

ASSESSMENT OF THYROID FUNCTIONS AND ITS ROLE IN BODY GROWTH IN THALASSEMIA MAJOR

Manish Jain
R.S.K. Sinha
Harish Ghellani
N.K. Anand

ABSTRACT

The present study was done to establish the role of thyroid gland in causing growth retardation in regularly transfused thalassaemic children.

Growth, skeletal maturation and thyroid functions were assessed in 25 patients of thalassaemia major in the age range of 5-17 years (mean age 10.3 ± 3.6 years). Thirteen patients were migrants from Pakistan and 12 were of Indian origin. Twenty-five age and sex matched children who were not anemic served as controls.

Thalassaemic children received multiple blood transfusions ranging from 36-350 units with a mean of 168.4 ± 98.9 (± 1 SD). The mean pretransfusion hemoglobin was 8.7 ± 1.6 g/dl. Twenty eight per cent patients were below the 5th percentile for height and another 24% between 5th and 10th percentiles. The height age retardation was more pronounced than bone age retardation. The mean serum total T3 and T4 levels were significantly lower ($p < 0.001$) and the mean serum TSH levels were significantly higher ($p < 0.005$) in patients with thalassaemia major as compared to the controls. Eight patients had high TSH levels; of these 5 had compensated primary subclinical hypothyroidism (elevated TSH with normal T3 and T4)

Thalassaemia is one of the common hemoglobinopathies and approximately 3-10% of people in Indian subcontinent carry a thalassaemia gene(1). Over the past 25 years, with the introduction of new treatment regimen and prolongation of life span of patients with thalassaemia major, the well known complications of growth retardation and delayed skeletal and sexual maturation have assumed greater clinical importance(2).

Various studies in the past have observed that patients with thalassaemia

and 3 had uncompensated primary sub-clinical hypothyroidism (elevated TSH, low T4 and normal T3). Two patients had low T4 with normal T3 and TSH levels. Thyroid dysfunction was not related to age, sex, hemoglobin levels and country of origin but transfused iron load (units/kg, units/year) was significantly higher in patients with hypothyroid function compared to those with euthyroid function ($p < 0.005$). Height age, weight age and bone age retardations were more pronounced in patients with hypothyroid function; however, the difference was not statistically significant.

It is concluded that hypothyroidism is unlikely to be the sole cause of growth retardation; however, it may have a potentiating or permissive role. The strong association of high transfused iron load and decreased thyroid function stresses the need for intensive chelation therapy.

Keywords: *Thalassaemia major, Blood transfusion, Growth retardation, Thyroid functions.*

From the Departments of Pediatrics and Nuclear Medicine, Safdarjang Hospital, New Delhi 110 029.

Reprint requests: Dr. N.K. Anand, Consultant and Head, Department of Pediatrics, Safdarjang Hospital, New Delhi 110 029.

Received for publication: February 14, 1994;

Accepted: June 29, 1994

major tend to fall below normal standards both for height and weight, as a result of subnormal rates in growth for height, weight and skeletal maturation. However, the exact etiology of growth retardation is still obscure(3-7).

Recently it has also been observed that with rising hemoglobin level and intense chelation therapy, the percentage of patients exhibiting normal growth and puberty remains low(8-10). The role of endocrine glands especially thyroid gland has gained importance. However, the exact defect has not been established(2,11,12). The present study was, therefore, undertaken to assess thyroid functions and its possible role, if any, in growth retardation in thalassemia major patients.

Material and Methods

The study was conducted in the Departments of Pediatrics and Nuclear Medicine, Safdarjang Hospital, New Delhi. Study subjects comprised of 25 cases of transfusion dependent thalassemia major in the age group 5-17 years (18 M, 7F). Thirteen children of these 25 were of Pakistan descent.

All the children were examined and diagnosis of thalassemia major was established by clinical and hematological parameters and presence of thalassemia trait in the parents. Detailed history regarding age of presentation, number of transfusions received (intravenous or subcutaneous) was also taken. Equal number of age and sex matched children who were not anemic and attended the hospital for unrelated mild acute illness served as controls. All children with maternal history of thyroid dysfunction, children with clinical

evidence of endocrine abnormality, especially thyroid and children with clinical goitre were excluded from the study. The nature and purpose of the study was carefully explained to the parents of all the patients and controls prior to obtain their voluntary consent to participate.

