The Prevalence of Hypothyroidism Among Patients with Beta-Thalassemia Major , Western Iraq

Sahar Jabbar Kadhum

ABSTRACT:

BACKGROUND:

Thyroid dysfunction is well documented in patients with thalassemia major those required frequent blood transfusions.

OBJECTIVE:

To determine the prevalence of hypothyroidism among
patients suffering from B-thalassemia major and their association with treatment protocol.

PATIENTS &METHODS:

Descriptive cross sectional study conducted in Al-Ramadi maternity and children teaching hospital from 1st of January 2013 to the 1st of January 2014. Sixty patients with thalassemia major aged 2-20 years were studied.

Age ,sex ,age of 1st blood transfusion, frequency of blood transfusion per year, doses ,duration and method of chelating agent administration were recorded .Hb level ,serum ferritin concentration and thyroid function test(T4,T3,TSH) were measured.

RESULTS:

thyroid dysfunction recorded in 8(13.3%)cases,3(5%)overt hypothyroidism,5(8.3%)subclinical hypothyroidism , mean age 19±1 years. serum ferritin level, Hb level and age of first transfusion were statistically significant in patients with thyroid dysfunction while TSB and liver enzymes levels were statistically insignificant in studied cases.

CONCLUSION:

Hypothyroidism is an important problem in thalassemia major patients. Regular annual follow-up is essential for early detection and appropriate replacement therapy . the use of effective combined chelating therapy in sufficient quantities as well as regular blood transfusion may lead to prevention of hypothyroidism in beta thalassemic patients

KEY WORDS: thalassemia major ,hypothyroidism, western Iraq.

INTRODUCTION:

Beta-thalassemia major (BTM) is an inherited blood disorder caused by defective synthesis of beta-chain of hemoglobin causes severe transfusion dependent anemia and extra medullary ineffective erythropoiesis with rapid erythrocyte breakdown resulting in advanced heart failure and death in early childhood[(1)]. BTM associated with severe anemia usually hemoglobin below 7 g/dl , therefore, blood transfusion is needed every2-5 weeks to maintain a pre transfusion hemoglobin level above 10 g/dl to maintain normal life [(2)].Frequent blood transfusion can lead to iron overload which may accumulate in key organs such as liver, heart, and endocrine glands of BTM patients like thyroid gland due to the lack of physiological pathway for iron excretion [(3,4)]. When the serum ferritin level reaches at 1000 ng/ml (usually after 10th to 12th transfusion), it is generally taken as the point to initiate iron chelation therapy [(5)].So Successful iron chelation therapy is essential for prevention of iron overload ,it's play an important role in improving the lifestyle and prolong life of transfusion- dependent patients [(6)]. Deferroxamine (DFO) therapy in BTM patients must undergo parenteral doses of approximately 40mg/kg/day for up to 8-12 hours a day and 5-7 nights a week via portable infusion device [(7)].Several studies concluded that poor adherence to the regular subcutaneous infusion DFO therapy can be a cause of poor survival in patients with BTM [(7,8)] . Thyroid dysfunction is one of the endocrine complications that occur in thalassemia major patients who need frequent blood transfusions.[(8)] The widespread form of thyroid dysfunction seen in BTM patients is primary hypothyroidism caused- abnormalities of the thyroid gland which results in insufficient production of the thyroid hormones. The prevalence of hypothyroidism shows a

Medical College,Ibn- Sina University for Medical Science and Pharmacy. Baghdad, Iraq.

discrepancy depending on the region, quality of management and treatment protocols[8,9].

The aim of the study to determine the prevalence of hypothyroidism in patients with homozygous B-thalassemia major and their association with treatment protocol (blood transfusion and parental iron chelating therapy like deferroxamine).

PATIENTS AND METHODS :

