Clinical review

Fortnightly review

The thalassaemias

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The thalassaemias, the commonest monogenic diseases, are a family of inherited disorders of haemoglobin synthesis characterised by a reduced output of one or other of the globin chains of adult haemoglobin. They are likely to pose an increasing health problem for many developing countries during the early part of the new millennium.[1] This review focuses mainly on their control and management, a subject of increasing importance not only for parts of the world in which the disease is particularly common but for any country which has an immigrant population from these regions.

Summary points

- The thalassaemias, the commonest monogenic diseases, result from over 200 different mutations of the α and β globin genes
- Thalassaemia is associated with a wide spectrum of clinical disability, ranging from intrauterine death to extremely mild, symptomless anaemia
- Treatment with regular blood transfusion and adequate iron chelation therapy has improved the prognosis for the severe forms of thalassaemia
- Thalassaemia is a recessive disorder; symptomless carriers can be identified by simple haematological analysis
- The thalassaemias can be diagnosed by fetal DNA analysis following chorion villus sampling early in pregnancy
- Pregnant women of the appropriate racial groups, or people with mild hypochromic anaemias that do not respond to treatment with iron, should be screened for thalassaemia and offered expert counselling

Methods

This article is based on a literature survey of the field since 1980, recent monographs[2,3] and review series[4] that cover the thalassaemia field, and a detailed appraisal of the statistical analysis of the validity of screening techniques.[5] Various aspects of the disease were discussed at the 26th congress of the International Society of Haematology held in Singapore in August 1996, the published proceedings of which provide a valuable, up to the minute account of some aspects of current practice.[6-10]

Genetic control of haemoglobin

All the human haemoglobins consist of two different pairs of globin chains combined with haem, the iron containing moiety that binds oxygen. Embryonic haemoglobin has ζ chains and ε chains ($\zeta_2\varepsilon_2$); fetal haemoglobin, the synthesis of which continues throughout fetal life and declines after birth, has α chains and γ chains ($\alpha_2\gamma_2$), and in adults there is a major component called haemoglobin A ($\alpha_2\beta_2$) and a minor fraction, haemoglobin A_2 ($\alpha_2\delta_2$). The α-like chains—that is, ζ and α—are controlled by genes at the tip of the short arm of chromosome 16 and the genes that control the ε, γ, β, and δ chains form a linked cluster on chromosome 11 in the order ε, γ, δ, β. Both the α and γ genes are duplicated.

The sequence of DNA that comprises the globin genes and the chromosomal regions around them has been determined. Each gene consists of three coding regions (exons) and two non-coding regions (introns). When a globin gene is transcribed, a mirror image molecule called messenger RNA is copied from one of the strands of DNA of the particular gene. While it is still in the nucleus of the red cell precursor, the intron sequences are removed and the exon sequences spliced together in the correct order to form the template for the production of a globin chain. This processed molecule moves into the cytoplasm, where it acts as the blueprint whereby appropriate amino acids are strung together to form a definitive globin chain. In adult red cells α and β chains synthesised in this way combine with haem to form definitive haemoglobin molecules. There are also critical regulatory regions of DNA that are involved in ensuring that globin chains are produced in appropriate amounts in the correct tissues at the right time of development. The thalassaemias result from mutations or gene deletions that involve one or other of these complex steps.

