

Longitudinal study on thyroid function in patients with thalassemia major: High incidence of central hypothyroidism by 18 years

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ABSTRACT

Introduction: Primary hypothyroidism is one of the most frequent complications observed in-patients suffering from thalassemia. We investigated and reviewed the thyroid function in all thalassemic patients attending the Pediatric Endocrine Clinic of Hamad Medical Center, Doha, Qatar during the last 10 years of follow-up. **Patients and Methods:** A total of 48 patients with β -thalassemia major between 5 years and 18 years of age. Thyroid dysfunction was defined as follows: Overt hypothyroidism (low Free thyroxine [FT4] and increased thyroid-stimulating hormone [TSH] levels $>5 \mu\text{IU/ml}$); subclinical hypothyroidism (normal FT4, TSH between $5 \mu\text{IU/ml}$ and $10 \mu\text{IU/ml}$) and central (secondary) hypothyroidism (low FT4 and normal or decreased TSH). **Results:** A total of 48 patients (22 males and 26 females) completed a 12 year-period of follow-up. During this period, hypothyroidism was diagnosed in 17/48 (35%) of patients. There was no significant difference in the prevalence in males 7/22 (32%) versus females 10/26 (38%). Sixteen of the patients had hypothyroidism after the age of 10 years (94%). The prevalence of overt hypothyroidism had risen from 0% at the age of 7 years to 35% at the age of 18 years. None of the patients had high anti-thyroperoxidase antibody titers. Out of 17 patients, 13 patients with hypothyroidism had normal or low TSH level (not appropriately elevated) indicative of defective hypothalamic pituitary response to low FT4 (central hypothyroidism). Three patients (6.3%) had subclinical hypothyroidism (TSH between $5 \mu\text{IU/ml}$ and $10 \mu\text{IU/ml}$ and normal FT4). The general trend of FT4 level showed progressive decrease over the 12 years, whereas, TSH levels did not show a corresponding increase. These data suggested defective hypothalamic pituitary thyroid axis involving both TSH and FT4 secretion in patients with thalassemia major over time. There was a significant negative correlation between serum ferritin and FT4 ($r = -0.39$, $P = 0.007$), but no correlation was found between ferritin and TSH. **Conclusions:** Worsening of thyroid function was observed in 35% of the studied thalassemic patients by the age of 18 years. The lack of proper increase of TSH in response to the low circulating levels of FT4 in 13/17 (76%) of these patients indicates a relatively high incidence of defective pituitary thyrotrophic function in these patients.

Key words: Ferritin, free thyroxine, growth, hypothyroidism, prevalence, thalassemia, thyroid stimulating hormone

INTRODUCTION

Thalassemia is one of the most common genetic disorders caused by a reduction of the globin chains leading to chronic

hemolytic anemia from birth. The mainstay of treatment is blood transfusion to maintain adequate levels of hemoglobin. Iron overload in β -thalassemia major (TM) patients is secondary to multiple blood transfusions and increased iron absorption.^[1-3] Excessive iron potentially catalyzes free-radicals generation and impairment in cellular function and integrity. Extensive iron-induced injury develops in the heart, liver, pancreas, and endocrine system.^[4,5]

The reported thyroid dysfunction seen in patients with TM includes primary hypothyroidism-caused abnormalities of the thyroid gland, subclinical hypothyroidism as well as secondary hypothyroidism.^[5-10] The frequency of

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hypothyroidism shows a discrepancy depending on the region, quality of management, and treatment protocols.^{16,71} The reported frequency of thyroid dysfunctions ranges between 13% and 60% in different studies and occurs after 10 years of age regardless of difference in the rate of prevalence, largely as in the form of subclinical hypothyroidism.^{16,71} Primary hypothyroidism is characterized by an elevated thyroid-stimulating hormone (TSH) level and decreased (low) T4. Secondary or central hypothyroidism characterized by decreased T4 and low TSH.

