THYROID DYSFUNCTION IN MULTI-TRANSFUSED IRON LOADED THALASSEMIA PATIENTS

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ABSTRACT

Seventy-two transfusion-dependent iron loaded thalassemia patients were investigated for thyroid dysfunction by estimating circulating thyroid hormones (T_4 and T_3) and basal thyroid stimulating hormone (TSH). They were also evaluated for their liver function (biochemically) and iron overload by estimating serum ferritin. Thyroid failure (hypothyroidism) was documented in 14 patients (19.4%). In all, 3 groups were seen, i.e., Group 1: Normal T_4, T_3, TSH (58 patients: 80.6%); Group 2: Compensated hypothyroidism characterized by normal T_4, T_3 and raised TSH (9 patients: 12.5%); Group 3: Decompensated hypothyroidism characterized by decreased T_4 and increased TSH (5 patients: 6.9%). Interestingly, impaired thyroid function could not be correlated with age, amount of blood transfused, liver dysfunction or degree of iron overload. It is postulated that an inter-play between chronic hypoxia, liver dysfunction and iron overload may be responsible for the thyroid damage.

Key words: *Ferritin, Iron overload, Liver function, Thalassemia, Thyroid.*

With the advances in the management of thalassemia major, many patients, even in India, now have improved long term survival(1). Expensive iron chelation therapy, however, is not available to majority of them, as a result of which various organ damages are responsible for significant morbidity and mortality(1). Besides heart and liver, endocrine organs of the body bear the brunt of iron mediated insult(2). Of these, diabetes mellitus and failure of physical and sexual growth are the most commonly discussed effects(2). In addition, some data is available regarding damage to parathyroid, thyroid and adrenal glands(3-12). The present work was undertaken to study the thyroid functions of 72 transfusion-dependent iron loaded thalassemics.

Material and Methods

Seventy-two patients of transfusion dependent iron loaded thalassemics with the mean age of 12.4±7.1 (7-22 years) were studied. Male to female ratio was 2.6 : 1 (M = 52, F = 20). Thirty seven (51.4%) patients were splenectomized. Most of these patients received hyper-transfusions only for last 5-6 years, *i.e.*, since 1986. Prior to this, their pre-transfusion hemoglobin levels used to be between 5-8 g/dl. During hyper-transfusion therapy, they received transfusions every 14-28 days so as to maintain pre-transfusion hemoglobin value at around 10 g/dl.

Only 7 patients (9.7%) received adequate desferrioxamine (DFO) therapy

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which was defined as >30 mg/kg/day of DFO >4 times per week for minimum of 8 hours per day subcutaneously using syringe driver(1,2). Rest of them were receiving inadequate DFO therapy (33 patients–45.8%) usually in form of 1-2 g of DFO as intravenous infusion together with blood transfusion), or no DFO therapy (32 patients–44.5%).

Records were analyzed with respect to age at diagnosis, age at first transfusion, mean transfusion requirement, duration of transfusion and total blood received. Height and weight were analyzed and percentile growth was calculated according to the charts of Tanner(13,14).

Blood samples were collected to assess serum levels of thyroxine (T_4), tri-iodo-thyroxine (T_3) and thyroid stimulating hormone (TSH) using specific RIA or IRMA (for TSH) technique with reagents supplied by BARC(15), liver function tests (serum protein, albumin, SGOT, SGPT, alkaline phosphates, GGTP, S. bilirubin, cholesterol, LDH) and serum ferritin using the ELISA technique. Blood was collected at least 2 weeks after last transfusion. The normal value (range and mean) for various hormones were as follows: T_3: 86-187 ng/dl (122 ± 53), T_4: 4.5-12.5 μg/dl (8.3 ± 4.7), TSH: 0.3-5.0 μIu/ml(3.8 ± 0.9).

According to thyroid function, patients were divided into 3 groups: (*i*) Euthyroid (normal T_3, T_4 and TSH), (*ii*) Compensated hypothyroid (normal T_3, T_4 and raised TSH), and (*iii*) Decompensated hypothyroid (decreased T_4 and increased TSH).