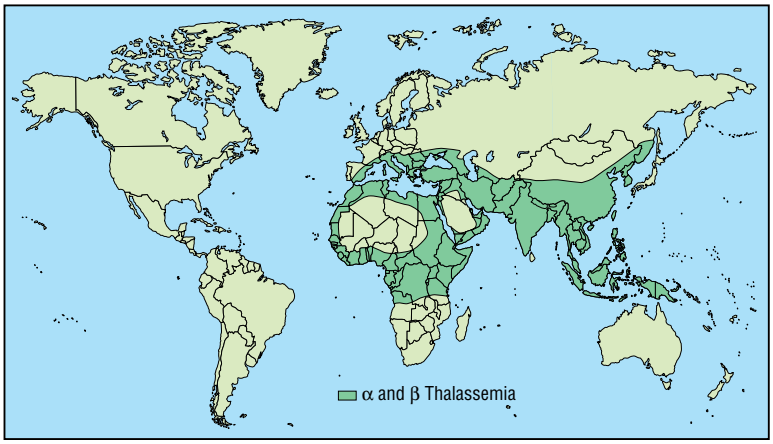

Fig 1 Regions where thalassaemia is endemic

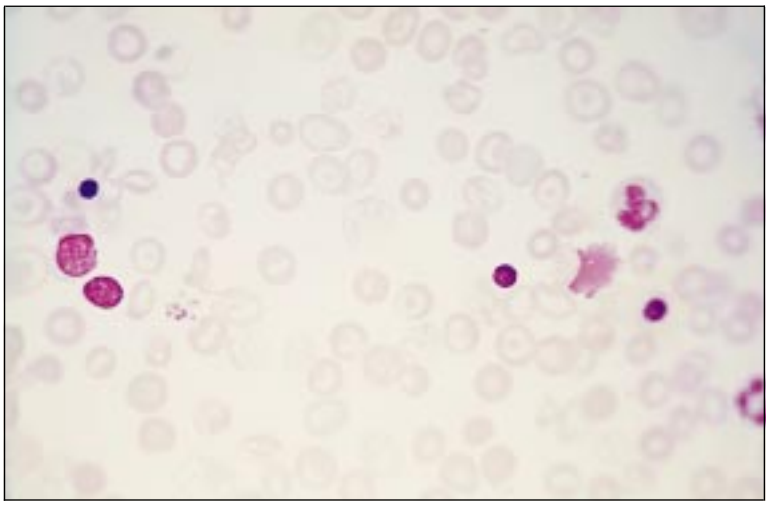

Fig 2 Peripheral blood film of a child with β thalassaemia major, showing morphological changes of red cells and presence of nucleated red blood cells

Definitions and classification

The thalassaemias are classified, according to the particular globin chain that is ineffectively produced, as the α, β, δβ and γδβ thalassaemias. The α and β thalassaemias are by far the most important. In many populations in which thalassaemia is common, the genes for structural haemoglobin variants such as haemoglobins S, C, and E are also common, so it is not unusual for individuals to inherit a gene for thalassaemia from one parent and that for a haemoglobin variant from the other. The most important diseases of this type are sickle cell thalassaemia and haemoglobin E thalassaemia.

Most of the important forms of thalassaemia are inherited in a Mendelian recessive fashion; carrier parents who are symptomless have a one in four chance of having a severely affected child.

Population distribution

The thalassaemias are distributed across the Mediterranean region, the Middle East, the Indian subcontinent, and throughout southeast Asia in a line stretching from southern China down the Malaysian peninsula to the Indonesian islands (fig 1). In many of these countries gene frequencies for the different thalassaemias and structural haemoglobin variants are high. As social conditions improve in developing countries and childhood mortality due to infection and malnutrition declines, children with thalassaemia who would previously have died early in life are now surviving long enough to require treatment. The reason for the very high frequency of thalassaemia is that carriers are protected from the consequences of infection with *Plasmodium falciparum* malaria.[11]

Clinical features

The β thalassaemias

The β thalassaemias[9 12] result from over 150 different mutations of the β globin genes that result either in the absence of the β globin chains (β° thalassaemia) or a reduction in their output (β⁺ thalassaemia). This results in imbalanced globin chain synthesis and production of an excess of α chains, which precipitate in the red cell precursors, leading to their destruction in the bone marrow or peripheral blood. This process causes severe anaemia (fig 2), which in turn leads to increased erythropoietin production and expansion of the ineffective bone marrow, bone deformities (fig 3), splenomegaly, and growth retardation (fig 4). Treatment by regular blood transfusion reverses these pathological mechanisms so that growth and development is normal.[13 14] But if excess iron derived from transfusion is not removed, patients die in the second or third decade from iron loading of the myocardium, liver, and endocrine organs (fig 5).

