



Evaluation of hypothyroidism in β -Thalassemia Major

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ABSTRACT

The aim of this study was to determine the status of hypothyroidism in a group of patients with β -thalassemia major & to know the correlation between thyroid function and the degree of iron overload represented by S. ferritin level. The cross-sectional study did 100 cases of β -thalassemia major, 50 patient >10 years of age and 50 patient between 5-10 years of age by using the principle of measuring T3, T4, TSH, and serum ferritin combines an enzyme immunoassay competition with a final fluorescent method (ELFA). A total number of patient 100, 50 patient >10yr. of age 5 cases (10%) with elevated TSH 5-10 μ IU/ml & normal T4 who diagnosed as subclinical hypothyroidism and 2 cases (4%) with elevated TSH & low T4 who diagnosed as overt hypothyroidism. While another group 50 patient [age < 10 years] of them only there are 4 cases (8%) of subclinical hypothyroidism. Patients with lack of clinical symptoms of hypothyroidism sometimes involved subclinical cases. Standard follow-up for early recognition and appropriate managements of this complication might make the patient's life better.

Keywords: β -thalassemia major; hypothyroidism; TSH.

INTRODUCTION

The word "thalassemia" point to a blood disease that characterized by decreased or absent globin chains. Most thalassemia is inherited recessive traits (GALANELLO and CAO, 1998). From a medical viewpoint, the utmost important kinds are alpha and beta thalassemia, due to reduced one of the two kinds of chains (alpha or beta) which constitutes the normal adult hemoglobin molecule (HbA, alpha 2 beta 2) (Origa and Galanello, 2011; Viprakasit, 2013; Viprakasit et al., 2004). Thalassemia is a main trouble in "the Mediterranean Sea, the Middle East and Trans-Caucasus, India, and the Far East" (Viprakasit et al., 2013). The main treatment is blood transfusion to preserve sufficient levels of hemoglobin. Iron burden in β -thalassemia major (TM) patients is resultant to multiple transfusions and increased iron absorption (Farmaki et al., 2010; Skordis et al., 2006; Toumba et al., 2007). Too much iron catalyzes free radical's generation and causing impairment in cellular function. widespread iron-induced injury develops in many organs as liver, heart, pancreas, and other endocrine organs (Borgna-Pignatti et al., 2005; Kurtoglu et al., 2012). Endocrine disorders such as hypogonadism, insulin-dependent diabetes, hypothyroid-

ism and hypoparathyroidism which can be seen in several inherited hemolytic diseases as a result of treatment (Badfar et al., 2017; Maggio et al., 2011).

Hypothyroidism typically appears in the 2nd decade of life and it is considered to be linked to iron overload in patients with thalassemia major. Chelation therapy combined with frequent blood transfusion has prolonged these patients lifespan, transmuting thalassemia due to a hastily lethal illness of infantile to a chronic disease well-matched with an expanded lifespan (Higgs et al., 2012). Conversely, numerous transfusions, poor compliance, iron overload and long lasting the problem take donated to the entire range of consequences such as "cardiac troubles, hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism and further endocrine and metabolic dysfunctions" in patients suffering from thalassemia major (Chen et al., 2017). In recent years, authors reported a high rate of endocrine problems in those suffering from thalassemia major (Tiosano & Hochberg, 2001). The most common kind of thyroid abnormality is "subclinical hypothyroidism" due to inadequate secretion of T3 and T4, the occurrence of hypothyroidism differs according to the area that involved, type of treatment that used (Shamshirsaz et al., 2003). The following grades of hypothyroidism in thalassemia are (De et al., 2014) "sub-clinical hypothyroidism" is connecting with a high TSH with normal T4 level and overt hypothyroidism that include high TSH with low T4. Depending on usable chelation regime, the occurrence of hypothyroidism in thalassemia major patients varieties from 6 to 30% (Toumba et al., 2007). Little occurrence of hypothyroidism was establish in patients with low iron levels as assessed by serum ferritin (Darbari et

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al., 2014). Prognosis rely on the quantity and the period of iron overload. Hence, the aim of the study was to determine the frequency and the type of hypothyroidism in those patients with β -thalassemia major and its affiliation with thyroid function and the degree of overload.