The objective of this longitudinal study was to determine the prevalence and type of hypothyroidism in all transfusion dependent patients with TM treated in Hamad Medical Center (HMC) for 12 years and correlate thyroid function with the degree of iron overload represented by the mean ferritin level over a 12-year period.

PATIENTS AND METHODS

In this analytical descriptive cross-sectional study, 48 patients with TM who was treated with blood transfusion in HMC were studied. They were treated with repeated blood transfusion every 3-5 weeks and desferoxamine (desferal) therapy after 20 blood transfusions and changed to oral Deferasirox for the past 3 years. All patients with TM (26 females and 22 males) were non-splenectomized, and none had a family history of hypothyroidism. All had complete sexual maturation (Tanner 4 or 5 maturity rating) either spontaneously ($n = 44$) or through sex steroid replacement ($n = 4$).

Free thyroxine (FT4) and thyrotrophic hormone (TSH) were determined yearly and serum ferritin concentrations were followed 3 times yearly for 12 years. Totally 48 patients completed the study up to the age of 18 years.

Diagnoses of thyroid dysfunction were based on the following

1. Primary hypothyroidism is diagnosed when FT4 is <12 pmol/L, and TSH is >5 mIU/ml
2. Subclinical hypothyroidism is diagnosed when T4 is normal, and TSH is >5 mIU/ml

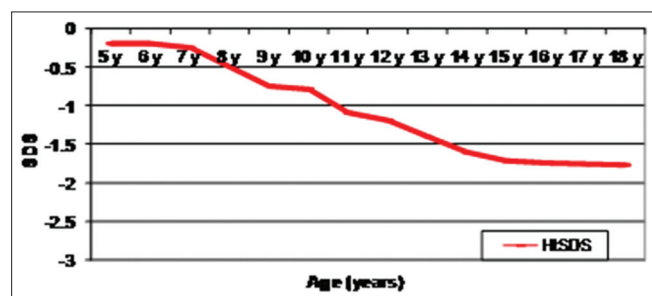


Figure 1: Changes of height SDS in patients with thalassemia over 12 years

3. Central hypothyroidism is diagnosed when FT4 is <12 pmol/l and TSH is low or normal.

FT4 was measured by radioimmunoassay, and TSH was measured by immunoradiometric assay using kits purchased from Genprice Inc, Santa Clara, CA 95054. The inter-assay and intra-assay coefficients of variations of FT4 were 6.6%, and 3.9%, respectively, and those of TSH were 6.1%, and 2.4%, respectively. The normal range for FT4 was 12-18.5 pmol/L and TSH was 0.25-4.5 mIU/L. Iron overload calculation was based on the mean ferritin level over a 12-year period. Normal serum ferritin value in our lab = 15-75 ug/L. (Serum ferritin concentrations between 500 ug/L and 1000 ug/L is considered good control, between 1000 ug/L and 2000 ug/L is considered fair control, and > 2000 ug/L is considered bad control). The normal ranges for FT4 and TSH in our lab were (11.59-19.3 pmol/L) and (0.3-4.2 uIU/L) respectively.

RESULTS

Forty eight patients completed a 12 year-period of follow-up. During this period hypothyroidism was diagnosed in 17/48 (35%) of patients. Sixteen of them were diagnosed after the age of 10 years (94%). Anthropometric data of patients showed that both height SDS (HtSDS) and body mass index SDS (BMISDS) decreased progressively with age [Figures 1 and 2] respectively.

The prevalence of overt hypothyroidism had risen from 0% at the age of 7 years to 35% at the age of 18 years [Figure 3]. There was no significant difference in prevalence in males 7/22 (32%) versus females 10/26 (38%). Sixteen of the patients had hypothyroidism after the age of 10 years (94%). None of the patients had high anti-thyroperoxidase antibody titers. 13 out of the 17 patients with hypothyroidism had normal or low TSH level (not appropriately elevated) indicative of defective hypothalamic pituitary response to

