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Original Research Article

Prospective Observational Assessment of the Thyroid Profile in Patients of Thalassemia with Multiple Blood Transfusions and High Serum Ferritin

Jeetendra Mahato[1], Vivek Kumar[2], Gopal Shankar Sahni[3]

[1]Assistant professor, Department of Pediatrics, SKMCH, Muzaffarpur, Bihar, India
[2]Senior Resident, Department of Pediatrics, SKMCH, Muzaffarpur, Bihar, India
[3]Associate professor and HOD, Department of Pediatrics, SKMCH, Muzaffarpur, Bihar, India

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Corresponding author: Dr. Vivek Kumar
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Abstract

Aim: Thyroid profile in patients of thalassemia with multiple blood transfusions and high serum ferritin.

Methods: This prospective observational study was done in the department of Paediatrics, SKMCH, Muzaffarpur, Bihar, India, for the period of 1 year. 100 Children 3 to 18 years age group with proven Betathalassemia major, Child received blood transfusions for more than 2 years and children with serum ferritin level >700(ng/ml) were included in this study. A detailed history was obtained from each patient regarding the age of diagnosis, frequency of transfusions, compliance to transfusion, andchelation was noted. 3ml of fasting blood sample from venous blood under strict aseptic precautions is taken to assess serum levels of thyroxine (T4), tri-iodo-thyroxine (T3), thyroid-stimulating hormone (TSH) and Ferritin using Chemiluminescence Immunoassay method.

Results: In the study 59% were males and 41% were females. In the present study, 27% were in the age group below 5 years, 52% were in the age group 5 to 10years and 21% were in the age group above 10 years. The mean age of subjects was 8.12 ± 3.12 years. In the study 7% were Underweight (<3rd Centile), 71% were Normal (3rd to 90th Centile), 15% were Overweight (90th - 95th) and 6.7% were Obese (>95th Centile). In the study, the mean height was 166.25± 16.87cms, and the mean weight was 21.98 ± 9.02 kgs. Mean Hb was 7.25 ± 1.87 g/dl, mean Ferritin (ng/ml) was 1300.87 ± 1022.87, mean T3(pg/ml) was 2.52 ± 1.11, mean T4(ng/dl) was 3.26 ± 2.87 and mean TSH (mIu/L) was 4.66 ± 2.32.

Conclusion: Thalassemia patients have a high prevalence of endocrinological abnormalities. Several studies at different centers have demonstrated the increased prevalence of endocrinopathies in patients with thalassemia. Improvements in protocols of transfusion regime and chelating therapy should hopefully improve the care and quality of life of these patients.

Keywords: Thalassemia, endocrinopathies, thyroid profile

Introduction

Meta (β)-thalassemia is a genetic disorder of beta globulin fiber gene. In β thalassemic patients, β-globulin fibers are not enough (β+) or do not exist (β0). More than 200 mutations can cause β-thalassemia, but 20 incident alleles bring 80% of thalassemia in the world. [1]

The gene prevalence of thalassemia has been reported all over the world in average of 3%. However, the gene prevalence on thalassemia jones is about 2.5-15% which include Mediterranean seaboard, Arabian Peninsula, Turkey, Iran, India, Southeast Asia specifically Cambodia, Thailand and southern China. [2,3] 4% of Iranians are carriers of thalassemia. In northern Iran provinces, like Mazandaran and Golestan, 10-13% of their population is carriers of thalassemia gene. There are 2000 thalassemic patients in the U.S whereas, 15000 patients suffer from thalassemia in Iran. [2]

The combination of transfusion and chelation therapy has dramatically extended the life expectancy of thalassemic patients who can now survive into their fourth and fifth decades of life. [3] However, frequent blood transfusion in turn can result in iron overload which may lead to various complications. [4] Thalassemia's complications can be a result of many mechanisms. Most complications are caused by increased iron sedimentation in tissues like heart, endocrine glands and these results in heart failure, arrhythmia, hypothyroidism, diabetes mellitus and so on. [4,5] Most of these complications occur slowly and appear in the second decade of a patient's life Decrease production of thyroid hormones according to body demand or defect in thyroid hormone receptors cause hypothyroidism.

