects have been detected. Unlike α-thalassaemia, the majority of genetic lesions are point mutations rather than gene deletions. These mutations may be within the gene complex itself or in promoter or enhancer regions. Certain mutations are particularly frequent in some communities and this may simplify antenatal diagnosis aimed at detecting the mutations in fetal DNA.

β —

β —

THEN.....

β β

25%

Normal hemoglobin

β —

50%

Beta thal trait

— —

25%

Cooley's anemia

Adapted from Colley's Anemia Foundation, with permission.

Clinical features

1. Severe anaemia becomes apparent at 3–6 months after birth when the switch from γ- to β-chain production should take place. Typically the infant presents in the first year with failure to thrive, pallor and a swollen abdomen.

2. Enlargement of the liver and spleen occurs as a result of excessive red cell destruction, extramedullary haemopoiesis and later because of iron overload. The large spleen increases blood requirements by increasing red cell destruction and pooling, and by causing expansion of the plasma volume.

3. Expansion of bones caused by intense marrow hyperplasia leads to a thalassaemic facies and to thinning of the cortex of many bones with a tendency to fractures and bossing of the skull with a ‘hair-on-end’ appearance on X ray.

4. Thalassaemia major is the disease that most frequently underlies transfusional iron overload. Regular transfusions are usually commenced in the first year of life and unless the disease is cured by stem cell transplantantion, are continued for life. Also iron absorption is increased because of low serum hepcidin levels because of release of proteins, e.g. GDF 15 from increased numbers of early red cell precurssors in the marrow. In the children, failure of growth and delayed puberty are frequent, and without iron chelation, death from cardiac damage usually occurs in teenagers.

5. Infections occur frequently. In infancy, without adequate transfusion, anaemia predisposes to bacterial infections. Pneumococcal, Haemophilus and meningococcal infections are likely if splenectomy has been carried out. Yersinia enterocolitica occurs, particularly in iron-loaded patients being treated with deferoxamine; it may cause severe gastroenteritis. Iron overload itself also predisposes to bacterial infection, e.g. Klebsiella, and to fungal infection. Transfusion of viruses by blood transfusion may occur. As a result of reduction of deaths from cardiac iron overload by improved chelation therapy, infections now account for an increasing proportion of deaths in thalassaemia major.

6. Liver disease in thalassaemia is most frequently a result of hepatitis C but hepatitis B is also common where the virus is endemic. Human immunodeficiency virus (HIV) has been transmitted to some patients by blood transfusion. Iron overload may also cause liver damage.

7. Osteoporosis may occur in well-transfused patients. It is more common in diabetic patients with endocrine abnormalities.

8. Hepatocellular carcinoma incidence is increased in those with iron overload and chronic hepatitis B or C. Ultrasound and measurement of serum alphafetoprotein every 6 months is advisable in such patients.

Laboratory diagnosis

1. There is a severe hypochromic, microcytic anaemia with normoblasts, target cells and basophilic stippling in the blood film.
2. High performance liquid chromatography (HPLC) is now usually used as the first-line method to diagnose haemoglobin disorders. HPLC or haemoglobin electrophoresis reveals absence or almost complete absence of Hb A, with almost all the circulating haemoglobin being Hb F. The Hb A2 percentage is normal, low or slightly raised. DNA analysis is used to identify the defect on each allele important in antenatal diagnosis