This descriptive cross sectional study conducted in Al-Ramadi maternity and children teaching hospital ,western Iraq from 1st of January 2013 to 1st of January 2014.All thalassemia patients (BTM) attending the thalassaemic clinic in Al-Ramadi maternity and children teaching hospital during the study period were enrolled in the study. Cases of B.thalassemia minor and intermedia were excluded, and none of studied cases had been splenoctomized. Data collected from studied cases or their parents include age , sex, age (time) of initiation and frequency of blood transfusion per year as well as doses, duration and the method of chelating agent administration. (Subcutaneous infusion of deferroxamine as chelating agent,40 mg per kg per day for 8-10hrs,5-7 days each week consider as an adequate therapy)[8]. All patients(or parents) were asked about symptoms of hypothyroidism(lethargy ,poor appetite ,excessive loss of hair and increase weight.).Five ml of pre transfusion blood samples were drawn from patients. One ml in EDTA material used for hemoglobin (Hb) level. Normal Hb range are(11.5-15.5) g/dl and(13-16) g/dl for age groups(6-12 years) and (12-18) respectively[10] .The remaining 4 ml was used for estimation serum TSB,SGOT, SGPT, s.Ferritin and thyroid function test .Serum ferritin concentration measured by a micro titer ELISA method human ferritin (Enzyme–linked Immune Sorbent Assay) which purchased from (diagnostic automation inc , USA). Normal value of serum ferritin <300 ng/ml in males and <200 ng/ml in females [11].Thyroid function test were made by ELFA (Enzyme –linked Fluorescent Assay) Mini VIDAS report, (Biomerieux , France) using ready use kits [12] .The normal range T4 60-120 nmol/L,T3(0.92-2.33) nmol/L,TSH 0.25-5 µIU/ml [12]. Hypothyroidism defined as low T4,T3 levels and high TSH. The nature of the study were explained to parents of BTM patients to obtain their voluntary consent to participate .the results were statistically analyzed using SPSS V. 22.0 , P-value < 0.05 was considered significant.

RESULTS:

Sixty patients with beta thalassemia major(BTM) were included in this study,37(61.7%)males, 23(38.3%) females with ♂:♀ ratio (1.6:1), their age ranged 2-20 years with mean age 9.2±6.4 years .Their mean (±SD) serum ferritin concentration was 1550±530.4ng/ml ,mean age of first diagnosis7.5±4.9 months. 10(16.7%) patients with no chelating therapy , their age range 2-6 years with mean age 3.3±1.4 years. fifty(83.3%) patients had inadequate chelating therapy, 31 (73.8%) of them received chelating therapy after (4 years) of blood transfusion. Regarding method of desferroxamine administration , 35(58.3%)of cases treated by infusion pump and 15(25%) by intramuscular route. Normal thyroid function test (euthyroidism) recorded in52(86.7%) BTM patients while thyroid dysfunction recorded in 8 (13.3%) cases ,overt hypothyroidism in3(5%) and subclinical hypothyroidism in 5 (8.3%), (Table 1).Four of them were males and 4 were females with equal ♂:♀ ratio, their mean age 19±1 years. None had symptoms of hypothyroidism. Twenty (33.3%) BTM patients their age below 10 years, while 40 (66.7%) of cases their age more than10 years. Two(3.3%) of hypothyroid cases and 14(23.3%) of euthyroid cases their age range 11-15 years, while 6(10%) of hypothyroid cases and18(30%) of euthyroid cases their age range (16-20)years,(Table 2). In our study BTM patients received irregular blood transfusion with mean age(±SD) of first transfusion therapy was 7.5±2.1months ,which is statistically significant in hypothyroid cases when compared to euthyroid cases (Table 3). Significant statistical difference was found between High mean serum ferritin level in hypothyroid BTM patients (4600±280.4) when compared to(1088.9±789.4) in euthyroid cases. Regarding Hb level, low mean(±SD) Hb level (8.3±1.21)was statistically significant in hypothyroid BTM patients in comparism with 11.8±1.02 in euthyroid cases. Mean(±SD) numbers of blood transfusion per year in hypothyroid BTM patients were higher than that of euthyroid BTM patients but it was statistically insignificant (Table 4) .Mean (±SD) of T3,T4 of hypothyroid BTM cases(0.3±0.09),(47.5±3.5) respectively were significantly lower ($p<0.05$) than that of euthyroid cases, (1.9± 0.4), (72. ±414.4) respectively. Regarding mean(±SD) TSH

level ,it was significantly higher(9.75±1.06) in hypothyroid BTM patients P(<0.05) as compared to (2.7±1.04)in euthyroid BTM patients (Table 4).

Table 1:Distribution of BTM patients according to thyroid function test.

Thyroid Function Test		NO.(%)
Normal (Euthyroid)		52(86.7)
Hypothyroidism	Overt hypothyroidism	3(5)
	Subclinical hypothyroidism	5(8.3)
Total		60(100)

Table 2 :Distribution of BTM patients accordingnto thyroid function test in different age groups.