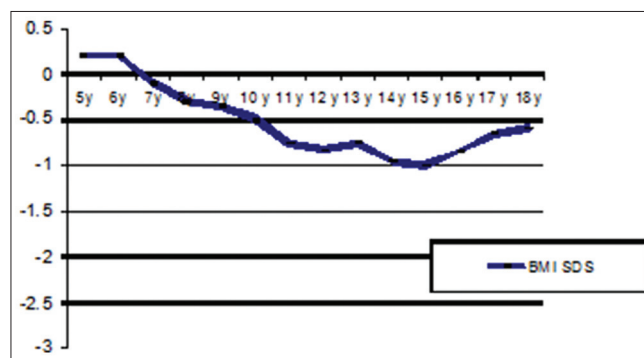


Figure 2: Changes of body mass index SDS in patients with thalassemia over 12 years

low FT4 (central hypothyroidism). Three patients (6.3%) had subclinical hypothyroidism (TSH between 5 uIU/ml and 10 uIU/ml and normal FT4).

The mean serum ferritin for the period of the 12 years (2758 ± 592 ug/L) denoted improper iron chelation. Ferritin level did not differ between hypothyroid and euthyroid thalassemic patients [Table 1].

The general trend of growth in all patients with thalassemia showed progressive decrease of Ht SDS and BMISDS over 12 years. The HtSDS and BMI of thalassemic patients with hypothyroidism (-1.49 ± 0.55 and -0.52 ± 0.1 respectively) did not differ significantly compared to patients with normal thyroid function (-1.38 ± 0.62 and -0.48 ± 0.12). The general trend of FT level showed progressive decrease over the 12 years, whereas TSH levels did not show a corresponding increase. These data suggested defective hypothalamic pituitary thyroid axis involving both TSH and FT4 secretion in patients with TM over time [Figure 4a-c]. The height SDS and bilirubin and ferritin concentrations did not differ between hypothyroid and euthyroid patients [Table 1].

The age of thalassemic patients was correlated negatively with the FT4 ($r = -0.595$, $P < 0.0001$) [Figure 5] and ferritin ($r = 0.33$, $P = 0.026$) [Figure 6] concentrations. There was a significant negative correlation between serum ferritin and FT4 concentrations ($r = -0.39$, $P = 0.007$) [Figure 5] but no correlation was found between ferritin and TSH concentrations [Table 2]. There was no significant correlation between FT4 and serum alanine transferase (ALT) or bilirubin concentrations.

We found no significant correlation between serum ferritin concentrations and FT4 or TSH levels in thalassemic patients [Figure 7].

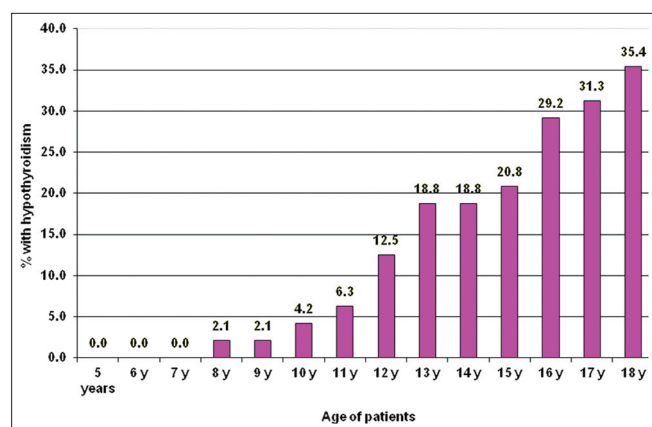


Figure 3: Prevalence of hypothyroidism in thalassemic over 12 years of follow-up

DISCUSSION

Thyroid dysfunction is known to occur frequently in thalassaemia major, but its prevalence and severity varies in different cohorts and the long-term natural history is incompletely described.^[5-10] We evaluated the pituitary/thyroid axis in TM patients in a longitudinal study and correlated FT4 and TSH secretion with the mean ferritin level over a 12-year period in non-splenectomized indices of iron overload.

