Personal practice

Management of thalassaemia major

B MODELL AND M PETROU

Department of Obstetrics and Gynaecology, University College Hospital, and Faculty of Clinical Sciences, University College London

Although children with thalassaemia major in Britain are usually of Cypriot or Asian origin, a few are of Chinese or Italian extraction. Seventeen percent of the Cypriot population is heterozygous for the β^+ thalassaemia gene, which allows 10% of the normal amount of haemoglobin A (HbA) synthesis.⁴ The incidence of β thalassaemia trait is 10% or more among some groups of East African Asians and about 3% among Sikhs. Among Pakistanis with 6% incidence, the frequency of homozygote births is increased by a high rate of consanguineous marriage. The Asian form is usually β^0 thalassaemia (no HbA is made).

Since 1975 the Asian population in the UK has grown, while fetal diagnosis has reduced the birth-rate of thalassaemia major in the London Cypriot community.⁵ Thalassaemia is now therefore an increasing problem among the Asians of the Midlands and the North of England.

An expert group convened by the World Health Organisation has recently reviewed the management and prevention of the haemoglobinopathies.^{1,2} The recommended management scheme for thalassaemia major has become more intensive than that previously practiced by our unit.³

Presentation: the differential diagnosis of thalassaemia intermedia

Homozygous β thalassaemia is diagnosed on the basis of anaemia with a raised proportion of fetal haemoglobin (HbF) after 6 months of age, and the presence of β thalassaemia trait in both parents. Most homozygous patients present in the first year of life with a haemoglobin of 7 g/dl or less and the clinical picture of severe thalassaemia major. The major problem at presentation is to distinguish the minority with mild thalassaemia intermedia, since their management may be radically different. Thalassaemia intermedia is defined as a homozygous β thalassaemia syndrome that is milder than usual, so that the patient can survive without transfusion.

There may be many genetic reasons for a relatively mild disease.⁶ Consequently, the clinical picture ranges from a child with a haemoglobin of 7.5 g/dl and a severe disease just compatible with life to a child with a haemoglobin of 10 g/dl and minimal symptoms.

Management

The decision whether, and when, to start a patient with thalassaemia intermedia on regular transfusions and the associated iron chelation treatment may be remarkably difficult. As long as the patient grows well, eats well, sleeps well, does not have severe bone changes, and above all does not have a raised serum ferritin value indicating excessive gastrointestinal iron absorption, he should not be started on a regular transfusion programme. A benign picture is uncommon unless the mean haemoglobin is more than 8.5 g/dl, but patients may be remarkably well with a haemoglobin of around 7 g/dl, when more than 40% HbA is present. Late presentation (after age 2 years) with a haemoglobin of more than 8 g/dl and a raised serum bilirubin concentration (around 25 mol/l) are useful indicators of mild disease. These patients require careful monitoring and often need splenectomy. In Britain, most have finally been started on regular transfusion at anything from 3-16 years of age because of complications such as failure to thrive, iron overload of gastrointestinal origin, recurrent pathological fractures, or leg ulcers.

By comparison, the management of thalassaemia major is straightforward—regular transfusion, splenectomy when indicated, and treatment with iron chelating agents to control transfusional iron overload.

Transfusion. Our former practice was to raise the Hb value from about 9 g/dl to 14 g/dl by transfusion every 4-6 weeks, giving a mean Hb of about 11.5 g/dl,³ but there is good evidence from America,⁷

Italy,^{8,9} and Cyprus, where large numbers of patients are treated as day cases, in favour of a 'supertransfusion' scheme where the patients' Hb value is never allowed to drop below 12 g/dl and is raised regularly to 14 or 15 g/dl, by small transfusions every 2–3 weeks. The advantages of supertransfusion are excellent quality of life and suppression of the bone marrow so that abnormal cells are cleared from the peripheral blood. This abolishes both the excessive gastrointestinal absorption of iron associated with bone marrow expansion¹⁰ and the stimulus to hypersplenism, which has almost disappeared where patients are treated by supertransfusion.

In thalassaemia major, bone marrow expansion leads to blood volume expansion and introduces an important dilutional element in the anaemia.¹¹ Therefore, when β^0 thalassaemic patients are shifted from an intermediate scheme to supertransfusion there is a temporary increase in blood requirement for 6 months, but the marrow is gradually suppressed, blood volume returns to normal, and by one year the blood requirement returns to the initial value of about 360 ml/kg/year.^{8,9} In β^+ thalassaemia, which is slightly milder, supertransfusion causes a modest increase in blood requirement. Gastrointestinal iron absorption is also reduced to normal, so in β^0 thalassaemia high transfusion reduces rather than increases the total rate of iron loading, while in β^+ thalassaemia it remains constant. Finally, supertransfusion maintains the blood requirement at a minimum by preventing hypersplenism. It is now recommended for all forms of severe thalassaemia. Because it depends on frequent brief transfusions, patients can easily be treated as day cases.