Growth Assessment

Growth was assessed by height (cm) and weight (kg). Growth charts of Indian Council of Medical Research were used to calculate the percentile of height and weight(13). Linear growth was expressed as height age or the age at which the patient's height would be the 50th percentile for normal children. Skeletal maturation was assessed by roentgenogram of wrist and hand and were compared with standards of Modi(14); Skeletal retardation was obtained as the difference between the normative development for a given chronological age and the bone age of the patient.

Thyroid Function Tests

Thyroid functions were determined by measuring serum thyroxin (T4) and tri-iodothyronine (T3) levels by specific radio immunoassay technique and serum levels of thyroid stimulating hormone (TSH) was measured by immuno radio metric assay (IRMA) using the commercial kits supplied by Bhabha Atomic Research Centre, Bombay. All samples were taken from the patients on the morning of attendance for regular blood transfusion just prior to the transfusion (atleast two weeks had elapsed after the last transfusion) in order to avoid possible measurement of exogenously transfused hormones. For

hormonal assay, serum was separated and stored at -20°C until analyzed.

All children were screened for hepatitis B virus and human immuno deficiency virus (HIV) infection.

Statistical analysis was done using Student's 't' test. Null hypothesis was rejected with level of significance <0.05 .

Results

Twenty five diagnosed cases of thalassemia major who had received multiple transfusion regularly were studied. The age of patients ranged from 5-17 years with a mean of 10.3 ± 3.6 year (± 1 SD). Study group had 18 males and 7 females. Of these 25, thirteen children were of Pakistani origin and 12 were of Indian origin. None could attain puberty and all of them were clinically euthyroid, with no palpable goitre. One child was splenectomized at the age of 8 years.

The age range of controls also ranged from 5-17 years with a mean of 10.2 ± 3.6 years (± 1 SD). The mean age at first transfusion was 18.3 ± 21 months with a range of 4-108 month. The first transfusion was required at an earlier age (13.9 ± 6.7 mo) in migrants from Pakistan as compared to those of Indian origin (22.8 ± 30.1 mo). The mean interval between the two consecutive transfusions was 17.2 ± 4.2 days (range 10-30 days). The pretransfusion hemoglobin level maintained was 8.7 ± 1.6 g/dl (range 5-12.4 g/dl). The mean of total units of blood transfused was 168.4 ± 98.9 (range 36-350 units). All children received desferoxamine only with blood transfusions and none by regular subcutaneous infusion.

Table I depicts the comparison of the percentile of height in children of thalassemia major and the controls. Seven children (5 M and 2 F) of thalassemia major were below the 5th percentile for height. Six patients (5 M, 1 F), however, were between 5th and 10th percentile for height. None of the parents reached beyond 50th Percentile. Height age was significantly less than the chronological age ($p < 0.05$). Although the weight and bone age followed the same pattern, the retardation was less marked. Height age retardation was more pronounced than bone age retardation (*Table II*). Retardation in height, weight and bone age progressed with increasing age. No significant correlation was found between growth retardation and sex, anemia and transfused iron load.

Table III represents the comparison of thyroid function tests in study and control groups. The mean serum T3 and T4 levels were significantly low in thalasseemics as compared to the controls ($p < 0.001$). TSH levels were significantly higher in patients as compared to controls ($p < 0.005$). Eight children had elevated TSH levels indicating primary subclinical hypothyroidism. Among these, three had uncompensated (elevated TSH, low T4, normal T3) and five had compensated (elevated TSH, normal T4 and T3) primary hypothyroidism. None had frank bio-chemical or clinical hypothyroidism. There was no significant variation in the levels of hormones with regard to age, sex and presence of anemia. The level of iron load when computed indirectly from units of blood transfused was significantly high in patients with thyroid

TABLE I—Height Percentiles in Study and Control Children.

	Mean ± 1 SD (cm)	Percentile					
		<5	5-10	10-25	25-50	50-75	>75
Cases n = 25	119.9 ± 16.3	7 (28%)	6 (24%)	8 (32%)	4 (16%)	0	0
Control n = 25	133.1 ± 18.4				5 (20%)	15 (60%)	5 (20%)

TABLE II—Comparison of Height, Weight and Bone Age with Chronological Age.

	Chronological age	Height age	Weight age	Bone age
Mean ± 1 SD (months)	123 ± 42.8	100.5 ± 37.3*	103 ± 40.7	104.1 ± 37.3#
Range (months)	60 ± 204	48-162	45-177	48-168

* p < 0.05; # p > 0.05.

TABLE III—Serum T3, T4 and TSH in Study and Control Children.

