Growth of Children with Thalassaemia: Effect of Different Transfusion Regimens

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Kattamis, C., Toulitos, N., Haidas, S., and Matsaniotis N. (1970). *Archives of Disease in Childhood*, 45, 502. **Growth of children with thalassaemia: effect of different transfusion regimens.** Growth was studied in 74 children with homozygous β -thalassaemia aged 1 to 11 years, treated with three different transfusion regimens.

In group I (38 cases) haemoglobin levels were maintained above 8 g./100 ml.; in group II (14 cases), pretransfusion haemoglobin levels ranged between 6 and 8 g./100 ml.; in group III (22 children), pretransfusion haemoglobin levels were below 6 g./100 ml.

Children in group I grew normally, both in weight and height; those in groups II and III were retarded, particularly those in group III.

Frequent transfusions, in spite of their disadvantages, at present constitute the treatment of choice.

Homozygous β -thalassaemia (thalassaemia major) is a severe chronic haemolytic anaemia due to an inherited defect of β -chain synthesis. The clinical symptoms of the untreated disease are extreme anaemia, mongoloid facies, and hepatosplenomegaly, together with growth retardation, and malnutrition, retardation of bone age, severe osteoporosis with spontaneous fractures, and increased susceptibility to infections.

Before the advent of transfusion treatment, patients died of severe anaemia at a very young age, but life expectancy increased considerably after the introduction of transfusions (Erlandson, Brilliant, and Smith, 1964). The indications for transfusion are still a matter for debate. Some years ago a transfusion was generally given either when the patient became symptomatic, or when a low Hb level was reached, usually 5.0 to 6.0 g./100 ml. (Schorr and Radcliff, 1964). More recently a different policy has been advocated. Since most symptoms seem to be secondary to severe anaemia and to bone marrow hyperplasia with ineffective erythropoiesis, it was thought that regular frequent transfusions, by maintaining higher Hb levels, would have a beneficial effect on many of the clinical manifestations, including growth retardation, bone changes, and splenomegaly, as well as on life expectancy

(Wolman, 1964; Orsini *et al.*, 1968). However, contradictory results have been reported on the effectiveness of different transfusion regimens in maintaining normal growth (Erlandson *et al.*, 1964; Johnston and Krogman, 1964; Johnston, Hertzog, and Malina, 1966; Brook *et al.*, 1969).

In this report, data are presented on the growth of 74 patients with homozygous β -thalassaemia, who were under three different transfusion regimens.

Patients and Methods

Studies were made of 74 children with thalassaemia major (39 boys and 35 girls). The haematological data obtained from each patient included Hb, haematocrit, red cell counts and morphology, MCV, MCH, MCHC, reticulocyte and nucleated red cell counts, fetal Hb, starch gel Hb electrophoresis, and quantitation of HbA₂. Routine laboratory procedures were used for these determinations (Dacie and Lewis, 1963). The diagnosis of homozygous β -thalassaemia was established and confirmed by the presence of β -thalassaemia trait in both parents.

Patients with the clinical picture of thalassaemia intermedia and Hb levels of 7–10 g./100 ml. were excluded. They were found to have HbH disease, high F thalassaemia, or microdrepanocytic disease. Patients older than 11 years were also excluded, so that our groups could be matched for age.

Measurements of body weight, height, and recumbent length were obtained according to the recommendations

TABLE I
Groups of Patients with Homozygous β -thalassaemia

Groups	Pre-transfusion Hb (g./100 ml.)	No. of Cases	Males	Females	Age (yr.)		
					Mean	SD	Range
I	> 8	38	20	18	4.25	± 1.7	1-11
Ia		33	17	16	3.1	± 1.1	1-9
Ib		5	3	2	6.1	± 2.1	5-11
II	6-8	14	8	6	4.6	± 3.37	1-10
III	< 6	22	11	11	4.0	± 2.5	1-11
Total		74	39	35			1-11

of the Children's Medical Center, Boston. The weight and height of each patient on his last visit to our department were entered on the centile chart of this Center. Serial measurements were obtained for most patients.

On the basis of pretransfusion Hb levels and the

frequency of transfusions, patients were divided into three groups (Table I).

Group I consisted of 38 children, in whom Hb was maintained above 8 g./100 ml. In 33 children (group Ia), aged 1-9 years, frequent transfusions were initiated as soon as thalassaemia was diagnosed, whereas the regimen of the remaining 5 children (group Ib), aged 5-11 years, was changed to frequent transfusions for at least the last three years.

Group II included 14 patients, aged 1-10 years, whom we were unable to follow up regularly; their pretransfusion Hb ranged from 6 to 8 g./100 ml. These patients either were of very low socio-economic status or had to travel a very long distance for transfusion.

Group III comprised 22 patients, aged 1-11 years, who were transfused only when Hb fell below 6 g., usually below 5 g./100 ml. All three groups were matched for age. The mean age in years was 4.25 for group I, 4.6 for group II, and 4.0 for group III.

