Original Article

Thyroid function in major thalassemia patients: Is it related to height and chelation therapy?

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Abstract

Background: One of the most common endocrine problems in major beta-thalassemia is hypothyroidism (HT). The aim of this study was to evaluate thyroid function status in major β-thalassemia patients older than 10 years old.

Methods: This cross sectional study was carried out on thalassemia major patients registered on Thalassemia Center of Amirkola Children Hospital in Babol. A questionnaire was filled out by the patients to evaluate the demographic information, quality of their last transfusions and chelation therapy. Growth parameters were evaluated. We assessed serum T_4, TSH, T_3RU and FTI in all patients and those with hypothyroidism, anti-thyroglobulin and anti-thyroid proxidase antibodies were checked

. ***Results:*** One hundred-thirty patients (56 males and 74 females) were enrolled in this study. The mean age was 20.95±7.8 years. Short stature was seen in 41(31.3%) patients. In 53(40.8%) patients, weight was under normal range. HT was found in 19 patients (14.6%); 2 primary overt HT, 3 secondary HT and 14 subclinical HT were detected. No patient with HT had significant serum level of anti-thyroid antibodies. Correlation between HT and serum ferritin level was not significant (p=0.584) but it was significant for HT and short statures (p=0.002), also regular transfusion and chelation therapy were correlated with ferritin level.

Conclusion: High prevalence of HT among thalassemic patients signifies the importance of regular screening for evaluation of endocrine function in these patients; especially when short stature is present.

Keywords: Major thalassemia, Hypothyroidism, Serum ferritin.

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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 (β^0). 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 details 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 patients of Mazandaran province to introduce hypothyroidism in correlation with short stature, regular transfusion and chelation therapy, anti-thyroid antibodies and serum ferritin level in this state.

Methods

This cross-sectional study was carried out on 130 patients older than 10 years old and they have been selected from 214 registered patients at Thalassemia Center of Amirkola Children Hospital in 2009. Those who had other kinds of thalassemia (Intermedia) or younger than 10 years-old or those who could not continue the further survey were excluded. Patients who agreed to participate in the study, completed a questionnaire consisted of demographic information, age of disease onset, frequency of time of monthly transfusion and its interval time, times of using desferal every week, last amount of blood ferritin & history of endocrine problems and referral to endocrinology clinic. The patient's height and weight were measured on the base of NCHS growth charts that were interpreted. Serum ferritin was measured and patients with serum ferritin lower than 1500 ng/ml were categorized in good controlled group. Patients with serum ferritin more than 1500 ng/ml were categorized in poor controlled group. Patients had to use iron chelators such as defroxamine, defrospridon and deferasiron. Drug prescription and blood transfusion was different for each patient and it depended to their needs and hematologist's diagnosis. On this field, patients were categorized in good and poor groups. The patients who exactly followed hematologist prescription entered in the good group and those who did not do that completely, entered in the poor group.

Initially, requested tests were similar for all the patients. We measured serum level of T_3RU (T_3 Resin uptake), TSH (thyroid stimulating hormone), T_4 (thyroxin), FTI (Free thyroxin index) and ferritin. In hypothyroid patients, anti-thyroid peroxidase and anti-thyroglubolin antibodies would be checked. Normal range and methods were mentioned in table 1.

Table 1. Unit, Company and normal range of tests.

Test	Method	Production Company	Unit	Normal range
T_3RU	ELISA	Monobind	percent	25-38
TSH	ELISA	Monobind	MIU/l	0.5-5
T_4	ELISA	Monobind	µg/dl	M: 4.4-10.8 F: 4.8-11.6
AntiTPO*	ELISA	IBL	IU/ml	Neg: <150 Borderline: 50-75 Pos: >75 µIU/ml
Anti TG**	ELISA	Aesseco	IU/ml	Neg: <100 Borderline:100-150 Pos: >150 µIU/ml
Ferritin	ELISA	Pishtaz	ng/ml	M: 30-300 F: 20-150

