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Nutritional factors and thalassaemia major

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Abstract

Abnormal growth is a common feature of thalassaemia major in children. In an attempt to determine whether it has a nutritional cause, 12 children aged 1 to 3 years with thalassaemia major were studied under metabolic ward conditions. Nutritional status was assessed by anthropometry and biochemistry before and after an intensive nutrition regimen. Five children had wasting or stunting on admission. As a result of the nutrition intervention, mean weight for height improved significantly. The mean height increase of 0·4 cm after one month was not significant. Plasma zinc, depressed in half the children on admission, improved, as did α tocopherol, while copper decreased. Plasma insulin-like growth factor-I also increased commensurate with improved growth. Fat absorption was normal in all children. Undernutrition is an important cause of associated growth disturbances in children with thalassaemia major. Malnutrition was primarily caused by inadequate nutrient intake, as indicated by the capacity to gain weight appropriately when provided with nutrition support, and by the absence of intestinal malabsorption. While long term studies are required to determine if nutritional support will prevent stunting, these results underscore its central role in preventing nutritional deficiencies and in promoting normal growth in thalassaemic children.

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β Thalassaemia major is associated with impaired growth velocity, generally beginning after 6–8 years, which results in stunting and delayed or absent puberty.[1 2] While hypertransfusion regimens modify the pattern of growth disturbances, delayed growth and development remain common, even in transfused children.[1 3–5] Investigations of the aetiology of the growth abnormalities have produced conflicting results. Various factors have been implicated, including abnormal hypothalamic-pituitary-gonadal axis function, impaired hepatic synthesis of insulin-like growth factor-I (IGF-I), the effects of desferrioxamine treatment, cellular hypoxia due to anaemia, and intestinal malabsorption, among others.[6–10] Many children with thalassaemia also have deficiencies of micronutrients, including zinc, folic acid, and vitamin B-12.[11–14] Vitamin E deficiency and low retinol, carotenoids, and retinol binding protein have also been recorded.[15–17] In an analysis of the growth of 128 non-splenectomised thalassaemic children, we noted a pattern of anthropometric abnormalities consistent with malnutrition as a cause of growth failure.[18] Despite the coexistence of β thalassaemia and deficits of several specific micronutrients, general undernutrition as a principal cause of growth abnormalities has not been thoroughly investigated. Our study was designed to assess the effect of nutrition support on the growth and nutritional status of a group of children with homozygous β thalassaemia.

Methods

SUBJECTS AND STUDY DESIGN

Twelve non-splenectomised children with homozygous β thalassaemia were systematically sampled (the first 12 children who met the selection criteria) at the time of their routine follow up assessment from the thalassaemia clinic at the Maharaj Nakorn Hospital, Chiang Mai, Thailand. Selection criteria included age (1–3 years), HIV seronegativity, and informed consent by a parent after explanation of study objectives. Diagnosis was established according to established criteria.[19] All were being treated with a chronic low transfusion regimen without chelation treatment and were taking 5 mg of folic acid per day. The children were admitted to the metabolic ward for one month for a nutrition intervention programme and testing. The study protocol was reviewed and approved by the human ethics committee of Chiang Mai University and the Louisiana State University Medical School institutional review board.

ANTHROPOMETRY

Naked weights were obtained to the nearest 100 g using an electronic digital scale (Seca, model 770), standardised with a 1 kg standard weight before each weighing. Standing height was determined with a locally constructed instrument, using the pressure technique, in which a metal tape measure is extended between a footplate and head bar. The mean of two consecutive measurements to the next succeeding 0·5 cm was recorded as the observed value. All measurements were subsequently compared to the National Center for Health Statistic data and the percent of median determined and categorised according to the system of Waterlow[20 21] as per cent weight for height (WH%) and per cent height for age (HA%).

BIOCHEMISTRY

Fasting morning specimens were obtained for plasma mineral determinations by venepuncture using trace mineral-free plastic syringes and stainless steel needles and put into heparinised (50 IU/ml) plastic tubes. Glass tubes and plastic syringes were rendered trace mineral-free for collection and analysis by overnight soaking in 50% nitric acid, rinsed three times with doubly deionised water and allowed to drain dry. Zinc, copper, magnesium, calcium, and iron concentrations were then measured by atomic absorption spectrophotometry (Perkin-Elmer Model 3100).