The clinical picture of inadequately treated β thalassaemia is characterised by profound anaemia, splenomegaly, bone changes, and being prone to infection. However, the severity of the disease is extremely variable and these so called major forms of the illness reflect the severe end of a spectrum that stretches from less severe anaemias, which do not require transfusion, through intermediate forms of β thalassaemia to the completely symptomless conditions that are identified only by chance. The reasons for this clinical heterogeneity are not entirely clear, although coexistent α thalassaemia, which reduces the

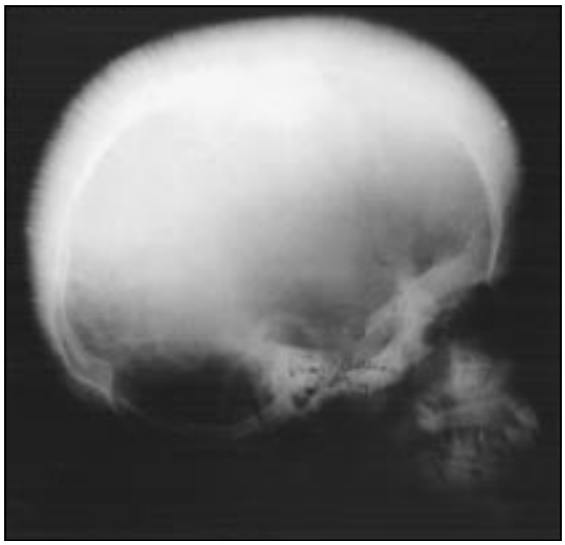

Fig 3 Radiological appearance of skull of a patient with severe β thalassaemia, showing a typical "hair on end" appearance due to marrow expansion

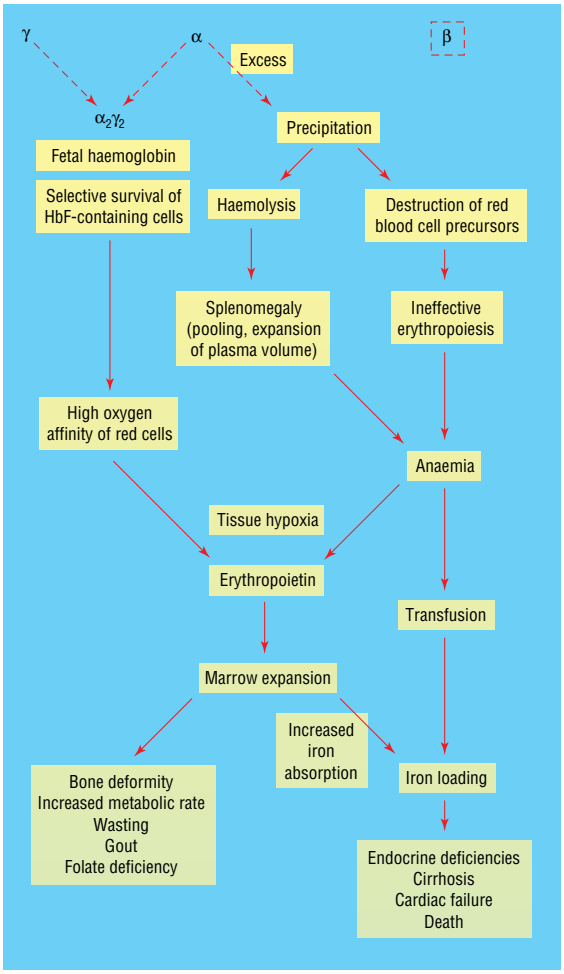

Fig 4 Summary of pathophysiology of β thalassaemia

excess of α globin chains that are produced, and a genetically determined ability to produce high levels of fetal haemoglobin, are important factors.[15]

Heterozygotes for β thalassaemia have mild hypochromic anaemia with small red cells and a raised concentration of haemoglobin A_2.