Patients were also interrogated and examined for symptoms and signs of hypothyroidism. An attempt was made to correlate hypothyroidism with age, physical growth, liver function, amount of blood transfused and iron overload. All the patients in Group III received replacement therapy using thyroxine.

Results

Thyroid dysfunction (hypothyroidism) was detected in 14 patients, *i.e.,* 19.4%. These could be divided into two groups: (*Table I*: Group II and Group III) *i.e.,* compensated hypothyroidism–9 patients (12.5%) and decompensated hypothyroidism–5 patients (6.9%). Fifty eight patients, *i.e.,* 80.6% were euthyroid (Group I). Two patients belonging to Group III had clinical symptoms and signs suggestive of hypothyroidism and other iron overload effects. One was 14 years old male who complained of marked increase in weight (over 10 kg in 6 months) despite average or poor appetite, lethargy, excessive fall of hair and mental dullness. He had evidence of congestive cardiac failure secondary to iron induced cardiomyopathy. He has done remarkably well within 3 months of replacement therapy with loss of 6.5 kg weight, improvement in appetite and activity (both physical and mental). The second patient was a female aged 16 years who had diabetic mellitus and complained of increased weight, altered voice, roughening of skin and anorexia. There is overt improvement in her appearance, skin texture, appetite as well as voice. Other 3 patients belonging to Group III are also on thyroxine replacement.

A total of 79.3% euthyroid patients and 85.7% of hypothyroid patients (*Table II*) were below the 3rd percentile in height. However, the difference was not statistically significant. A total of 12.1% of euthyroid and 14.3% of hypothyroid were between 3rd and 10th percentile of height. Once again the difference was not statistically significant. However, 8.6% of euthyroid and none of hypothyroid were above

TABLE I—*Thyroid Function Tests in 3 Groups*

	Tests		
	T_3 (ng/dl)	T_4 (μg/dl)	TSH (μIU/ml)
Normal			
Range and	86 -187	4.5 - 12.5	0.3 - 5.0
(Mean)	(122 ± 53)	(8.3 ± 4.7)	(3.8 ± 0.9)
Group I			
(Euthyroid)	97 -172	4.5 - 11.8	0.3 - 4.7
(58 pts: 80.6%)	(136 ± 71)	(7.1 ± 5.8)	(3.7 ± 1.2)
Group II			
(Compensated	88 -151	4.7 - 10.9	10.6 - 30.5
hypothyroid)	(128 ± 62)	(7.9 ± 6.1)	(14.6 ± 6.2)
(9 pts: 12.5%)			
Group III			
(Decompensated	102 -169	0.6 - 3.7	15.6 - 52.8
hypothyroid)	(122 ± 56)	(2.1 ± 3.3)	(23.4 ± 7.6)
(5 pts: 6.9%)			
Significance (p value)			
N *vs* I	NS	NS	NS
N *vs* II	NS	<0.05	<0.001
N *vs* III	NS	<0.02	<0.001

TABLE II—*Height of Patients in Percentiles, Grouped According to Thyroid Dysfunction*

	Height in percentiles				
	<3	3-10	10-25	25-50	50-75
Group I					
Euthyroid	46	7	5	Nil	Nil
(58: 80.6%)	(79.3%)	(12.1%)	(8.6%)		
Group II & III					
Hypothyroid	12	2	Nil	Nil	Nil
(14: 19.4%)	(85.7%)	(14.3%)			
Significance (p value)	NS	NS	<0.02		

the 10th percentile in height and this was statistically significant($p<0.02$).

No significant difference could be found with respect to iron overload as assessed by *S. ferritin* between the various groups (*Table III*). Similarly, there was no difference between the liver dysfunction of the different groups (*Table III*). There was no correlation between thyroid status and age at diagnosis, age at first transfusion, mean hemoglobin, amount and duration of transfusion, splenectomy, overt attacks of jaundice and DFO therapy (data not shown).

Discussion

Thyroid gland is an important gland to maintain the normal physiology of the body. Besides various causes, iron overload is an important, although rare etiological factor in thyroid failure(16,17). Practically all endocrine organs are susceptible to damage by iron(18,19). Of these, diabetes mellitus and failure of physical as well as sexual growth are most commonly detected, investigated and treated(18,19). In thalassemia patients, variable results have been published regarding damage to parathyroid, thyroid and adrenal glands(3,6-9,16,17). Various authors have found normal thyroid function(3,7,8) while others have reported a high incidence of decompensated primary hypothyroidism(6,17).