Plasma specimens for retinol and α tocopherol concentrations were placed on ice, shielded from light, centrifuged within 30 min, and stored at −20°C until analysis by high pressure liquid chromatography using a modification of the method of Thurnham *et al.*[22 23] Samples for albumin and total protein were collected in tubes without anticoagulant. Serum ferritin was determined by solid phase enzyme immunoassay[24] and serum IGF-I was quantitated by a sensitive specific radioimmunoassay (Incstar) after ODS-silica extraction. Samples were centrifuged within 30 min and the serum stored at −20°C until analysed. Values are reported in nmol/l (25 nmol/l=1 unit/ml). The normal ranges of IGF-I concentration by sex and age according to the test manufacturer are used as reference values.

FAT BALANCE

Faeces were collected for fat balance in the first week of the study period as previously described.[25] Faecal fat was determined by the Van de Kamer method, and apparent fat absorption was estimated from the intake minus faecal excretion.[26] Net fat absorption is expressed as a percentage of intake (coefficient of absorption) and results compared to age adjusted normal values.[27] The fat content of different lots of the study formula was determined and was within 10% of the value stated by the manufacturer. Since this was within the error of the assays, the manufacturer's stated value was used to calculate absorption data, together with an estimation of additional fat supplied by corn oil.

NUTRITION INTERVENTION

Children were admitted to the metabolic unit of the Research Institute for Health Sciences (RIHES) for one month of intensive oral nutritional intervention. The study diet consisted of Enfapro liquid formula (Mead Johnson) with added dextrose and corn oil to achieve an energy density of 1·1 kcal/ml, in addition to vitamins and minerals. Each child had one to one nursing and was actively encouraged to consume a volume of the study diet equivalent to that used in our unit in the rehabilitation of children with primary protein energy malnutrition. This volume was calculated to provide approximately 150 kcal and 4 g protein per kg body weight and 150% of the recommended daily allowance (RDA) of selected vitamins and minerals.[28] Because zinc deficiency is often associated with thalassaemia, an additional 1·5 mg/kg/d of elemental zinc was provided to bring the total zinc intake to approximately two to three times the RDA.

STATISTICAL ANALYSIS

χ^2 Tests of independence or Fisher's exact test were used to examine differences in proportions. Group comparisons of continuous data were made by Student's *t* test or Mann-Whitney U test, and differences in measurements before and after nutritional intervention from individual children were compared by Wilcoxon ranked sums. Regression analysis was used to investigate relations between dependent and one or more independent variables. Data are expressed as mean (SD) for ease of interpretation, and statistical significance is defined as $p<0·05$.

Results

Seven girls and five boys aged 20 to 36 months (mean 28 months) with a mean haemoglobin of 7·6 g/l (median 7·8 (2·0)) were enrolled into the study. Seven children were of appropriate weight for height and five had first degree malnutrition, which was fully corrected after the one month period (table 1). The baseline nutritional status distribution (height for age, weight for height) of the study participants was representative of the population of thalassaemic children attending the clinic (data not shown). The children consumed a mean volume of 1183 (244) ml per day of the study formula, which provided 119 (20) kcal and 2·7 (0·5) g protein/kg/d throughout the study. This intake is approximately 17% greater than normal for age.[29] Mean weight increased 1·2 kg and resulted in a significant increase in weight for age and weight for height ($p=0·003$) (table 2). Weight velocity was 43 g/d during the study period compared with the normal rate of daily weight gain for age of approximately 7 g/d. Seven children were of normal height for age on admission, while four had first degree and one had second degree short stature. As anticipated, with the relatively short duration of dietary intervention, mean height and height for age did not change significantly. However, of the five children with stunting, two grew at a height velocity that exceeded the median, one achieved the median, and the remaining two grew below the median.