In several studies, hypothyroidism has been reported to be correlated with serum ferritin level; although in some studies there were no such correlations. Contrarily to significant iron deposition in thyroid gland, low activity remains about subclinical hypothyroidism. [6,7] Thyroid dysfunctions are well documented in patients with thalassemia major requiring frequent and recurrent blood transfusion. These have recently been discussed in detail in the literatures. [5-12] Also, growth retardation is another complication that usually occurs. However, it almost will not happen with sequential transfusion. Nonetheless, defroxamine overuse causes growth retardation by itself. [4] Although many studies report endocrinopathy in thalassemic patients, results are controversial and different, according to genetic and geographic characteristics of states, thus, we decided to study the thyroid profile in patients of thalassemia with multiple blood transfusions and high serum ferritin.

Material and methods

This prospective observational study was done in the department of Paediatrics, SKMCH, Muzaffarpur, Bihar, India, for the period of 1 year.

Inclusion and exclusion criteria

100 Children 3 to 18 years age group with proven Beta thalassemia major, Child received blood transfusions for more than 2 years and children with serum ferritin level >700(ng/ml) were included in this study.

children with thalassemia minor or intermedia, children less than 4 years of age, children with primary thyroid dysfunction and other endocrinal dysfunction, children on thyroxine, any antithyroid drugs, or any other hormonal therapy and children with any other chronic illness were excluded from this study.

Methodology

A detailed history was obtained from each patient regarding the age of diagnosis, frequency of transfusions, compliance to transfusion, and chelation was noted. 3ml

of fasting blood sample from venous blood under strict aseptic precautions is taken to assess serum levels of thyroxine(T4), tri-iodo-thyroxine (T3), thyroid-stimulating hormone (TSH) and Ferritin using Chemiluminescence Immunoassay method.

Data were entered into a Microsoft Excel datasheet and were analyzed using SPSS 20 version software. Categorical data was represented in the form ofFrequencies and proportions. Chi-square test or Fischer's exact test (for 2x2 tables only) was used as a test of significance for qualitative data. Continuous data were represented as mean and standard deviation. Independent t-test or Mann Whitney U test was used as a test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively. Pearson correlation was done to find the correlation between two quantitative variables and qualitative variables respectively. p-value (Probability that the result is true) of <0.05 was considered as statistically significant. MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

Results

In the study 59% were males and 41% were females. In the present study, 27% were in the age group below 5 years, 52% were in the age group 5 to 10 years and 21% were in the age group above 10 years. The mean age of subjects was 8.12 ± 3.12 years (Table 1)

In the study 7% were Underweight (<3rd Centile), 71% were Normal (3rd to 90th Centile), 15% were Overweight (90th - 95th) and 6.7% were Obese (>95th Centile) (Table 2).

In the study, the mean height was 166.25± 16.87cms, and the mean weight was 21.98 ± 9.02 kgs (Table 3).

Mean Hb was 7.25 ± 1.87 g/dl, mean Ferritin (ng/ml) was 1300.87 ± 1022.87, mean T3(pg/ml) was 2.52 ± 1.11, mean T4(ng/dl) was 3.26 ± 2.87 and mean TSH (mIu/L) was 4.66 ± 2.32 (Table 3).

In the present study, 3(3%) had a haemic murmur,1(1%) had hepatomegaly,84(84%) had hepatosplenomegaly and 12(12%) had splenomegaly.

In the study, 4 subjects (4%) had a history of use of chelators and 96 (96%) subjects were not on chelators. In this study, 2% had A- blood group, 25% had A+ve blood group, 20% had AB+ ve, 2% had B-ve, 34% had B+ve and 17% had O+ve blood group. In this study,9% had mild anemia, 38% had moderate anemia and 53% had severe anemia.