Our longitudinal data showed a relatively higher prevalence of hypothyroidism in thalassemic patients during their second decade of their life (35% at the age of 18 years) than reported by other studies.^[5-10] The age of patients with TM was correlated significantly with the FT4 and ferritin levels. In addition, ferritin level was correlated negatively with FT4. These findings indicated that in patients with TM progressive deterioration of thyroid function with time, and this is related to iron overload.

In the majority of the cross sectional studies primary rather than secondary hypothyroidism had a higher prevalence.^[5-10] In a longitudinal study, Filosa *et al.* reported progressive increase of hypothyroidism increased over a period of 12 years to 13.9% by the age of 25.7 ± 1.7 years.^[11] Zervas *et al.*^[8] reported that approximately 1 of 5 β -thalassemic patients with normal thyroid hormone values showed an exaggerated TSH response to TRH test. However, unlike their thalassemic patients, who had elevation of TSH, our patients had a slowly progressive decrease of FT4 over

Table 1: Height SDS, ferritin and bilirubin in hypothyroid versus euthyroid patients

	Hypothyroid patients	Euthyroid patients
Number	17	31
Height SDS	-1.89 ± 0.55	-1.72 ± 0.69
BMISDS	-0.59 ± 0.27	-0.65 ± 0.29
Ferritin ug/L	2955 ± 532	2658 ± 622
Hemoglobin (before transfusion) g/dl	8.1 ± 1	8.2 ± 0.8
Alanine transferase (ALT (U/L)	53 ± 19	49 ± 14
Bilirubin (mg/dl)	1.12 ± 0.35	1.22 ± 0.55

* $P < 0.05$, ALT: Alanine transferase, BMISDS: Body mass index SDS, SDS: standard deviation score

Table 2: Correlation between FT4, TSH and ferritin concentrations

	Age	TSH	T4	Ferritin
Age	1			
TSH	-0.27	1		
T4	-0.595*	0.27	1	
Ferritin	0.326*	-0.04	-0.3906*	1