In Britain most thalassaemic children are transfused every four weeks and stay overnight in hospital. If this pattern must be retained, it is suggested that the Hb value should be raised regularly from 11 g/dl to 15 g/dl (mean Hb 13 g/dl).

Splenectomy. Since there is increasing hope for a reasonable prognosis in thalassaemia, the long term risks of splenectomy assume greater importance. Early splenectomy increases the danger of life threatening infections indefinitely in thalassaemia,¹² and as patients live longer more of these infections will be seen (viz a recent pneumococcal septicaemia in a well treated patient of age 22 years whose spleen had been removed at age 7 years). It is wise to give immunisation with Pneumovax and prophylactic penicillin (125 mg bd). The patient must take the penicillin regularly; otherwise it may be positively dangerous because it can mask a serious infection if

taken only when the patient feels ill. One alternative is to give an injection of long acting penicillin each month before transfusion (to allow for monitoring any allergic reactions).

Arterial hypoxaemia and abnormalities of lung function are common in thalassaemia and may represent long range complications of splenectomy. They seem to be caused by microembolism of platelet aggregates in the lungs: in a group of splenectomised Thai patients platelet aggregation was prevented and the arterial oxygen tension normalised with aspirin or dipyridamole (Persantin).¹³ Pending more information, splenectomised thalassaemic patients should be treated with aspirin or dipyridamole (5 mg/kg daily in divided doses).

Splenectomy is indicated when hypersplenism increases the blood requirement to more than 1.5 times the standard values calculated by Modell³ and Gabutti *et al.*⁸ For high transfused patients (mean Hb >11.5 g/dl) the annual blood requirement should not exceed 500 ml/kg (whole prepared blood). It now seems, however, that 'partial vascular disconnection of the spleen' can reduce excessive blood requirement while retaining splenic function,¹⁴ so this approach should be investigated further. Patients so treated must subsequently be maintained on supertransfusion or hypersplenism may recur.

Iron chelation treatment. The life expectancy of high transfused thalassaemic patients with β^+ thalassaemia major who receive no treatment for iron overload is mean (SD) 16 (5) years—death is caused by cardiac failure as a result of iron deposition. Regular treatment with desferrioxamine (Desferal) whether by intramuscular injection or subcutaneous infusion, in doses as low as 20 mg/kg/day, leads to improved survival.¹⁵ Regular intramuscular injection of desferrioxamine at least 5 times weekly stabilises the body iron load at about 16 g and prevents the development of cirrhosis.^{16,17} Subcutaneous infusion of desferrioxamine from a portable syringe driver over 8 hours, from 3–7 nights per week is far more effective. It stabilises the body iron load at about 3 g in small children¹⁸ and causes impressive negative iron balance in heavily iron loaded patients.¹⁹ Large doses given intravenously at the time of transfusion may also cause excretion of a large amount of iron in the stools, even in patients who have been on long term chelation treatment.²⁰ A modest dose of vitamin C given orally (200 g daily) may double the iron excretion in response to desferrioxamine. If intensive treatment with subcutaneous infusion is started early, there is reasonable hope for a good

prognosis, including marriage and possibly even reproduction.

The present recommendation is to give an average weekly dose of desferrioxamine of at least 35 mg/kg/night, by subcutaneous infusion from a lightweight portable syringe driver (MS18, Graseby Dynamics). Preferably this should be given over 8 hours on 5 nights per week (50 mg/kg/night), but in case of difficulties with small children or non-compliant adolescents, it may be given over 3 nights (80 mg/kg/night). At least 5 ml of distilled water is needed per gram of drug or the solution, being hypertonic, will fail to disperse under the skin. Specially long, thick walled butterfly extension tubes which do not kink are available (Vygon or Graseby Dynamics). At the time of transfusion up to 6 g of desferrioxamine should be given intravenously over 8 hours. This can be done most conveniently by putting the drug in 20 ml of water in the patients' own syringe driver at the bedside, and inserting the butterfly needle into the rubber of the drip set. Vitamin C, 200 mg, is taken every time that desferrioxamine is infused. The effectiveness of treatment should be monitored by 6 monthly serum ferritin estimation.

Though past policy was to start intramuscular injections of desferrioxamine at 3 years of age, subcutaneous infusion should be started in newly presenting patients from the second or third transfusion onwards, for several reasons:

- (1) Because subcutaneous infusion is so effective, it is logical to combat iron overload, as far as possible, from the outset.