*Anti TPO= Anti thyroid peroxidase

**Anti TG= Anti Thyrogluboline

We categorized hypothyroidism in three sets: 1) Primary overt hypothyroidism: low FTI, TSH>15 µIU/ml; 2) Secondary hypothyroidism: low FTI, low TSH response; and

3) Subclinical primary hypothyroidism: normal FTI, TSH: 5-15 µIU/ml (9). According to patients' data, relation between hypothyroidism with short stature, ferritin level and cooperation in blood transfusion and chelator therapy was evaluated.

Analysis was performed by SPSS version 18. Student's t-test, the Mann-Whitney and λ^2 test were used for analysis. $p<0.05$ was considered statistically significant.

Results

This study surveyed 130 patients (56 males and 74 females) suffering from β-thalassemia. Their ages ranged from 10 to 47 years, with the mean age of 20.13±6.7 years for females and 21.99±7.4 years for males. The average weight in females was 46.41±10.28 kg and in males 49.9±11.08 kg. Mean for measured height was about 160±13.2 cm in males and 149±7 cm in females. Growth in sufficiency was detected in 37% (27 females) of women and 34% (25 males) of men. On the base of patients and physician logrolling to inject defroxamine, other chelators, and blood transfusion, 69(53.1%) patients cooperated with the physician (Good group of chelator therapy). The mean of serum ferritin of patients were 1786±871 µg/L (1778±884 µg/L in females and 1796±862 µg/L in males), in 12%, serum ferritin was >3000µg/L. The frequency of ferritin is described in fig 1.

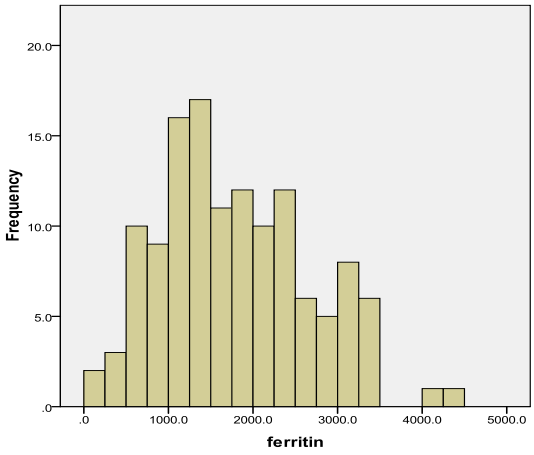

Figure1. The serum Ferritin level in thalassemic patients.

It would be notable that there was a significant relationship between serum ferritin and desferal injection patients' acceptance ($p<0.001$). Mean serum TSH was about 3.40±4.68 mIU/lit. Sixteen patients had excess TSH density (10 men, 6 women). Primary Overt Hypothyroidism was detected in 2 male patients and secondary hypothyroidism was detected in 3 patients (2 women and 1 man) and subclinical hypothyroidism was detected in 14 patients (8 men and 6 women) as showed in chart fig 2. There was no significant titer of anti-TPO and anti-TG antibodies. There was no relation in HT and patients' gender ($p=0.36$) but there was significant relationship between ferritin level and the patients' cooperation ($p<0.001$). Also, short stature was associated with hypothyroidism ($p=0.002$). But there was not such relation between ferritin level and hypothyroidism ($p=0.584$).

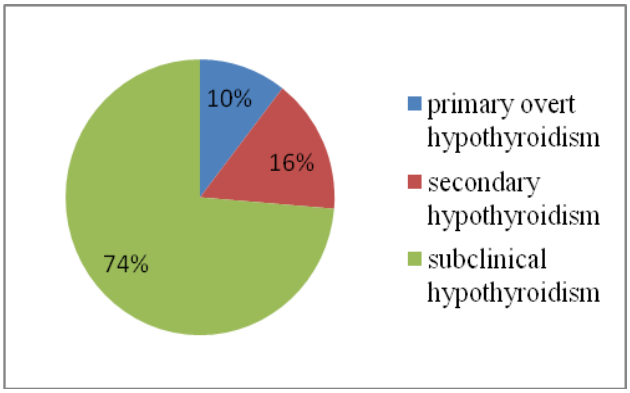

Figure 2. The frequency of hypothyroidism in thalassemic patients.