* $P < 0.05$, TSH: Thyrotrophic hormone, FT4: Free thyroxine

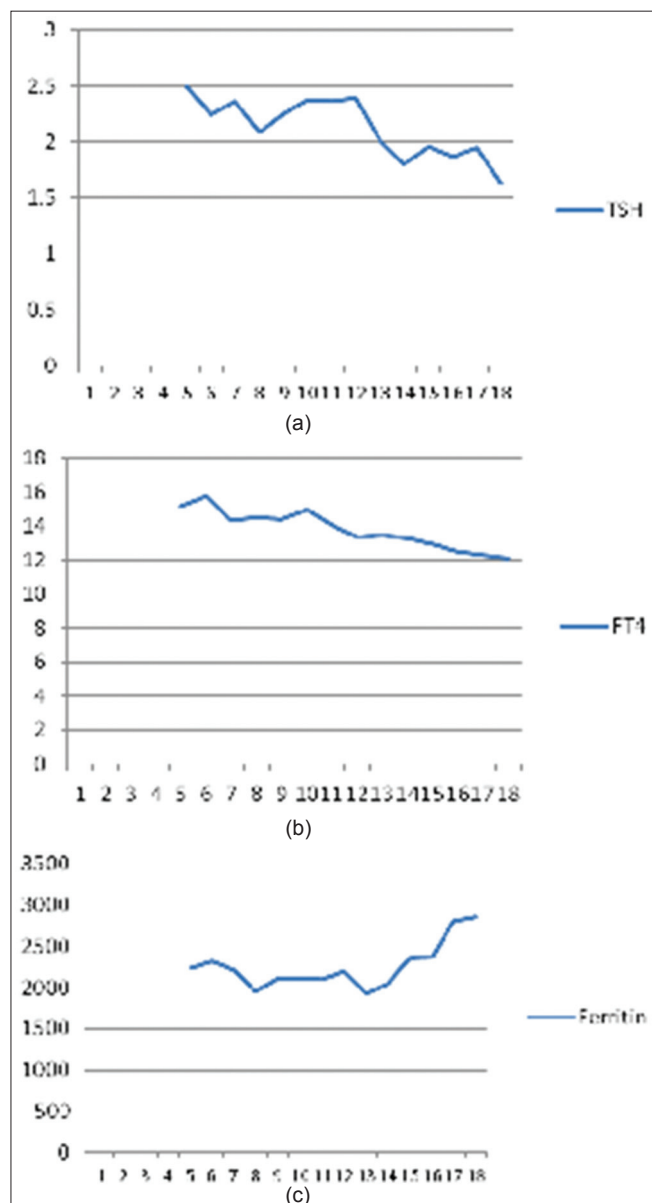


Figure 4: Mean changes of serum concentrations of thyroid-stimulating hormone (uIU/ml) (a), free thyroxine pmol/L (b) and ferritin (c) over 12 years in thalassemic patients

the 12 year-period associated with a corresponding slow decrease of TSH. These data indicated progressive slow dysfunction of the thyroid gland with a degree of pituitary insensitivity to the low FT4 level (central component of hypothyroidism). In 13 of 17 of our hypothyroid patients with TM, there was no increase of TSH associated with the decrease of their FT4 secretion. In support of this finding Hashemi *et al.* reported a higher incidence of secondary hypothyroidism (12%) compared to primary hypothyroidism (2%) in their thalassemic patients.^[12] But other studies reported higher prevalence of primary hypothyroidism in their thalassemic patients.^[3,7,8] This discrepancy in the frequency of pituitary-thyroid axis affection may be partially explained by discrepancy

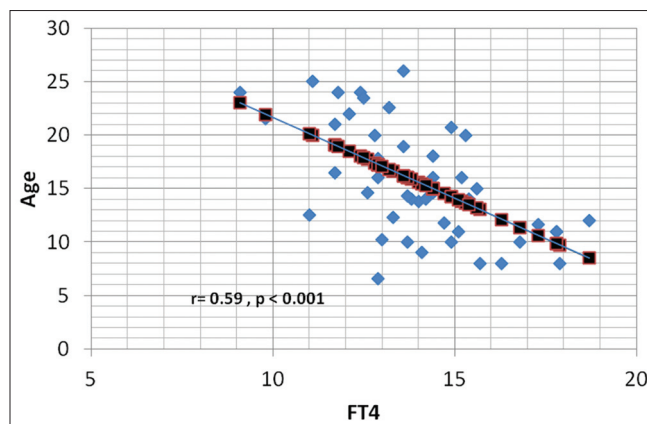


Figure 5: Correlation between age and free thyroxine in thalassemic patients

depending on the region, quality of management and treatment protocols.^[8-11] Variable degree of dysfunction of central (pituitary) and peripheral endocrine glands; namely the pituitary-growth (GH-IGF-I) axis and pituitary-gonadal axis have been reported in thalassemic patients.^[1-8]

In our patients, the mean serum ferritin over 12 years was higher than 2000 ug/L denoting improper chelation of iron. Additionally, ferritin concentrations were correlated negatively with FT4 levels. These data point out to the major role played by the excess iron in the pathogenesis of hypothyroidism in these patients. The precise underlying mechanism(s) of iron-induced organ dysfunction presently remains unclear. However, when iron level in the body becomes high, this leads to saturation of transferrin, and hence non-transferrin-bound iron (NTBI) species circulate in the plasma. Unbound iron, within cells or in plasma, is labile and able to redox cycle between Fe^{2+} and Fe^{3+} , thereby generating reactive oxygen species, leading to lipid peroxidation.^[12,13] The result of lipid peroxidation, under conditions of iron overload, leads to generation of both unsaturated (malondialdehyde and hydroxynonenal) and saturated (hexanal) aldehydes. Both have been implicated in cellular dysfunction, cytotoxicity and cell death.^[14,15]

Certain tissues are particularly susceptible to excess iron incorporation when NTBI is present. Thyrotrophin (TSH) - releasing hormone stimulates TSH beta promoter activity by two distinct mechanisms involving calcium influx through L type Ca^{2+} channels (LTCCs) and protein kinase C.^[16] The most recent evidence suggests that LTCCs are the front-runners for mediating NTBI transport in iron overload conditions.^[17,18] LTCCs are highly expressed in pancreatic beta cells as well as moderately in thyrotrophs and gonadotrophs. These tissues appear to be at the greatest risk in iron overload.^[16-21] In addition, protein kinase C has been shown to be regulated by iron