Treatment

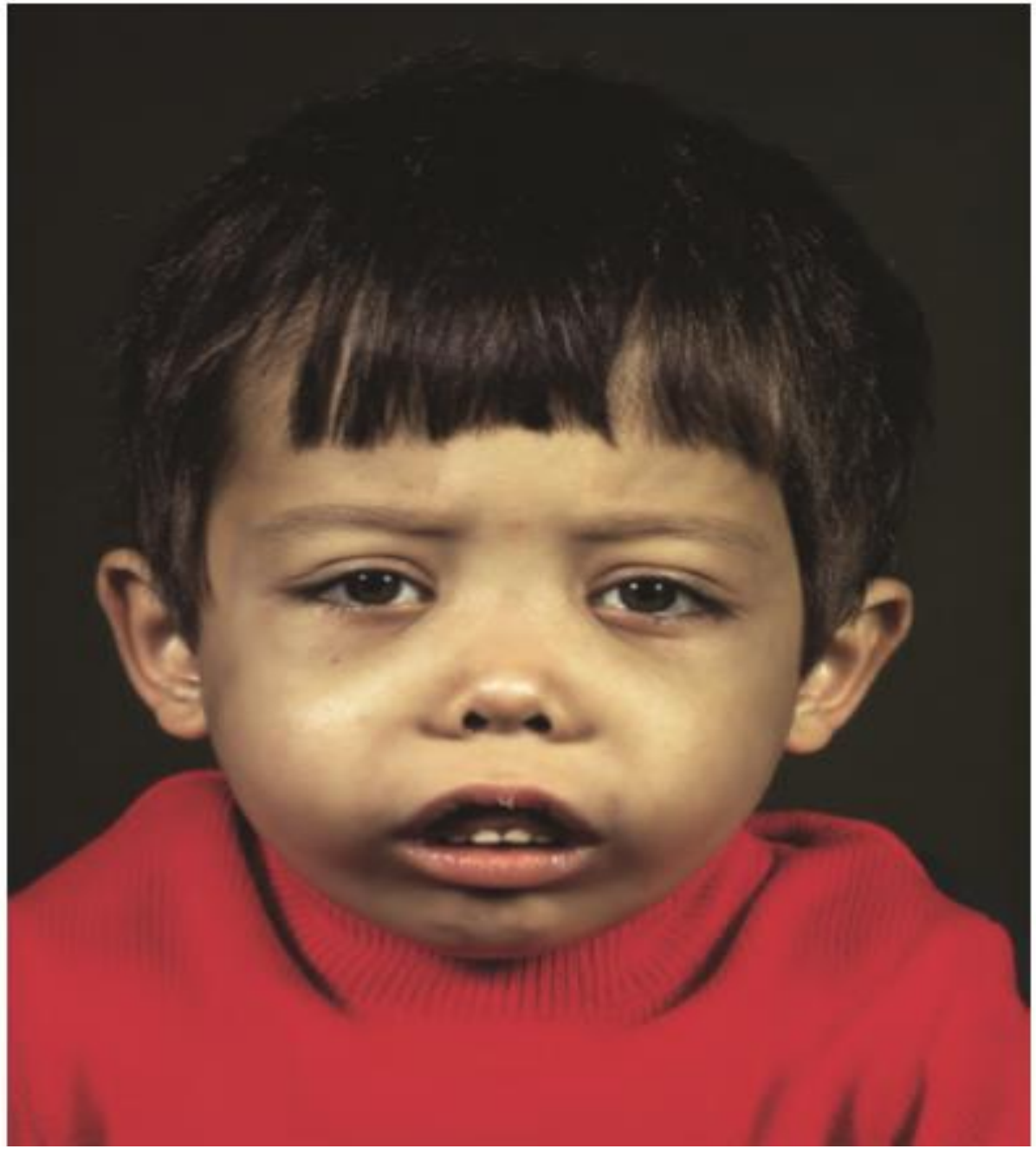
1. Regular blood transfusions are needed to maintain the haemoglobin over 100 g/L at all times. This usually requires 2–3 units every 4–6 weeks. Fresh blood, filtered to remove white cells, gives the best red cell survival with the fewest reactions. The patients should be genotyped at the start of the transfusion programme in case red cell antibodies against transfused red cells develop.
2. Iron chelation therapy is essential and available drugs have considerably improved life expectancy.
3. Regular folic acid (e.g. 5 mg/day) is given if the diet is poor.
4. Splenectomy may be needed to reduce blood requirements. This should be delayed until the patient is over 6 years old because of the high risk of dangerous infections postsplenectomy. The vaccinations and antibiotics to be given.
5. Endocrine therapy is given either as replacement because of end-organ failure or to stimulate the pituitary if puberty is delayed. Diabetes will require insulin therapy