PATIENTS AND METHOD

A cross-sectional study was conducted in the maternity & children teaching hospital in thalassemia department in Al-Diwaniya city from March 2014 to January 2015, patients were involved in the study 100 patient, 50 patient > 10 years age and 50 patients between 5 and 10 years of age. Inclusion criteria included confirmed the diagnosis of thalassemia major by hemoglobin electrophoresis, age more than 5 years, all patient on frequent transfusion and on iron chelating therapy either DFO or DFX. Information where recorded including; name, age, age at diagnosis, time of 1st blood transfusion, the time of starting ICT, type of ICT, level of T3, T4, TSH, and serum ferritin. Exclusion criteria were patients whose loss follow up and patients less than 5 years of age.

Methods

2ml of blood was collected from the patient by using plastic syringe then sera separated, samples were taken by pipette with disposable tip 100 μ l for measuring S.ferritin and T3, 200 μ l for measuring T4 and TSH. Assay principle combines enzyme immunoassay competition method with a final fluorescent detection (ELFA). All steps were done automatically by instrument, samples were taken & transferred into the well containing the antigen of [ferritin, T3, T4 or TSH] labeled with alkaline phosphatase (conjugate). Competition occurs between the antigen present in the sample & labeled antigen for specific anti- [ferritin, T3, T4 or TSH] antibodies, the conjugate enzyme catalyzes the substrate into fluorescent material measured by the nanometer. The fluorescence intensity was set to the amount of antigen in the sample.

Statistical analysis

Data analysis was done by using Statistical Package for Social Sciences, SPSS Software for Windows (Windows 7 Ultimate). The outcome was expressed as a mean $\pm$ standard deviation for the study parameters "age, thyroid profile and serum ferritin levels" using t-test. The outcome for gender was expressed as frequencies and percentages using "Chi-square (with 95% confidence interval)". P value <0.05 was considered significant.

RESULTS

The study involved 100 cases of a patient who's divided into 2 groups; Group1 age >10 years [G1], Group2 age between 5 -10 years [G2]. The results of current study revealed that more cases of hypothyroidism are subclinical, 100 case of thalassemia major patients all with frequent transfusion, on ICT, patient divided to 2 groups 1st group >10 years of age mean of age (17.24 $\pm$ 6.965) whose 50 patient, mean s.ferritin (4882.8 $\pm$ 3506.4),

mean T3 (1.856 $\pm$ 0.5246), mean T4 (74.426 $\pm$ 15.759), mean TSH (8.242 $\pm$ 4.29) where endocrine complication more common in the 2nd decade of life and we found that 10% of cases (5 patients), mean age (16.75 $\pm$ 2.63) mean T3 (1.725 $\pm$ 0.7719), mean T4 (76.375 $\pm$ 18.644), mean TSH (6.75 $\pm$ 0.9256), mean s.ferritin (6033 $\pm$ 3592.1) are subclinical hypothyroidism, 4% of cases (2 patients) mean age (12.5 $\pm$ 2.121) mean T3 (1.414 $\pm$ 1.4), mean T4 (54.518 $\pm$ 39.15), mean TSH (35.75 $\pm$ 34.295), mean s.ferritin (4998.5 $\pm$ 4823.5) is overt hypothyroidism, according to our data there is significant correlation between TFT and ferritin, also highly significant relationship between age & S.ferritin with no significant correlation between age & TFT. The 2nd group of patient < 10 years mean of age (7.58 $\pm$ 1.357), mean of s.ferritin (2801.2 $\pm$ 1832.9), mean T3 (2.216 $\pm$ 0.376), mean T4 (87.068 $\pm$ 13.904), mean TSH (2.904 $\pm$ 1.442) where endocrine complication less common in 1st decade of life, we find that subclinical hypothyroidism 8% (4 patient), mean age (8.25 $\pm$ 0.5) mean T3 (2.1 $\pm$ 0.383), mean T4 (85.625 $\pm$ 6.759), mean TSH (6.325 $\pm$ 2.127), mean s.ferritin (2674.5 $\pm$ 2033.6), with no cases of overt hypothyroidism according to our data, and there is very significant relationship between TFT & s.ferritin, also significant relationship between age of patient & s.ferritin with no significant relationship between age and TFT. In the current study, the comparing different variable in both age group we found that s.ferritin level was statically highly significant variable, while other variants with no statistical significance as shown in table 2.