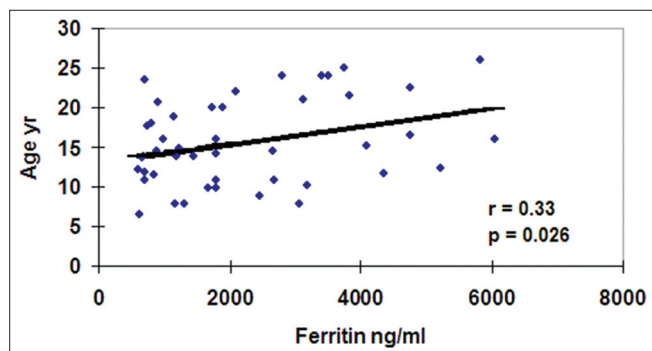


Figure 6: Correlation between age and ferritin in thalassemic patients

with possible deleterious effect of excess iron on its function.^[21-23] Both mechanisms appear to be affected by iron overload and can explain the defective TSH secretion in response to low FT4 in thalassemic patients. The deposition of iron in the pituitary gland and its deleterious effects on pituitary size and functions has been reported in many studies.^[24-26]

However, in hereditary hemochromatosis although the thyroid gland is the site of substantial iron deposition, thyroid dysfunction is considerably uncommon. In 154 consecutive patients, (123 male, 31 female) primary hypothyroidism was identified in 0.6% and subclinical hypothyroidism in 1.3% of patients.^[27] Additionally, the higher prevalence of hypothyroidism in thalassemia intermedia, without high iron overload,^[28,29] and the variable prevalence of endocrinopathies according to the variability of the underlying genetic defect in TM^[2] suggest that other factors contribute significantly to the pathogenesis of hypothyroidism in TM.

The iodine excretion in children and adults in Qatar has been shown to be normal in a recent survey ruling out the possibility of iodine deficiency as a cause of hypothyroidism in these patients.^[30] Furthermore, the liver has an important role in deiodination to activate and deactivate thyroid hormones and performs functions relating to thyroid hormone transport and metabolism.^[31] However, the mild increase of ALT in our patients and the absence of correlation between ALT and FT4 levels disagree with a significant effect played by the liver.

The discrepancy between the different prevalence of hypothyroidism and the presence or absence of the central component can be partially explained by applying different protocols of blood transfusions and iron chelation with variable affection of the thyroid and pituitary with the excess iron and/or anemia. In addition, genetic variability to the toxic effect of iron on different organs have been documented in thalassemia.^[32-34]

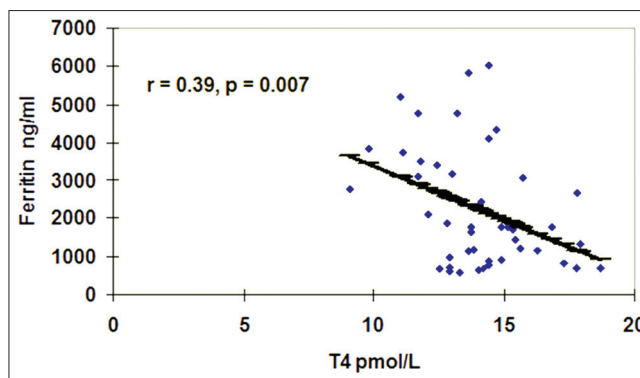


Figure 7: Correlation between ferritin and free thyroxine in thalassemic patients

In summary: We documented worsening of thyroid function in 35% of the studied thalassemic patients by the age of 18 years. The lack of proper increase of TSH in response to low circulating levels of FT4 in 13/17 (76%) of these patients indicated a relatively high incidence of defective pituitary thyrotrophic function in these patients.

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