- (2) If 'the pump' is started in a small baby it is already familiar by the time the child becomes a toddler. An infusion lasting hours requires compliance, which may not be forthcoming if it is initiated at the age of 2 or 3 years.

- (3) Treatment is associated with two major crises for the parents—starting transfusion and starting 'the pump'. Combining the two spares them one or two years of dreading what sounds as drastic but is in fact a tedious form of treatment.

Problems of older patients

A cohort of adolescent and young adult patients is now appearing in every community where thalassaemia is common. They have special physical, emotional, and social problems. As a consequence of ill health and transfusional iron overload in their early years, many have failed to pass through puberty, and some have additional complications such as hypoparathyroidism or diabetes. In the Mediterranean countries, and probably elsewhere,

chronic hepatitis is common.²¹ They may have difficulty in gaining acceptance for higher educational courses or appropriate work, simply because of their diagnosis and former poor prognosis. Depression is common, and may lead to rejection of iron chelation treatment and, therefore, to death.

Failure of puberty is a consequence of disturbance of the hypothalamic/pituitary axis secondary to iron overload and is usually associated with growth retardation at 11 years onwards. Replacement treatment is indicated and studies are under way to discover whether sex hormones, gonadotrophins, or even pituitary hormone releasing factors are the treatment of choice. Optimal treatment may depend on the individual patient, so it should be started only in close consultation with a reproductive endocrinologist.

Diabetes is a common complication in thalassaemic adolescents and young adults. When there has been poor compliance with iron chelation treatment, diabetes may lead to a further deterioration in compliance. As insulin and desferrioxamine may be given through the same needle with no adverse effect, the morning insulin can be given through the pump butterfly just before removing the desferrioxamine infusion. This scheme has the added advantage of encouraging desferrioxamine compliance in these especially vulnerable patients.

Prevention

Fetal diagnosis. Fetal diagnosis for thalassaemia at 18 weeks' gestation has proved highly acceptable to Cypriots (98% uptake) but somewhat less so to Asians (60% uptake).⁵ Diagnosis at 8–12 weeks' gestation is now possible by combining chorionic villus sampling with restriction enzyme analysis of the fetal DNA thus obtained.²² Since this permits suction termination of affected pregnancies before 12 week's gestation, it will probably increase the acceptability of prevention still further.

Prospective screening. For thalassaemia the diagnosis usually requires family studies because it depends on linkage between the β thalassaemia gene and polymorphic restriction enzyme sites in the flanking non-coding regions of DNA.²³ Gene mapping is available in England (see postscript) and should be done prospectively for all families with a thalassaemic child where the parents are still of reproductive age, so that they can find out whether first trimester diagnosis is a possibility in further pregnancies. Prospective screening for thalassaemia trait together with genetic counselling should be offered to siblings of the parents and their offspring,

and they should be put in touch with one of the thalassaemia associations (see postscript).

Heterozygote diagnosis

Heterozygote diagnosis and genetic counselling is now of the first importance for members of at risk communities. When a child is incidentally found to have β thalassaemia trait, certainly one parent is a carrier, and the chance that both are is 1/6 among Cypriots and 1/6–1/30 among Asians, depending on their social group. Thalassaemia should always be suspected in a child not of North-European origin when the routine Coulter blood count shows a mean cell haemoglobin (MCH) value of less than 24 pg, and a definitive diagnosis should be made by HbA₂ estimation. In our experience this is a reliable indicator of β thalassaemia trait even in the presence of iron deficiency. β thalassaemia trait is by far the commonest cause of microcytosis among Cypriots, but among Asians the lower incidence of β thalassaemia trait and a high incidence of α thalassaemia and iron deficiency may cause confusion.

Prospects for future improvements in treatment

It is important to discuss realistic future possibilities with parents and patients, to help maintain an optimistic approach. The following possibilities, discussed in references 1,6, and 23 show varying degrees of promise.

(1) **Oral iron chelating agents.** Some promising new compounds presently under investigation could become available in three to four years, if they prove safe.

(2) **Transfusion of young red cells.** This could lead to fewer transfusions and a slower rate of iron deposition, if it could be managed economically.

(3) **Bone marrow transplantation.** The first successful transplants have been achieved,²⁴ and most families are aware of this possibility. When successful methods are available it will be important to request HLA typing of the patients' immediate family to establish whether a potential donor exists for future use. Where the patient is the offspring of a first cousin marriage, it is reasonable to extend the search into the wider family.

(4) **Gene replacement and gene switching.**²³ These offer a hopeful long term prospect after a great deal more fundamental work has been done.

Postscript

For gene mapping for thalassaemia, contact Dr John Old, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford. The UK Thalassaemia Society, 117 Nightingale Lane, London N8 offers contacts and a newsletter (in English) for families of thalassaemic children, and for heterozygotes detected by screening. Though predominantly Cypriot it is interested in patients of all ethnic groups.