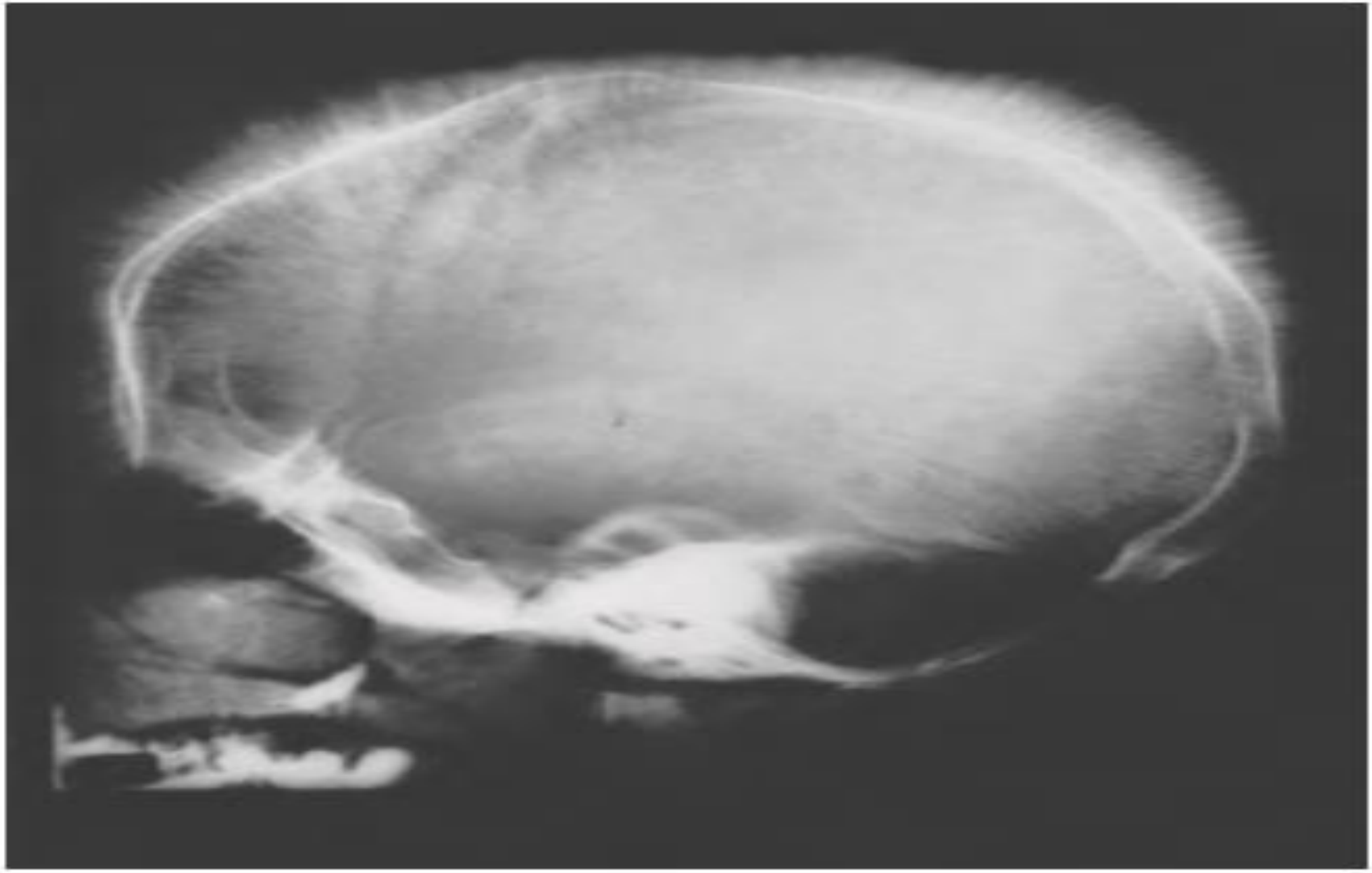
6. Immunization against hepatitis B should be carried out in all non-immune patients. Treatment for transfusion-transmitted hepatitis C is given if viral genomes are detected in plasma.

7. Allogeneic stem cell transplantation offers the prospect of permanent cure. The success rate (long-term thalassaemia major-free survival) is over 80% in well-chelated younger patients without liver fibrosis or hepatomegaly. A human leucocyte antigen matching sibling (or rarely other family member or matching unrelated volunteer) acts as donor. Failure is mainly a result of recurrence of thalassaemia, death (e.g. from infection) or severe chronic graft-versus-host disease.

β-Thalassaemia trait (minor)

This is a common, usually symptomless, abnormality characterized like α-thalassaemia trait by a hypochromic, microcytic blood picture (MCV and MCH very low) but high red cell count (>5.5 × 1012/L) and mild anaemia (haemoglobin 100–120 g/L). It is usually more severe than α thalassaemia trait. A raised Hb A2 (>3.5%) confirms the diagnosis. The diagnosis allows the possibility of prenatal counselling. If the partner also has β-thalassaemia trait there is a 25% risk of a thalassaemia major child.





THANK YOU