Thyroid functions Mean ± 1 SD	T3 (ng/ml)	T4 (µg/dl)	TSH (µIU/ml)
Cases (n=25)	0.97 ± 0.273*	6.87 ± 1.424*	3.750 ± 2.610#
Control (n=25)	1.342 ± 0.356	9.976 ± 1.676	2.050 ± 1.017

* p < 0.001; # p < 0.005.

hypofunction as compared to those with euthyroid function (p < 0.05).

Table IV depicts the relationship between the thyroid function status and growth of thalassemic patients. Though the height age, weight age and bone age retardations were more pronounced in

patients with hypothyroid function as compared to those with euthyroid functions, the difference was not statistically significant. Thyroid hormone levels of those children who were below the 5th percentile when compared with those who were above 5th percentile, showed no significant difference.

TABLE IV—Relation Between Thyroid Status and Growth of Study Cases

Thyroid status	Height age retardation (CA-HA)	Weight age retardation (CA-HA)	Bone age retardation (CA-BA)
Hypothyroid (n=8)	26.6 ± 23.2*	20.5 ± 25.7*	21 ± 20.9*
Euthyroid (n=17)	21.5 ± 11.1	19.4 ± 10.8	18.8 ± 11

CA: Chronological age, HA: Height age, WA: Weight age, BA: Bone age; * p >0.05.

All patients were free from hepatitis B and HIV infection.

Discussion

Although, the prognosis for thalassemia major has greatly improved with more intense transfusion regimens, timely splenectomy and chelation therapy, the percentage of patients with growth retardation and delayed puberty still remains high(7,9,15,16). All children in the present study received regular transfusion, had mean pretransfusion hemoglobin 8.7 g/dl and were on regular desferoxamine therapy with blood transfusion. Twenty eight per cent patients were still below the 5th percentile and none of 25 patient could reach the 50th percentile. The present study being a cross sectional, the role and pattern of growth could not be studied. However, it was observed that none of 8 children in the age group 12-17 years attained puberty. Pignetti *et al.* found 37% of children, to be 2 SD below the mean for normal height and weight in a group of 250 patients in a multi-centric study(19). Eighty per cent of the children in the present study had delayed skeletal maturation and delay

was more than one year in 68% and more than 6 months in 12% of the patients. The mean height age retardation was more marked than the mean bone age. This is supported by earlier published reports of delay in height and bone age(9,17). However, Laor Eva *et al.* reported severe skeletal retardation upto 42.6% in the age group 9 months -7 years reaching upto 73% and then declining, a finding not supported by the present study(20).

The delay in height and bone age in regularly transfused thalassemic children led various workers to study the role of thyroid gland in these children. Serum tri-iodothyronine (T3) and thyroxine (T4) levels in the present study were significantly low (p <0.001) and mean TSH levels were significantly elevated in thalassemia major cases as compared to control children, indicate relative thyroid hypofunction in frequently transfused population of thalassemic children. A state of compensated hypothyroidism and pre-clinical uncompensated primary hypothyroidism has been observed in 32% and 12% of patients, respectively. These observations

are also supported by many authors(2,12,18); however, Zappulla *et al.* did not find any alteration in hypothalamo-hypophyseal thyroid axis(21). Sick euthyroid syndrome or "Low T3 syndrome has been observed in two patients in the present study. Such a condition which is normally found in acute systemic illness or severe malnutrition was also found by Sabato and Cavallo *et al.*(2,18).

Serum iron and ferritin studies could not be done but when thyroid hypofunction was correlated with amount of blood transfusion, a significantly higher number of transfusions/kg body weight, transfusion/year and total units of blood transfused were found in patients with primary hypothyroidism as compared to those patients who had normal TSH levels. It may be hypothesized that thyroid hypofunction may be related to iron overload and iron related toxicity. Cavallo *et al.* in his longitudinal studies to iron overload was excluded, found serum ferritin levels to be strictly correlating with the variations in TSH levels(18). In thalassemia major, iron deposition in endocrine gland as a consequence of chronic iron overloading by regular transfusion therapy has well been documented histologically(22).

Retardation in growth and development is the hall mark of hypothyroidism in children and bone age retardation is more marked than height age retardation. In our study through both height age and bone age were retarded in patients with hypothyroidism as compared to euthyroid cases but the retardation and height age was more pronounced than retardation of bone age.

This is a finding which goes against the direct cause and effect relationship between thyroid hypofunction and growth retarded patients. Also when groups were compared according to the degree of growth retardation, there was no significant difference in thyroid function of patients below 5th centile and more than 10th percentile.