We found that in G1 which include 50 patients [>10 years of age] 5 cases (10%) with subclinical hypothyroidism, 2 cases (4%) with overt hypothyroidism while in G2 which consist of 50 patient [5-10 yr. of age] there were 4 cases (8%) with subclinical hypothyroidism, with no cases of overt hypothyroidism as shown in table-3 and figure 1. In both age group, there were 27 males [54%] and 23 female [46%] as shown in figure 2. In assessing the statistical significance of different variable to sex we found that no statistical significance of age, T3, T4, TSH in relation to sex, also S.ferritin in G1 had no statistical significance to sex, while there was an astatically significant relation between S.ferritin to sex in G2 as shown in table 4 and figure 3.

There was no statistical significance of ICT to age, T3, T4 & TSH, while there was a highly significant relationship between S.ferritin & ICT both DFO & DFX as shown in table 5. and figure 4.

DISCUSSION

The prevalence of thyroid malfunction in patients with β -thalassemia has been established in several studies ranging from 0-12% (de Luca, 1980; Flynn, 1976; VULLO, 1990; Grundy, 1994; Masala, 1984; Oerter, 1993; Borgna-Pignatti, 2005; De Sanctis, 2006), to a high

Table 1: Parameters for diagnosis of cases

Parameter	T4	T3	TSH
Subclinical hypothyroidism	normal	Normal	Increased 5-10mU/L
Overt hypothyroidism	decreased	Normal or decreased	Increased >10mU/L
	T4	T3	TSH
Subclinical hypothyroidism	normal	Normal	Increased 5-10mU/L
Overt hypothyroidism	decreased	Normal or decreased	Increased >10mU/L
	T4	T3	TSH
Subclinical hypothyroidism	normal	Normal	Increased 5-10mU/L
Overt hypothyroidism	decreased	Normal or decreased	Increased >10mU/L
	T4	T3	TSH
Subclinical hypothyroidism	normal	Normal	Increased 5-10mU/L
Overt hypothyroidism	decreased	Normal or decreased	Increased >10mU/L

Table 2: Comparison of variables in the two age group

	Age <10yr Mean±S.D	Age >10yr Mean±S.D	P-value
Age	7.58±1.357	17.24±6.965	>0.05
T3	2.216±0.376	1.856±0.5246	>0.05
T4	87.068±13.904	74.426±15.759	>0.05
TSH	2.904±1.442	8.242±4.29	>0.05
S.ferritin	2801.2±1832.9	4882.8±3506.4	<0.001

P value <0.05 is significant

Table 3: Hypothyroidism cases in thalassemia by research

Age	Number of patients	Subclinical Hypothyroidism	%	Overt Hypothyroidism	%
G1	50	4	8%	-	-
G2	50	5	10%	2	4%