Detection of hypothyroidism is important as effective replacement therapy is available. More importantly, unlike other modalities of treatment in thalassemia, thyroid replacement is neither expensive or cumbersome and compliance rate is good.

In the present study, 2 (2.8%) patients had frank symptoms of hypothyroidism. However, attention was directed to them only after low T_4 levels were documented. Both have done extremely well on replacement therapy. Not much attention is paid to thyroid deficiency in patients of thalassemia major and hence such omission is not surprising. Subclinical deficiency of thyroid hormone (compensated or decompensated) was present in another 12 patients (16.7%). Overall, approximately 1/5th of the patients in the present study were hypothyroid. Interestingly, serum T_3 values were normal in all the patients. This is not surprising as similar findings are well known in thyroid disorders due to other diseases as well(18,19). Marked increase in TSH level in patients with reduced T_4 suggested primary hypothyroidism. It must be noted that iron induced damage at various

TABLE III—*Age, Other Clinical and Laboratory Characteristics of 3 Patient Groups*

Groups		Age (yrs) Range (mean)	S. ferritin (ng/ml) Range (mean)	SGOT (IU/L) Range (mean)
I.	Normal (Euthyroid)	7 - 20 (13.2 ± 8.1)	2740 - 7860 (6320 ± 2620)	18 - 530 (172 ± 130)
II.	Compensated (Hypothyroid)	7 - 21 (12.5 ± 6.2)	2160 - 8940 (7120 ± 2253)	14 - 460 (206 ± 126)
III.	Decompensated (Hypothyroid)	8 - 22 (12.8 ± 8.8)	4850 - 9680 (7228 ± 2812)	48 - 302 (164 ± 82)
	Significance (p value)	NS	NS	NS

levels of hypothalamic-pituitary-peripheral endocrine organ is well known in thalassemic patients(16,20).

Although iron overload is the commonest cause of endocrine damage in patients of thalassemia(1,2), no correlation could be made between the iron overload and thyroid status in the present study. Interestingly, the same has been found for the occurrence of diabetes mellitus as well. No one doubts that iron has an important role to play in endocrine damage, but there appear to be other factors as well. Italian workers have also noted the lack of correlation between hypothyroidism and the amount of blood received or the iron overload status(19).

Other factors which could damage endocrine organs in patients of thalassemia major include hypoxia (due to anemia), and liver dysfunction as metabolism of various hormones is altered once the liver is damaged(20). Unfortunately, the present study could not show any relationship between liver dysfunction, transfusion regimen and thyroid damage.

In conclusion, it appears that a significant number of thalassemia major patients develop thyroid damage. Replacement of thyroid hormone, being cheap and easy and without side effects, must be carried out as this would significantly improve the quality of life. In view of iron induced cardiac damage, the replacement should be gradual and careful. We recommend that thyroid studies must be carried out at yearly intervals, at least after the age of 8 years to detect sub-clinical cases. These studies, even by RIA, would not cost more than Rs. 600/-. Attempts should be made to avoid hypoxia, iron overload, and liver damage, as these are the likely factors in the occurrence of hypothyroidism. Adequate quantity of good quality blood and effective iron chelation, thus remain the cornerstone of conventional therapy of thalassemia.

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NOTES AND NEWS

CME PROGRAMME ON PREVENTION AND CONTROL OF NOSOCOMIAL INFECTION IN HOSPITALIZED PATIENTS

Under the scheme for Continuing Medical Education with the Medical Council of India, approved by the Ministry of Health and Family Welfare, Government of India, a Continuing Medical Education Programme on 'Prevention and Control of Nosocomial Infection in Hospitalized Patients' is to be held at Christian Medical College, Vellore from *October 29-31, 1992*, in collaboration with American Association of Physicians from India and USA.

The Organizing Secretary is Dr. M.K. Lalitha, Professor of Microbiology, Christian Medical College, Vellore.