Discussion

Thalassemia is one of the most important genetic diseases and thyroid dysfunction which is well documented in these patients. Iron overload of tissue is the most important complication of beta-thalassemia and is a major subject of management (13). After approximately one year of transfusions; iron starts to be accumulated in parenchymal tissues, where it may bring about substantial toxicity as compared with reticuloendothelial cells (14-15). Hypothyroidism may be partly related to the accumulation of iron in thyroid gland due to blood transfusion by iron

overload leading gland dysfunction (16). Despite the reports relating to the endocrine dysfunction with iron overload, it was recently demonstrated that the degree of iron overload, at least reflected by serum ferritin levels, was not associated with the development of endocrine complications (17-18). We studied 130 patients with major thalassemia from which 19 cases suffered from hypothyroidism (14.6%). There are some differences with other studies. Hypothyroidism was reported 7% in Shiraz by Karamifar, 16% in Tabriz by Najafpour and 7.7% in Tehran by Shamshirsaz, whereas, De Sanctis reported 21.6% in Italy (7, 9-11). Unlike ours, in these studies, there were primary hypothyroidisms but not secondary (7, 9-10, 12). Different results are because of genetic, geographic, cultural, economical factors and also quality of blood transfusion and chelators.

Almost 31% of our patients were short stature, and 40% were wasted while in other centers, different results were obtained. For example in Shiraz, short stature has been reported 59% of females and 51% of males. But wasting was reported in 40% of patients that was similar to our results (10). This confirmed to notice on growth charts of patients and supporting them with appropriate nutrition and complements during childhood and adolescence period and treatment of underlying cause as soon as possible. In our study and other similar studies, there was no significant anti-thyroid antibody (12, 19). Does it mean that thalassemia and multiple blood transfusions have a protective effect on autoimmune thyroid disease?

Mean serum ferritin level was 1786±871 µg/L and there was no significant difference between the males and the females. Twelve percent of patients' serum ferritin was more than 3000 µg/L. Karamifar reported serum ferritin of 50% of their patients was more than 3000 µg/L. He also stated that the average of serum ferritin was about 3365±2172 µg/L that is extremely more than our patients (10). Maybe this indicates that these patients use defroxamine much more in Thalassemia Center of Amirkola Children's Hospital.

We found that there was a significant relationship between serum ferritin and the patients' treatment acceptance ($p<0.001$) therefore, we can use serum ferritin level as a good marker of patient's cooperation in regular blood transfusion and chelation therapy. Obviously, if serum ferritin level increases, focusing on regularity of transfusion and chelation therapy will correct it.

We did not get any relevance between hypothyroidism and serum ferritin unlike in some other studies (7,10) but some others believe there is (20). A report by De Sanctis described a relationship between serum ferritin and serum TSH density (12) whereas he did not find this relevance in his last study (19). According to these controversial data, serum ferritin level cannot be a good marker in prevision of hypothyroidism.

The absence of the relationship between ferritin and HT may be explained by suggesting that the damage of endocrine glands caused by chronic ischemia is more pronounced than that caused by hemosiderosis as a consequence of iron collapse. Short stature is one of the most prevalent side effects in thalassemia. In Shiraz, more than 50% (10), in Tehran 39% (7), in Tabriz 52% (9) of patients were short stature. This study has detected significant correlation between short stature and HT ($p=0.002$) and because of no relation between HT and ferritin level or regularity in chelation therapy or blood transfusion, we should consider hypothyroidism monitoring especially in short stature thalassemic patients in conclusion.

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