Serum total protein and albumin were

Table 1 Weight for height (wasting) and height for age (stunting) before and after nutritional intervention

Anthropometric index (% median)	*Baseline*	*After nutrition*
Weight for height		
≥90%	7 (58%)	12 (100%)
80–90%	5 (42%)	–
70–80%	–	–
<70%	–	–
Height for age		
≥95%	7 (58·33%)	7 (58·33%)
90–95%	4 (33·33%)	4 (33·33%)
85–90%	1 (8·33%)	1 (8·33%)
<85%	–	–

Table 2 Direct anthropometric measurements of thalassemic children before and after nutrition intervention

Characteristic	Baseline (mean (SD))	After intervention (mean (SD))	p Value
Weight (kg)	10·90 (1·7)	12·10 (1·7)	0·003
Height (cm)	84·8 (6·0)	85·2 (6·0)	0·213
Weight for age (% median)	85 (10)	93 (10)	0·003
Weight for height (% median)	91 (1)	100 (7)	0·003
Height for age (% median)	96 (4)	96 (4)	0·845

normal in all children at baseline and were largely unaffected by the intervention programme (table 3). All children also had normal plasma retinol and α tocopherol concentrations at baseline, although the concentration of α tocopherol, unlike retinol, increased after nutrition intervention (p=0·005). Serum iron was greater than normal in nine of the 12 children, while serum ferritin was greatly increased in all children. Iron status was unchanged by the intervention programme. Low plasma zinc concentrations were common at admission, with levels <60 μg/dl present at baseline in six of the 12 children. Neither the mean WH% nor mean HA% was significantly different in the children with deficient plasma zinc compared to those with normal zinc concentrations (data not shown). The mean plasma zinc in the children with HA <95% (57 μg/dl) was not significantly different from that in children with HA >95% (70 μg/dl) (p=0·14), though a trend was evident. Children with mild wasting (WH 85–90%) had a lower mean plasma zinc (53 μg/dl) than children with normal WH% (73 μg/dl) (p=0·04). Zinc status improved in all children (p=0·03) and zinc deficiency resolved in those deficient at baseline following supplementation. High serum copper was observed in three children upon entry into the study; this reverted to normal as the mean serum copper of the group decreased (p=0·007) by the end of the intervention. Intestinal absorption of dietary fat was normal in all children and ranged from 91% to 98% (table 4).

Serum IGF-I concentrations were within the normal range in all children before intervention, but showed a mean 41% increase at the follow up determination compared to baseline (p=0·02) (figure).

Discussion

Our results show that general malnutrition together with micronutrient deficiencies are features of thalassaemia major in certain children. These findings are consistent with growth pattern abnormalities described in thalassaemic children, in which wasting predominates in the early years of life followed by stunting with advancing age, that is, a pattern of malnutrition and nutritional stunting.[18] The children in our study showed a normal capacity to gain weight commensurate with the amount of energy consumed, and without evidence of overtly increased needs resulting from a raised metabolic rate or nutrient malabsorption. Energy expenditure was not tested, but all children had normal fat absorption. Malnutrition and growth failure in thalassaemia are therefore unlikely to be the result of macronutrient malabsorption.

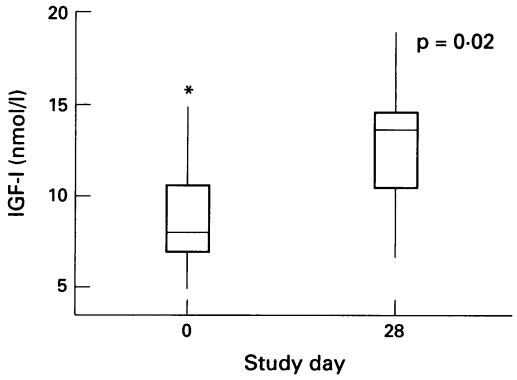
Serum IGF-I, a major mediator of linear growth and skeletal maturation, has been reported to be depressed in thalassaemic children and adults, and it has been suggested that this is due to inadequate hepatic synthesis.[9] IGF-I concentrations were normal at baseline in our subjects, perhaps because the children had normal weight for height or only first degree wasting. Nonetheless, IGF-I concentrations increased after one month of nutritional support, in parallel with an increase in weight velocity. A potential role for nutrition in the regulation of IGF-I metabolism has been recognised for some time. Energy appears to be more influential than protein in the induction of an IGF-I response.[30] Evidence from animal models also indicates that zinc is a regulatory factor of IGF-I metabolism.[31] Low plasma zinc was present in half our study population, but there was no correlation with