Table 1: Age and Sex distribution of subjectsin the study.

		No. of patients=100	**%**
Sex	Female	41	41
	Male	59	59
Age	Below 5 years	27	27
	5-10 years	52	52
	Above 10 years	21	21

Table 2: BMI distribution of subjects in thestudy

		No. of patients=100	**%**
BMI	Underweight (<3rd Centile)	7	7
	Normal (3rd to 90th Centile)	71	71
	Overweight (90th -95th Centile)	15	15
	Obese (>95th)	7	7

Table 3: Mean values of Weight, Height, Hb, Ferritin, and Thyroid profile of subjects.

Parameter	Mean	SD
Weight(kgs)	21.98	9.02
Height(cms)	166.25	16.87
Hb(g/dl)	7.25	1.87
Ferritin(ng/ml)	1300.87	1022.87
T3(pg/ml)	2.52	1.11
T4(ng/dl)	3.26	2.87
TSH (mIu/L)	4.66	2.32

Table 4: Correlation of Serum Ferritin with T3, T4, and TSH

Correlations					
		Ferritin (ng/ml)	T3 (pg/ml)	T4 (ng/dl)	TSH (mIu/L)
Ferritin(ng/ml)	Pearson Correlation	2	-0.377	0.187	0.489
	Sig. (2-tailed)		0.003	0.195	<0.001
	N	98	98	98	98
Correlation is significant at the 0.01 level (2-tailed)					

In this study, there was a significant negative correlation between Ferritin and T3 levels. i.e. with an increase in Ferritin level, there was a decrease in T3 levels and vice versa. There was a positive correlation between Ferritin and T4, TSH levels. i.e. with an increase in Ferritin level, there was an increase in T4, TSH levels, and vice versa. However, the correlation was significant with TSH.

In this study, 61% had normal T3, 39% haddecreased T3. 61% had normal T4, 7% haddecreased T4 and 32% had increased T4, 81% had Normal TSH and 19% had increased TSH levels.

In the study, 7% had overt hypothyroidism, 14% had subclinical hypothyroidism and 79% had euthyroid status. (Table 5).

Table 5: Hypothyroidism in the subjects

		Count	%
Thyroid condition	Overt Hypothyroidism	7	7%
	Subclinical Hypothyroidism	14	14%
	No Hypothyroidism	79	79%

Discussion

According to the Thalassemia International Federation, only about 200,000 patients with thalassemia major are alive and registered as receiving regular treatment around the world. [13] The combination of transfusion and chelation therapy has dramatically extended the lifeexpectancy of thalassemia patients but is complicated by citrate toxicity and subsequent iron overload resulting in a high incidence of endocrine abnormalities in children, adolescents, and young adults.

Endocrinopathies are now amongst the common complications of thalassemia but determining the exact prevalence is difficult because of differences in age of first exposure to chelation therapy and the continuing improvement in survival in well-chelated patients.

Among the endocrine complications, the current study has looked into

hypothyroidism as thyroid hormone is essential for the development and maintenance of normal function of CNS and regular follow-up for early detection and timely treatment ofsuch complications could improve the quality of life of these patients.

Thalassemic children show retardation of growth in the fetal, infantile, pre-pubertal, and pubertalperiods. [14] A study done by Karamifar et al have demonstrated that 62.9% of girls and 69% of boys affected with thalassemia were less than 2SD below the mean for normal height. [15] [10] Another study done by Roth et al showed that 40.6% of patients were short in stature (height below the third percentile). [16] Soliman et al reported a prevalence of short stature (<2SD) in 49% of their thalassemic patients. [17]

Thyroid dysfunction is a frequently occurring endocrine complication in thalassemia major, but its prevalence and severity are variable, and the natural history is poorly described. [18] Autoimmunity has no role in the pathogenesis of thalassemia related hypothyroidism. [19] Primary hypothyroidism is characterized by an elevated thyroid-stimulating hormone (TSH) level and decreased (low) T4.