Table 4: Relationship between sex and different variables

	Female Mean±S.D		Male Mean±S.D		P-value	
	G1	G2	G1	G2	G1	G2
Age	18.087±7.452	7.522±1.31	16.519±6.577	7.63±1.418	>0.05	>0.05
T3	1.783±0.5875	2.257±0.4187	1.919±0.4666	2.181±0.3397	>0.05	>0.05
T4	72.861±18.954	90.261±10.441	75.759±12.651	84.348±15.981	>0.05	>0.05
TSH	11.96±5.487	2.996±1.725	3.27±2.153	2.826±1.179	>0.05	>0.05
S.ferritin	5015.3±3783.1	2125.4±1745.1	4770±3321.5	3376.9±1733.8	>0.05	<0.001

Table 5: Relationship of ICT and different variables

	DFX Mean±S.D		DFO Mean±S.D		P-value	
	G1	G2	G1	G2	G1	G2
Age	18.308±8.564	7.571±1.399	16.217±4.631	7.2±1.304	>0.05	>0.05
T3	1.877±0.0.4966	2.224±0.3805	1.809±0.5624	2.26±0.3847	>0.05	>0.05
T4	80.142±8.662	88.195±13.733	67.387±19.221	81.18±17.999	>0.05	>0.05
TSH	3.415±2.103	2.924±1.492	12.003±5.351	2.06±0.4879	>0.05	>0.05
S.ferritin	2401±1661.6	2502.3±1464.4	7863.7±2634.1	5976.6±2018.8	<0.001	<0.001

p.value < 0.05 significant

prevalence of 16-35% (Masala, 1984; Oerter, 1993; Sabato, 1983; Muncie and Campbell, 2009; Zervas, 2002; De Sanctis, 2006). The prevalence discrepancies in those prior studies associated with dissimilar procedures used for diagnosis "serum thyroxine and thyrotropin concentrations, or thyrotropin-releasing hormone test", the patients ages (pediatric or adult), the quantity of transfused blood, as well as different doses of iron-chelating treatment (De Sanctis et al., 2006). Haydeh, (2013) found that Subclinical hypothyroidism was present in 7% patients (increased TSH, normal T4), with no primary hypothyroidism (Increased TSH, decreased T4 and/or

T3) (H., 2013). In Pakistan, Malik et al.(2010) have reported primary hypothyroidism approximately 18 (25.7%) out of seventy patients, seventeen of them had normal T4 concentration along with high TSH concentration compatible with the diagnosis of subclinical hypothyroidism, and one patient revealed a low T4 concentration concomitant with high TSH "an overt hypothyroidism". The mean age of patients with hypothyroidism was 9.2 ± 2.6 years. In Thailand, Jaruratanasirikul et al. (2007) found 9 patients (17.6%) had a TSH level above 5.00 mIU/L and were classified as compensated hypothyroidism. Of the 9 patients who had elevated TSH, 2

of them had low T4 levels. In the USA, Masala *et al.* (1984) found that the prevalence of hypothyroidism diagnosed by measuring T4 and TSH level was only 5%, while hypothyroidism diagnosed by TRH stimulation tests increased the rate of diagnosis of thyroid dysfunction higher than 35%. The sensitive recognition using TRH stimulation test along with usual FT4 and TSH assessments was clarified by 2 reasons; initially, TRH test can identify “subclinical primary hypothyroidism” by representing the overstated response of TSH in the company of expanded decreased normal FT4 levels, the other; procedures of FT4 assessment by RIA was the conventional technique. Meanwhile the paucity of TRH, the levels of T4 and TSH are frequently used and reliable for estimation of thyroid function (Al-zamili and Al-hamzawi, 2015). Athens, Greece, Zervas *et al.* (2002) study of 200 patient, 8 (4%) of the remaining patients had overt hypothyroidism, and 25 (12.5%) had subclinical hypothyroidism.