Results

Fig. 1 shows how weight and height of the 39 male patients fell on the centile chart. The weight of those in group I ranged from the 3rd to the 100th centile. In only 1 out of 20 was the weight below the 10th centile. The weight of males in group II was considerably lower, and in 4 out of 8 it was below the 10th centile. In group III the weight of all but 2 children was below the 10th centile.

The height of the three groups of boys followed the same pattern as the weight. Height was normally distributed in group I, in which only one boy was below the 10th centile. Height was retarded in both groups II and III, 5 boys in group II and 9 in group III being below the 10th centile.

A comparable pattern of growth was observed in 35 girls (Fig. 2). Weight and height in group I were normally distributed, whereas in groups II and III, particularly the latter, they tended to fall in the lower centiles.

The differences in weight and height between the groups are shown in Table II. The mean centile for weight in group I was 61.2 and that for height 55.9; in both groups II and III the means for weight

FIG. 1.—The height and weight in 39 boys with thalassaemia major.

TABLE II

Centiles for Weight in Three Groups of Patients

Groups	No. of Cases	Centiles					
		Weight			Height		
		Mean	± SD	Range	Mean	± SD	Range
I	38	61.2	28.7	3-100	55.9	32.2	3-100
Ia	33	60.9	22.9	3-100	56.8	28.9	3-100
Ib	5	62.5	25.9	18-90	50.0	33.9	10-97
II	14	22.5	17.8	3-60	22.2	24.7	3-97
III	22	9.9	7.8	0-50	7.0	6.4	0-25
Statistical analysis:		$p < 0.001$			$p < 0.001$		
I : II		$p < 0.001$			$p < 0.001$		
I : III		$p < 0.001$			$p < 0.001$		
II : III		$p = 0.02$			$p < 0.001$

FIG. 2.—The height and weight in 35 girls with thalassaemia major.

FIG. 3.—Growth chart of a girl who started intensive transfusions at 5 years.

and height were significantly lower. It is clear that patients in whom high Hb levels were maintained grew at a normal rate; while growth was retarded in those whose Hb was maintained at lower levels.

Fig. 3 illustrates the growth curves of a girl in whom Hb was maintained at 5–7 g./100 ml. for the first 5 years of life, and who had been splenectomized at the age of 3. Her growth was retarded at 5 years, both weight and height being below the 3rd centile. She was then given frequent transfusions so that Hb maintained at 8–12 g./100 ml.; her growth rate accelerated considerably, and when aged 9 both weight and height had risen to the 75th centile.

Discussion

Growth patterns in untreated children with homozygous β -thalassaemia have not been precisely studied, though a generally 'retarded' status is consistently mentioned. Johnston and Krogman (1964) concluded that growth was altered both in terms of statual expectation and of rate of growth.

Wolman (1964) noted that patients treated with intensive transfusion therapy appeared in better health, and their growth was closer to normal than those transfused only when Hb had fallen to low levels. On the other hand, Johnston *et al.* (1966) found that growth retardation was evident only after the fourth year of life, and that it was unrelated to pretransfusion Hb levels. Recently, Brook *et al.* (1969) showed that patients maintained with Hb levels above 6.6 g./100 ml. had a normal prepubertal growth pattern.

In our study the patients were carefully selected so that each group was more or less homogeneous as to pretransfusion Hb levels. Patients in group I were transfused when Hb fell to about 8g./100 ml. Similar levels are usually encountered in patients with certain types of congenital haemolytic anaemias, such as haemoglobinopathy H, micro-drepanocytic anaemia, and congenital spherocytosis; as a rule such patients grow normally. Normal growth has also been reported in patients with thalassaemia intermedia (Erlandson *et al.*, 1964), and haemoglobinopathy H (Kattamis *et al.*, 1968).

Our results indicate that the growth of thalassaemic children during the first decade largely depends upon the maintenance of fairly high Hb levels.

Presumably during this period hypoxia is the main factor retarding growth. In older children iron overload may be responsible for the delayed growth spurt observed in a few patients at puberty (Brook *et al.*, 1969). It has been suggested that the cause of growth retardation in thalassaemia is

hormonal, in view of the massive hemosiderosis of the pituitary, adrenal, thyroid, and gonads observed at necropsy (Fink, 1964).

Recent studies in mice showed that hypoxia combined with iron loading led to excessive deposition of iron in the heart, whereas iron loading alone did not do so (Necheles, Beard, and Allen, 1969). If this is the case, intensive transfusion therapy might be expected to cause less iron overload in the heart by correcting anaemia and preventing myocardial tissue hypoxia. However, it remains to be decided whether early institution of adequate treatment with chelating agents, together with frequent transfusions, will prevent iron overload and tissue damage.

We conclude that intensive transfusions constitute the treatment of choice of patients with homozygous β -thalassaemia, if normal growth is to be ensured. This regimen probably provides also short-term benefits to these children, which enable them to lead a normal life (Beard, Necheles, and Allen, 1969).

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