In the presence of chronic disease, non-specific symptoms due to hypothyroidism may not be recognized. Therefore, regular assessment of thyroid function is warranted in patients meeting the high risk criteria and in patients with compensated hypothyroidism. Though the hypothyroidism is unlikely to be the cause of growth retardation; however, it cannot be ruled out that hypothyroidism may have potentiating or permissive role. The strong association of a high transfused iron load and decreased thyroid function stresses the need for intensive chelation therapy to be individually monitored to provide negative iron balance with the aim of preventing the iron toxicity related complications.

REFERENCES

1. Madeddu C, Dore A, Marongiu A, Langer Costangi M. Growth retardation, skeletal maturation and thyroid function in children with homozygous P thalassemia. *Clinical Endocrin* 1978, 8: 359-365.
2. Sabato AR, De Sanctis V, Atti G, Capra L, Bagni B. Primary hypothyroidism and low T3 syndrome in thalassemia major. *Arch Dis Child* 1983, 58: 120-127.
3. Lassman MN, O'Brien RT, Pearson HA, Wise JK. Endocrine evaluation in thalassemia major. *Ann New York*

- Academy of Sciences 1974, 232: 226-237.
4. Arcasoy A, Cavdar A. Growth retardation in beta thalassemia. *J Pediatr* 1981, 99: 671-672.
 5. Pignatti C, De Stefamo P, Zontah, Dessanctis V. Growth and sexual maturation in thalassemia major. *J Pediatr* 1985, 106: 150-155.
 6. De Virgillis S, Congia M, Fran F, Varsi A, Sanno G. Desferoxamine induced growth retardation in patients with thalassemia major. *J Pediatr* 1988, 113: 661-669.
 7. Avcasoy A, Cavador A, Con S, Erten J. Effects of Zinc supplementation on linear growth in beta thalassemia (a new approach). *Am J Hematol* 1987, 24: 127-136.
 8. Modell B, Letsky EA, Flynn DM, Peto R, Weatherall DJ. Survival and desferoxamine in thalassemia major. *BrMedJ* 1982, 1: 1081.
 9. Piomelli S, Hart D, Crazian J, Grant G, Karpatker M. Current strategies in the management of Cooley's anemia. *Ann NY Acad Sci* 1985, 45: 256-267.
 10. Ehler KH, Giardina PJ, Lesser ML, Eagle MA, Hilgartner MW. Prolonged survival in patients with thalassemia major treated with desferoxamine. *J Pediatr* 1991, 118: 540-545.
 11. Flynn DM, Fairney A, Jackson D, Barbara E. Hormonal changes in thalassemia major. *Arch Dis Child* 1976, 51: 828-836.
 12. Phenekos C, Karamerou A, Pipis P, Constantoulabis M. Thyroid functions in patients with homozygous B-thalassemia. *Clinical Endocrin* 1984, 20: 445-450.
 13. Growth and Physical Development in Indian Infants and Children, Delhi, Indian Council of Medical Research. Tech Rep Series No. 18, 1972, (Reprint 1984).
 14. Modi JP. Textbook of Medical Jurisprudence and Toxicology, 17th edn. Ed. Modi NJ. Bombay, Tripathi Pvt Ltd., 1969.
 15. Pignatti BC, De Stefamo P, Zonta L. Growth and sexual maturation in thalassemia major. *J Pediatr* 1985, 106: 150-155.
 17. Lapatsanis P, Divoli A, Georgaki H, Patelakis S. Bone growth in thalassaemic children. *Arch Dis Child* 1978, 53: 963-965.
 18. Cavallo LA, Mautone MA, Pascazio A, Schettini F. Pituitary thyroidal functions in children with p thalassemia major. *Acta Endocrinol* 1981, 96: 59-64.
 19. Canale VC, Sleinberz P, Newn M, Earlandson M. Endocrine function in thalassemia major. *Ann NY Acad Sci* 1974, 232: 333-345.
 20. Laor Eva, Carfunkel A, Koyoumdjisky-Kaya. Skeletal and dental retardation in p thalassemia major. *Hum Biol* 1982, 54: 85-92.
 21. Zapulla F, Cassio L, Mazzan li L, colains B, Frezaville E. Funzione tiroidea in bambini con thalassemia major. English abstract. *Minerva Pediatrica* 1982, 34: 801-804.
 22. Costin C, Kogut MD, Hyman CB, Ortega JA. Endocrine abnormality in thalassemia major. *Am J Dis Child* 1979, 133: 497-502.