The α thalassaemias

The α thalassaemias[8 16] show several important differences from β thalassaemia. Because α chains are shared by fetal and adult haemoglobin the disease is manifest in both fetal and adult life. Furthermore, excess γ and β chains do not precipitate immediately in the bone marrow like α chains but produce the physiologically useless and unstable tetramers: γ_4, (haemoglobin Bart's) and β_4 (haemoglobin H). Since the α genes are duplicated the genetics of α thalassaemia is more complicated than that of β thalassaemia. The genetic makeup of normal individuals can be written αα/αα. Loss of both α genes on a chromosome is called α° thalassaemia, and is represented —/αα. Loss of one of the linked pairs of a globin genes is called α^+ thalassaemia, -α/αα. Usually these α genes are lost by deletion, though sometimes they are inactivated by a point mutation, as is the case in the β thalassaemias.

The homozygous state for α° thalassaemia produces intrauterine death with a profoundly anaemic and hydropic fetus: the haemoglobin Bart's hydrops fetalis syndrome. Mothers carrying babies of this type commonly have toxaemia of pregnancy and postpartum bleeding. Compound heterozygotes for α° and α^+ thalassaemia, —/-α, have a milder illness characterised by anaemia and splenomegaly which is called haemoglobin H disease. Carriers for α° thalassaemia (—/αα) and homozygotes for α thalassaemia (-α/-α) have a mild hypochromic anaemia, while carriers for α^+ thalassaemia have no haematological abnormalities.

Screening and prevention

The carrier states for all the important thalassaemias can be identified,[5 17] and methods for their prenatal diagnosis are well established. Where this approach is acceptable to families on religious and other grounds it is being adopted as a way of controlling thalassaemia.

Control programmes require screening, either at the population level if the disease is particularly common or, more usually, at the first visit to the antenatal clinic. Every woman of appropriate racial background should be screened for thalassaemia by a standard blood count with particular reference to the red cell indices. All the important carrier states for the different forms of thalassaemia are associated with a reduced mean cell haemoglobin concentration and cell volume (table 1). When a blood picture of this kind is encountered it should be followed by the estimation of the haemoglobin A_2 concentration, which is raised in all the common forms of β thalassaemia. The blood picture of a typical thalassaemia carrier in whom the haemoglobin A_2 concentration is normal may reflect the carrier state for α° thalassaemia (—/αα), the homozygous state for α^+ thalassaemia (-α/-α), or the carrier state for a rare form of β thalassaemia in which the haemoglobin A_2 concentration is normal. It is important therefore to obtain the help of an expert laboratory to distinguish between these possibilities. If a mother is a carrier for α° thalassaemia her pregnancy is at risk for the Bart's hydrops fetalis syndrome, whereas the worst possible outcome of a pregnancy involving a woman homozygous for α^+ thalassaemia is the much milder condition, haemoglobin H disease. The forms of β thalassaemia with normal haemoglobin A_2 concentrations may interact with the other thalassaemia genes to produce a severe phenotype.

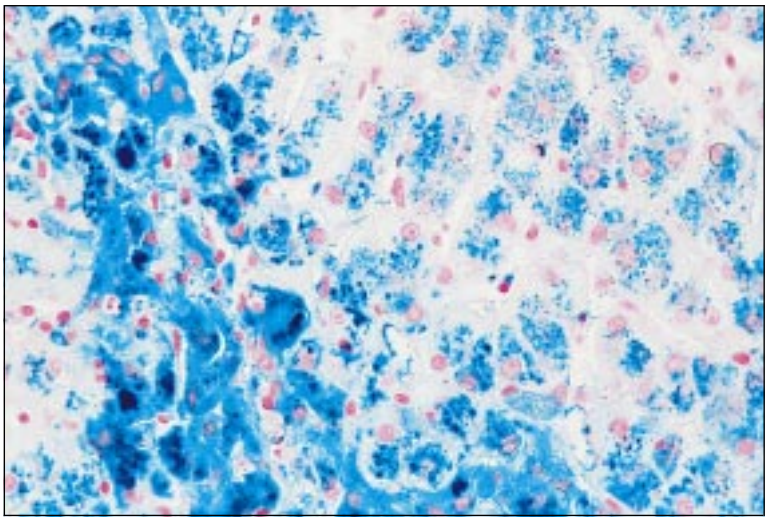

Fig 5 Iron stain of liver of child with β thalassaemia, showing extensive iron loading