Age (years)	Hypothyroid cases No.(%)	Euthyroid Cases No.(%)	Total No.(%)
≤ 5	_	10(16.7)	10(16.7)
6-10	_	10 (16.7)	10(16.7)
11-15	2(3.3)	14(23.3)	16(26.6)
16-20	6(10)	18(30)	24(40)
Total	8(13.3)	52(86.7)	60(100)

Table 3: Demographic and biochemical characteristic of hypothyroid and euthyroid BTM patients.

parameters	Hypothyroid Cases (mean±SD)	Euthyroid Cases (mean±SD)	P value
Age at first transfusion (months)	7.5±2.1	13.25±9.9	<0.05*
No. of blood transfusion/year	24±12	16.8±4.6	>0.05
Serum level of ferritin ng/ml	4600±280.4	1088.9±789.4	<0.05*
Hb g/dl	8.3±1.21	11.8±1.02	<0.05*

SD=standerd deviation
*significant

Table 4: Thyroid function tests among hypothyroid and euthyroid BTM patients.

thyroid function tests	Hypothyroid cases	euthyroid cases	P value
T3 nmol/l (mean ±SD)	0.3±0.09	1.9±0.4	<0.05*
T4 nmol/l (mean+SD)	47.5±3.5	72.4±14.4	<0.05*
TSH µIU/ml (mean+SD)	9.75±1.06	2.7±1.04	<0.05*

SD=standerd deviation
*significant

DISCUSSION:

Transfusion dependent BTM patients in the absence of chelating therapy develop progressive accumulation of iron which responsible for tissue damage and death[13].In the current study, , high serum ferritin in BTM patients may be related to the irregular chelating therapy with inadequate

and delay in the initiation of chelating therapy, we found that 83.3% of studied cases had inadequate chelating therapy. And 73.8% BTM patients received blood transfusion for more than 4 years before starting chelating therapy. These results support finding recorded by other studies suggest that chronic iron load secondary to hyper- transfusion is a major cause of multi endocrine dysfunction in BTM patients[14].In transfusion dependent BTM patients early detection of primary hypothyroidism is important as it can associated with growth retardation ,on other hand effective replacement therapy is available[14].Hypothyroidism was recorded in 13.3% of BTM patients in this study which was higher than 2.2%,4% , 6% and12.8% reported by Mehrvar A etal[15] ,Maebd etal [16],Karamifar H etal[17], and kurtoglu AU etal[18]respectively while lower than16.5%reported by Zervas a etal[19] , 20% reported by Hasan NA etal [20], 25.7%reported by Malik SA etal [9] and 35% reported by Soliman AT[21].This variation in prevalence of these studies can be related to different age of studied cases, different amount of blood transfusions, dosage of iron chelating therapy as well as different methods used for assessment of thyroid function study [22]. Regarding gender, similar to other studies reported by Karamifer H etal[17],Malik SA[9],no difference in rate of hypothyroidism between boys and girls in BTM patients of the current study. Our study showed that out of 40 (66.7%) BTM patients with age more than 10 years, 8(13.3%) had thyroid dysfunction ,5 (8.3%)of them subclinical hypothyroidism and 3(5%) overt hypothyroidism , which is consistent with other studies[9,23].Its was reported that thyroid dysfunction appear with frequency of 13-60% in BTM patients after 10 years of age regardless of difference in rate of prevalence, largely in form of subclinical hypothyroidism [9,24].In our study significant association was reported between high mean serum ferritin level and thyroid dysfunction which is consistent with other studies reported by Karamifer H et al 2003[17], and Malik SA etal 2010[9]. In this study , Statistical significant correlation between age of onset of blood transfusion and hypothyroidism in BTM cases which is consistent with other studies[23].this can be explained that early onset of blood transfusion can associated with earlier iron overload and iron accumulation in endocrine glands[9].

Lower mean Hb level was statistically associated with hypothyroidism when compared with euthyroid in BTM patients .It was seen that Apart from iron over load which related to irregular treatment and poor compliance ,other factors can be responsible for organ damage including anemia, chronic hypoxia that may potentiate the toxicity of iron deposition in endocrine glands, as well as viral infection and individual susceptibility[9,23].

CONCLUSION AND RECOMMENDATION:

Primary hypothyroidism, is a significant problem in beta thalassemia major patients support the need for regular follow up yearly, especially in those over 10 years old to ensure early detection and treatment of associated complications .the use of effective combined chelating therapy in sufficient quantities as well as regular blood transfusion may lead to prevention of hypothyroidism in beta thalassemic patients.
Further studies for assessment of other endocrine complications.

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