Secondary or central hypothyroidism is characterized by decreased T4 and low TSH. Up to 5% of thalassaemic patients develop overt clinical hypothyroidism that requires treatment whereas a much greater percentage have sub-clinical compensated hypothyroidism with normal T4 and T3but high TSH levels. [20]

In mild and overt hypothyroidism, symptoms such as growth retardation, decreased activity, above normal weight, constipation, reduced school performance, cardiac failure, and pericardial effusion may be seen. It usually occurs in iron overload thalassemic but is uncommon in optimally treated patients. The pathogenesis is again unclear but thought to relate to lipid peroxidation, free radical release, and oxidative stress.13 The incidence of hypothyroidism is directly related to the degree of iron overload. A study done by Agarwal MB et al shows thyroid failure was among 19.4%, postulating interplay of chronic hypoxia and iron overload responsible for thyroid gland damage. [21] Jain M et al carried out a study on 25 beta- thalassemia major patients with an age range of 5- 17 years,32% (8 out of 25) had thyroid dysfunction relating directly to transfused iron overload. [22]

An exaggerated TSH response to stimulation by thyrotrophin-releasing-hormone (TRH) was found by De Sanctis et al in 8 of 24 thalassaemias studiedand a third of those went on to develop sub-clinical or overt hypothyroidism three to eleven years later. [23] This suggests the development of thyroid disease may have a fairly protracted course. De Sanctis et al in another study showed that good compliance with chelation therapy appeared to improve thyroid function. [24]

In a study done by Jaipuria. R et al hypothyroidism was found in 23.3% (14out of 60) of β thalassemia patients. Out of these, compensated hypothyroid (normal T3 and T4 with raised TSH) was seen in 9 patients (15%) and decompensated hypothyroid (decrease T3 or T4 and Raised TSH) was seen in 5 patients (8.33%).

There was a significant positive correlation of TSH levels with serum ferritin levels, age, and transfusion index. [25] Parijat et al found that 5% (8 out of 163) of thalassemia patients had overt clinical hypothyroidism that required treatment whereas a much greater percentage have sub- clinical compensated hypothyroidism with normal T4 and T3 but high TSH levels. [26] A study done by Eshragi Pet al showed that hypothyroidism was diagnosed in 14% (19out of 130) of patients. [27] Chirico et al. followed up 72 thalassaemic patients demonstrated ferritin

levels correlate positively with both TSH and thyroid volume on ultrasonography and can predict progression of thyroid disease. [28]

In the study 59% were males and 41% were females. In the present study, 27% were in the age group below 5 years, 52% were in the age group 5 to 10 years and 21% were in the age group above 10 years. The mean age of subjects was 8.12 ± 3.12 years.

In the study, 7% had overt hypothyroidism, 14% had subclinical hypothyroidism and 79% had euthyroid status. National and international studies done on thyroid dysfunction in beta-thalassemia which were described by other author . [29]

In the present study, there was a positive correlation between Ferritin and T4, TSH levels. i.e. with an increase in Ferritin, there was an increase in T4, TSH levels. This is comparable with other few studies done on thyroid dysfunction in beta thalassemia and its correlation with serum ferritin levels which is described by another author. [30,31]

Conclusion

Thalassemia patients have a high prevalence of endocrinological abnormalities. Several studies at different centers have demonstrated the increased prevalence of endocrinopathies in patients with thalassemia. Improvements in protocols of transfusion regime and chelating therapy should hopefully improve the care and quality of life of these patients. Early recognition and treatment of endocrine failure in poly-transfused beta-thalassemia major patients is a significant part of the holistic management of the disease. This is particularly true for thyroid dysfunction because hypothyroidism could be implicated in growth problems so commonly envisaged in these patients.

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