Table 1 Values used for screening for α and β thalassaemia[5]

	Mean cell haemoglobin (pg) (2 SD)	Mean cell volume (fl) (2 SD)	% (SD) HbA_2
Normal	30 (3)	90 (10)	2.6 (0.5)
β Thalassaemia trait	21 (1)	70 (4)	4.9 (0.5)
α° Thalassaemia trait	22 (4)	70 (8)	1.9 (0.4)
Homozygous α^+ thalassaemia	23 (1)	72 (5)	2.0 (0.5)
β Thalassaemia trait with homozygous α thalassemia †	25 (1)	76 (3)	4.8 (0.5)

Usually, cut off values of a mean cell volume of <70 fl and a mean cell haemoglobin <25 pg are used to indicate HbA_2 estimation. However, in populations in which α and β thalassaemia are common, these values should be raised to 80 fl and 27 pg.
†This combination, or β thalassaemia trait and α° thalassaemia trait, produce a higher mean cell haemoglobin and mean cell volume; the HbA_2 concentration is raised.

Once a woman has been diagnosed as a carrier for one or other forms of thalassaemia her partner should be tested and the couple referred for expert genetic counselling. If they opt for prenatal diagnosis they should be referred as early as possible.

Early prenatal diagnosis, first by fetal blood sampling and later by chorion villus biopsy and direct analysis of the globin genes, is now extremely effective.[18] The error rate in experienced centres is now well under 1%, most of the mistakes resulting from either contamination of the fetal DNA by maternal tissue, non-paternity, or technical problems of DNA analysis.[19] The application of this approach in countries like Sardinia and Cyprus, where the disease is common, has greatly reduced the number of children born with the disease.[18] It has also been successful in certain communities in Britain, although as many as 50% of women at risk for carrying a thalassaemic child may still not be informed of the potential dangers of the disease and not offered prenatal diagnosis.[19]

Management

The management of severe forms of β thalassaemia entails regular blood transfusion backed up by chelation therapy to prevent the effects of iron accumulation. Children treated in this way, and who are able to comply with overnight infusions of desferrioxamine together with a low dose of vitamin C, grow and develop normally and do not succumb to the life threatening complications of iron overload.[13 14] Although it has been customary to follow progress with serum ferritin concentrations, recent work suggests that the total body iron load should be assessed by regular liver biopsy and direct estimation of the amount of iron.[20 21] Long term administration of desferrioxamine is associated with ocular and acoustic nerve complications[22] and, particularly in those treated with large doses and with a low total body iron concentration, with growth retardation and bone disease.[23] There is much interest in the oral chelating agent deferiprone, which is more acceptable to patients than desferrioxamine and carries a higher compliance rate.[10 24] However, this agent causes severe neutropenia and a transient arthritis in about 5% of patients and its long term efficacy has not yet been proved.

Bone marrow transplantation is effective, particularly if carried out in early life before complications such as iron loading have developed.[25] The main controversy revolves round the safety and efficacy of transplantation in older patients who already have iron loading. Transplantation in this group may carry a failure rate and mortality of up to 30%.[25]

Experimental approaches to the treatment of thalassaemia include the pharmacological stimulation of fetal haemoglobin synthesis and the development of somatic gene therapy to replace the defective globin genes. There have been some successes with the use of agents that raise fetal haemoglobin concentrations, but so far an ideal regimen has not been worked out and this type of treatment must remain experimental for the immediate future.[26] The administration of hydroxyurea, which reduces the frequency of painful crises in patients with sickle cell anaemia, also seems to be of value in managing sickle cell thalassaemia. The role of gene therapy is still uncertain.

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