We are grateful for financial support from the UK Thalassaemia Society and Prince Sultan bin Abdul Aziz of Saudi Arabia. This work is sponsored by the WHO.

References

- 1 WHO Working Group. Hereditary anaemias: genetic basis, clinical features, diagnosis and treatment. *Bulletin of the World Health Organisation* 1982;60:643–60.
- 2 Community control of hereditary anaemias: memorandum from a WHO meeting. *Bulletin of the World Health Organisation* 1983;61:83–80.
- 3 Modell B. Total management of thalassaemia major. *Arch Dis Child* 1977;52:489–500.
- 4 Angastiniotis MA, Hadjiminis MG. Prevention of thalassaemia in Cyprus. *Lancet* 1981;ii:369–70.
- 5 Modell B, Ward RHT, Fairweather DVI. Effect of introducing antenatal diagnosis on reproductive behaviour of families at risk for thalassaemia major. *Br Med J* 1980;280:1347–50.
- 6 Weatherall DJ, Clegg JB. *Thalassaemia syndromes*. 3rd edition. Oxford: Blackwell Scientific Publications, 1981.
- 7 Propper RD, Button LN, Nathan DG. New approaches to the transfusion management of thalassaemia. *Blood* 1980;55:55–60.
- 8 Gabutti V, Piga A, Nicola P, et al. Different haemoglobin levels and blood requirement in thalassaemia. *Arch Dis Child* 1982;57:156–8.
- 9 Masera G, Terzoli S, Avanzini A, et al. Evaluation of the supertransfusion regimen in homozygous β -thalassaemia children. *Br J Haematol* 1982;52:111–3.
- 10 de Alarcon PA, Donovan ME, Forbes GB, Landaw SA, Stockman JA. III. Iron absorption in the thalassaemia syndrome and its inhibition by tea. *N Engl J Med* 1979;300:5–8.
- 11 Blendis LM, Modell CB, Bowdler AJ, Williams R. Some effects of splenectomy in thalassaemia major. *Br J Haematol* 1974;28:77–87.
- 12 Smith CH, Erlandson ME, Stern G, Hilgartner MW. Post-splenectomy infection in Cooley's anemia. *Ann NY Acad Sci* 1964;119:748–57.
- 13 Wasi P, Fucharoen S, Youngchaiyud P, Sonakul D. Hypoxemia in thalassaemia. *Birth Defects* 1982;18: no.7:213–8.
- 14 Girot R, Revillan Y, Barritault L, Gire R, Beranger A, Jeannel F. Abstracts. Budapest: 19th Congress of the International Society for Haematology, 1982.
- 15 Modell B, Letsky EA, Flynn D, Peto R, Weatherall DJ. Survival and desferrioxamine in thalassaemia major. *Br Med J* 1982;284:1081–84.
- 16 Sephton-Smith R. Chelating agents in the diagnosis and treatment of iron overload in thalassaemia. *Ann NY Acad Sci* 1964;119:776–88.
- 17 Barry M, Flynn DM, Letsky EA, Risdon RA. Long-term chelation therapy in thalassaemia major: effect on liver iron concentration, liver histology, and clinical progress. *Br Med J* 1974;ii:16–20.

- ¹⁸ Pippard MJ, Callender ST, Letsky EA, Weatherall DJ. Prevention of iron-loading in transfusion-dependent thalassaemia. *Lancet* 1978;i:1178-81.
- ¹⁹ Propper RD, Cooper B, Rufo RR, *et al.* Continuous subcutaneous administration of desferrioxamine in patients with iron overload. *N Engl J Med* 1977;**297**: 418-23.
- ²⁰ Pippard MJ, Callender ST, Finch CA. Ferrioxamine excretion in iron-loaded man. *Blood* 1982;**60**:288-94.
- ²¹ Masera G, Jean G, Gazzola G, Novakova M. Role of chronic hepatitis in development of thalassaemic liver disease. *Arch Dis Child* 1976;**51**:680-5.
- ²² Old J, Ward RHT, Petrou M, Karagözü F, Modell B, Weatherall DJ. First-trimester fetal diagnosis for the haemoglobinopathies: 3 cases. *Lancet* 1982;ii:1413-6.
- ²³ Weatherall DJ. *The new genetics and clinical practice*. London: The Nuffield Provincial Hospitals Trust, 1982.
- ²⁴ Thomas ED, Buckner CD, Sanders JE, *et al.* Marrow transplantation for thalassaemia. *Lancet* 1982;ii:227-9.

Correspondence to Dr B Modell, University College Hospital, Obstetric Hospital, Huntley Street, London WC1E 6AU.