Short reports

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Beneficial effects of transfusing a patient with nontransfusion-dependent thalassaemia major

β -Thalassaemia major presents with progressive anaemia in early infancy which is so severe that in up to 90% of cases death is inevitable without transfusion. Transfusion-independent β -thalassaemia major has become known as thalassaemia intermedia, and the survival of these cases is well documented through to middle age (Bannerman *et al.*, 1967). Chronic anaemia, however, restricts life and growth, physical activity is severely curtailed, and puberty is late and sometimes incomplete (Canale *et al.*, 1974). Marrow hypertrophy is associated with a high cardiac output and recurrent fractures. A case of nontransfusion-dependent β -thalassaemia major is presented which had a number of parameters improved by the institution of a regular high transfusion regimen.

Case report

The second child of Greek Cypriot parents was born in the United Kingdom in October 1960. She presented at the age of 13 months after breaking her left arm in a fall. Before this she had had recurrent upper respiratory tract infections and gained weight poorly. Examination showed obvious pallor and hepatosplenomegaly, both weight and height were on the 3rd centile, and a soft ejection systolic murmur at the lower left sternal edge was noted. Hb was 6.9 g/dl, and the diagnosis of β -thalassaemia major was established with a Hb-F level of 32%. She was not transfused, and with folic acid supplements the mean Hb over the next 2 years remained at about 7 g/dl, gradually falling until at the age 3½ years with a Hb level of 5 g/dl she fractured both the left arm and right leg. It was decided that splenectomy was indicated for hypersplenism, large size of spleen (9 cm below the costal margin), and periodic abdominal pain thought to be related to the spleen. Histology of the spleen showed a myeloid reaction with some fibrosis. She was transfused immediately before the operation and the Hb level afterwards stabilized between 7 and 8 g/dl. During the remainder of her first decade she grew steadily along the 3rd centiles for height and weight, she broke her left arm at 6 years, and Hb remained constant at about 7–8 g/dl. She developed not only a thalassaemic but also an adenoidal facies. She had large tonsils and 'chronic serious otitis' with bluish tympanic membranes and she was going deaf. Adenotonsillectomy and myringotomy were recommended and at operation marrow was removed from the middle ear chamber. Grommets were inserted in both tympanic membranes.

From the age of 9 years height velocity began to fall from normal until at 12½ years she was 6 cm below the 3rd centile. She sustained a hearing loss of 60 decibels left and 30 decibels right for air conduction and wore hearing aids. She was unable to join in games at school because of shortness of breath. She had no signs of puberty (grade 1) and an investigation of endocrine function (McIntosh, 1976, Case 3) showed that despite insignificant quantities of intravenously loaded iron she had significant endocrine impairment of both adrenal and pancreas. At this stage it was thought reasonable to give regular blood transfusions to maintain mean Hb at about 11 g/dl (approximately every 6 weeks). It was thought this might (a) suppress marrow hyperplasia thus leading to improved hearing and less pathological fractures; (b) improve her exercise intolerance; (c) improve her height velocity; (d) improve her endocrine function; (e) offset any delay in the onset of puberty. Her serum ferritin before regular transfusion therapy was 330 mg/ml (mean for adult females 35).

In the 2 years after initiation of transfusion she abandoned her hearing aids, audiometrically halving her decibel loss. Insulin release from the pancreas in response to an oral glucose load became normal (Fig. 1); glucose values remained normal. Adrenal function tested by minimal adrenal stimulation test (Landon *et al.*, 1967) became normal (Fig. 2). At school she now plays netball and rounders with no difficulty. 6 months after starting transfusions (13 years) she entered stage 2 of puberty and after 20 months she had menarche. Her height velocity which in the year before transfusion was 2 cm/year improved to 9.5 and 7 cm/year in the 2 subsequent years of transfusion. Serum ferritin after 2 years and 35 pints of blood was 1350 mg/ml.

FIG. 1.—Oral glucose tolerance test. Insulin values in μ U/ml fasting and at periods after a 50 g oral glucose load. Δ , $\times 2$ tests before transfusion therapy; $\times$, 18 months after regular transfusion therapy; $\bullet$, 2 years after regular transfusion therapy.

FIG. 2.—Physiological adrenal stimulation test. Plasma cortisol ($\mu\text{g}/100\text{ ml}$) is plotted in the dexamethasone-suppressed patient given five increasing doses of intravenous tetracosactrin. Black columns represents the mean of 2 tests before transfusion therapy was started, the shaded columns represent 18 months after starting, and the open columns 2 years after starting regular transfusion therapy.

Discussion

The complications in the above case are almost certainly not unique. The hearing abnormalities are present in many cases both transfused and not transfused, but are more evident in those not transfused (J. W. P. Hazell, N. McIntosh, and C. B. Modell, unpublished). The improvement in height has been well recorded previously (Brook *et al.*, 1969). The endocrine impairment is interesting. In high transfused patients it is probably due to iron deposition in the endocrine glands similar to that seen in haemochromatosis, but it is also known that cases of thalassaemia intermedia develop endocrinopathy (Bannerman *et al.*, 1967). In these cases it has been presumed due to increased gastrointestinal iron absorption with deposition in endocrine organs. If serum ferritin levels do indeed represent total body iron (Jacobs *et al.*, 1972) then the iron load in this case was originally low and endocrine function has improved as iron load has increased. It seems likely that hypoxaemia in the untransfused patient owing to a combination of anaemia and the shift to the left of the oxygen dissociation curve has depressed endocrine function. These have been reversed with transfusion. There is some evidence in mice that hypoxia in addition to iron deposition is necessary to cause cardiotoxicity (Necheles, Beard, and Allen, 1969). The alternative possibility is that iron absorbed gastrointestinally is more toxic to the endocrine glands, but this is difficult to prove. Puberty is always delayed in patients with thalassaemia whether transfused or not (Canale *et al.*, 1974). It is impossible in this case

to prove that transfusion initiated puberty, but the growth velocity and puberty grading improved so dramatically that it seems likely that this was the case.

Summary

A case of nontransfusion-dependent thalassaemia major is presented showing growth retardation, recurrent fractures, late onset of puberty, deafness, and endocrine impairment of pancreas and adrenal gland. Regular blood transfusion to maintain mean haemoglobin at about 11 g/dl improved all these problems. It is suggested that this improvement was related to improved tissue oxygenation.

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Phalangeal microgeodic syndrome of infancy

The phalangeal microgeodic syndrome of infancy was first described as an entity by Maroteaux in 1970, but seems to be poorly documented in the subsequent published reports. We record a further case.