Table 3 Nutritional biochemistries before and after nutrition intervention

Chemistry	Before (mean (SD))	After (mean (SD))	p Value
Retinol (μmol/l)	2·34 (0·7)	2·75 (1·2)	0·224
α Tocopherol (μmol/l)	19·4 (6)	30·9 (7·0)	0·005
Calcium (mmol/l)	36 (27)	35 (26)	0·689
Magnesium (mmol/l)	0·83 (0·05)	0·78 (0·05)	0·067
Copper (μg/dl)	171 (53)	144 (39)	0·007
Zinc (μg/dl)	65 (17)	101 (43)	0·032
Iron (μg/dl)	145 (40)	149 (63)	0·824
Ferritin (ng/ml)	1551 (540)	1587 (646)	0·845
Total protein (g/dl)	7·54 (0·9)	7·23 (0·6)	0·407
Albumin (g/dl)	4·15 (0·3)	3·91 (0·3)	0·108
Globulin (g/dl)	3·39 (1·2)	3·33 (0·7)	0·929

Table 4 Fat absorption in children with thalassemia major

Subject	Fat intake (g/72 h)	Faecal fat excretion (g/72 h)	Coefficient of fat absorption (%)
1	137	4·5	96·7
2	211	5·7	97·3
3	178	4·0	97·7
4	156	3·9	97·5
5	162	10·8	93·3
6	155	9·4	94·0
7	151	3·5	97·7
8	138	13·2	90·5
9	221	4·5	98·0
10	147	4·1	97·2
11	154	3·9	97·5
12	127	3·1	97·6
Mean (SD)	161 (29)	5·9 (3)	96·3 (2)



Box-and-whisker plot of serum insulin-like growth factor 1 (IGF-I) in 12 children with thalassaemia major before and after nutritional support. Horizontal line across box, median; bottom and top of the box are first and third quartile, respectively; vertical line, range; asterisk, possible outlier.

stunting. Children with wasting but without short stature had a lower plasma zinc, indicating that zinc deficiency existed within the context of general undernutrition. If malnutrition is prolonged, nutritional stunting is a predictable consequence. Our data therefore suggest the probability that growth failure in thalassaemia results from inadequate nutrition in certain, perhaps many, children. Further, while zinc deficiency might be a growth limiting factor in some children, it appears unlikely that normal growth would be established solely with zinc supplementation and without attention to adequate provision of macronutrients, particularly energy.

Our study also shows that many of the abnormalities are amenable to treatment with nutritional support. The five children with first degree wasting recovered completely, and linear growth was maintained or accelerated in three of the five children with stunting. Although growth, as defined by appropriate weight for height, became normal with intervention, and growth velocity was maintained or accelerated in most of our children with stunting, the duration of intervention was too short to establish malnutrition as the primary cause of poor linear growth in children with thalassaemia major. However, there is circumstantial evidence that malnutrition due to inadequate intake is a principal aetiological factor. Firstly, the pattern of growth abnormalities in thalassaemic children, in which wasting is prominent early in life followed by stunting in the later years of childhood, is typical of nutritional stunting rather than endocrinological dwarfism.[18] Further, our study makes it clear that children with thalassaemia are capable of appropriate weight gain when given a suitable diet. In this regard, the children's growth rate was appropriate for the energy intake. Although additional energy and protein were needed for catch up growth in many of the children, there was no evidence of excessive requirements, disproportionate to their rate of weight gain.

In conclusion, our results indicate that an inadequate nutrient intake is probably an important cause of growth failure in thalassaemia major. General malnutrition, therefore, might be the unifying course in children previously described as showing abnormal growth, micronutrient deficiencies, and depressed IGF-I. We suggest that long term provision of adequate macronutrients and micronutrients would provoke normal growth. We recommend close monitoring to identify those thalassaemic children with evidence of growth faltering who might benefit from aggressive nutritional support.

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