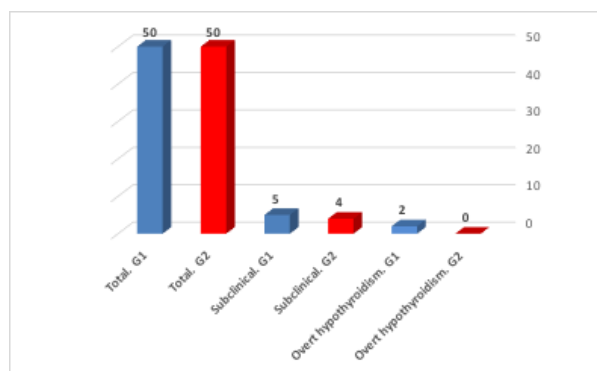


Figure 1: Hypothyroidism in thalassemia major

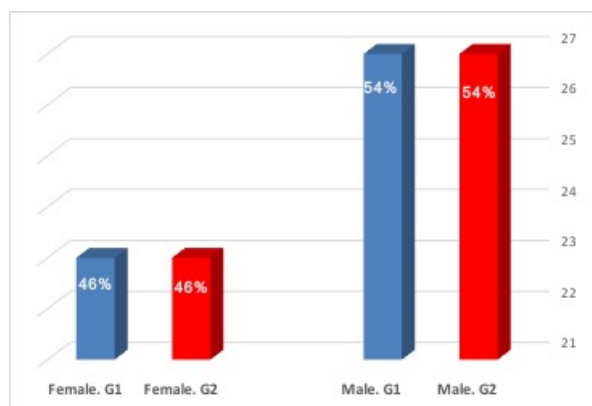


Figure 2: Sex ratio

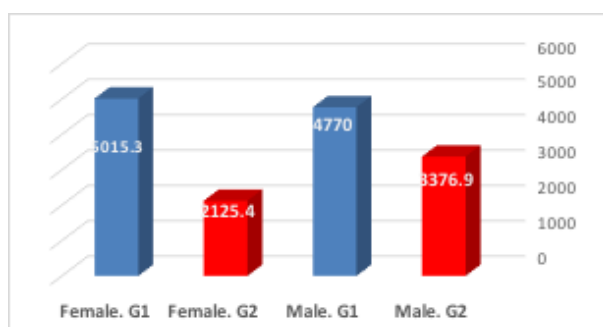


Figure 3: S.ferritin and Sex

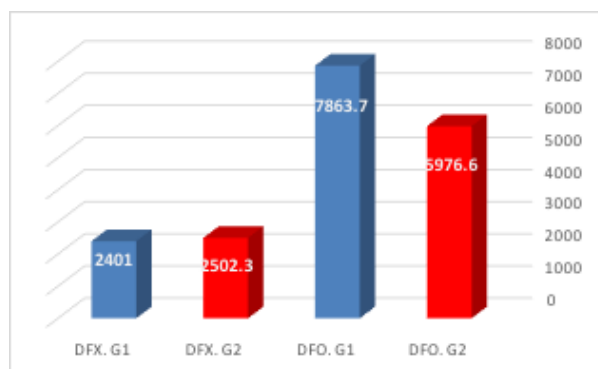


Figure 4: S.ferritin & ICT

So, the occurrence of hypothyroidism was related with high s. ferritin. “Primary hypothyroidism” arises in an important percentage of patients with thalassemia major in the lack of marked symptoms of hypothyroidism. Standard observations for early diagnosis and regular treatment of similar consequences might enhance quality of life in these patients (Dakhil, 2017). Also, viral infections, individual vulnerability, have been a part of resulting in endocrine malfunction. The results of current study are similar to the several studies somewhere else. Hypothyroidism has been established in 13-60% of patients with thalassemia, but its severity is different (H., 2013). Patients with thalassemia hypothyroidism have a larger occurrence for other consequences such as multi-endocrine abnormalities, deterioration of heart function, marked growth retardation and liver disorder (Sabato *et al.*, 1983).

CONCLUSION

“Subclinical hypothyroidism” happens in a considerable percentage in patients with thalassemia major in the absence of clinical symptoms of hypothyroidism. Standard observation for early diagnosis and appropriate management of the consequences can enhance the quality of life.

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