Assessment of Thyroid Dysfunction in Children with Beta – Thalassemia Major Attending Outpatient Clinic, Fayoum University Hospital

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Abstract: Background: Thalassemic patients need regular and frequent blood transfusion. So these patients suffer from iron overload and consequently endocrine complication such as hypothyroidism. **Aim of the study**: This work was aiming to assess the thyroid dysfunction in Beta- thalassemia major children attending outpatient clinic, Fayoum university hospital to highlight the problem in Fayoum government for early detection and timely treatment of such complication**. Subjects and Methods:** Across sectional study was conducted to 70 thalassemic patients (5-16 years) who are on regular blood transfusion. Patients are subjected to full history taking, medical examination and laboratory investigation including, complete blood count, serum ferritin level and thyroid function tests. 70 age and sex matched children without thalassemia constituted the control group. **Results:** Four (5.7%) children of the thalassemic patients (70 children) were found to have primary subclinical hypothyroidism. Also there is positive correlation between age of patients (p value <0.001), frequency of blood transfusion (p value <0.01) and developing iron overload and consequently hypothyroidism. For subjects who use iron chelating agents, they still suffer from iron overload and under risk of developing hypothyroidism, so they need closer and more regular follow up. **Conclusion:** Hypothyroidism is one of the endocrinopathies that may complicate beta thalassemia major, so regular and close follow up is required for early detection and treatment.

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1. Introduction

Beta-thalassemia major is an autosomal recessive hereditary anemia, which is incurable, caused by defective synthesis of hemoglobin, ineffective erytropoiesis and rapid erythrocyte breakdown, resulting in advanced heart failure and death in early childhood **[1].** 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 **[2].**

Trace elements are necessary for the regular functioning of the human. A deficiency of a trace elements results in problems with bodily functions. Similarly, an excess of a trace element leads to important problems **[3]**.

Nevertheless, frequent blood transfusion in turn can result in iron overload which may lead to various complications, including various endocrine complications such as thyroid dysfunction **[4]**. So, bone marrow transplantation remains the only definitive cure for thalassemics at present **[5]**.

The widespread form of thyroid dysfunction seen in thalassaemic patients is primary hypothyroidism which results in insufficient production of the thyroid hormones. Nonetheless, the frequency of hypothyroidism shows a discrepancy depending on the region, quality of management and treatment protocols **[6].**

Thyroid dysfunctions are well documented in patients with thalassemia major requiring frequent and recurrent blood transfusions **[7].** It is a general belief that thyroid dysfunctions appear with a frequency of 13-60% in these patients after 10 years of age regardless of difference in the rate of prevalence, largely as in the form of subclinical hypothyroidism **[8].**

2. Patients and methods

Study design; cross sectional study.

Study population and sampling: A cross sectional descriptive study was carried out from January 2014 to April 2014, in the outpatient clinic of Al Fayoum University Hospital in Al Fayoum Governorate, Egypt. It included 70 children with Beta –thalassemia major (The diagnosis of thalassaemia major was based on the usual hematological criteria i.e. peripheral blood evaluation and Hb electrophoresis)

Inclusion Criteria:

* Patients diagnosed as Beta thalassemia major
*Age ranged from 5-16 years *Both genders
*Blood transfusion more than 2 years

Exclusion Criteria

*Other types of chronic hemolytic anemia.
*Presence of other endocrinal disorders.
*Terminally ill.
*Family history of hypothyroidism.

Seventy age and sex matched healthy children constituted the control group.

These children will be subjected to:

1-Full history and examination, taking in consideration

-Onset of disease.

-Onset, amount and frequency of blood transfusion.

-Iron chelating agent as treatment; onset, type, dose, compliance, complication (according to parents/" reports).

-Weight and height of the patient in comparison to Egyptian percentile curves.

-Manifestation of hypothyroidism as weight gain, tiredness, baldness, cold intolerance, bradycardia, deterioration in mental skills and school performance.

2-Laboratory investigation: including:

-CBC

-Serum ferritin

-Free T4 and free T3 by using specific radio immune assay technique

-TSH by using immune radio metric assay (IRMA).

Hypothyroidism was defined as TSH level > 6.4μ IU/ml, T4 levels < 0.6 μg/dl and T3 levels < 2.4 μg/dl.

The thyroid function status of the patients was classified as compensated (increased TSH, normal T4, T3) and uncompensated (increased TSH, decreased T4 and/or T3) primary hypothyroidism, and euthyroidism (normal TSH, normal free T4) **[6].**

Statistical Analysis

- Data was collected, coded, translated to English to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using SPSS software version 18 under windows 7.
- Simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as measure of dispersion for quantitative parametric data, and inferential statistic test:

- **For quantitative parametric data:**
  - In-depended **student t-Test** used to compare measures of two independent groups of quantitative data
  - One way **ANOVA** test in comparing more than two independent groups of quantitative data.
- **For qualitative data**
  - **Chi square** test to compare two of more than two qualitative groups.
- **Bivariate correlation test** to test association between variables
  - The level $P \leq 0.05$ was considered the cut-off value for significance.

- Our study was accepted by Ethical Committee of Fayoum University to be done.

3. Results

Our study showed that the age of thalassemic patient ranged from 5-16 years with a mean of 9.6 year (± 3.5 SD). The study group included 32(45.7%) males and 38(54.3%) females. Of these patients, 36 (51.4%) children were from rural regions and 34(48.6%) were from urban regions. None of them were clinically hypothyroid, with no palpable goiter. 58.6% of cases were with positive consanguinity and 37.1% of them had similar condition in their family.

The mean age of the first transfusion was at 11.4 ± 7.2 months with a range of 4-36 months, The mean duration of blood transfusion was 8.5± 3.5 with a range of 3-15 years. The mean interval between the two consecutive transfusions was 4.5 ± 0.9 weeks (range 3-6 weeks) (table 1). Our results (table 2) showed that there was a statistically significant differences between case and control groups with *p*-value <0.05 as regards to hemoglobin level and T4 being lower among cases. While the serum ferritin and TSH level were higher in cases compared to control group.

The frequency of subclinical hypothyroidism in our study represents 5.7% (4 children) of thalassemic patients. They had elevated TSH levels and normal levels of T3&T4 with no clinical manifestation (table 3).

According to our study, no associations were found between the use of iron chelating agents and T3, TSH level and serum ferritin level (*p* value >0.05) (table 4). Whereas the mean level of T4 was higher among patients using iron chelating agents. In addition,that there is statistically significant difference between chelating groups with *p*-value <0.05 as regards to fT4 with lowest mean among patients taken combination of DEP and DFO. On the other hand there is no statistically significant difference as regards to fT3 and TSH level (table 5).

Furthermore, the present study (table 6) showed significant higher level of serum ferritin level in hypothyroid group as compared to euthyroid group (*p* value <0.001). Our study showed positive association of serum ferritin and TSH level and duration of transfusion (*p* value < 0.005). Our work (table 7) showed that there were statistically significant positive association (*p*-value <0.001) between TSH level and both age, and duration of transfusion, whereas negative correlation was reported between TSH and frequency of transfusion among thalassemic patients.

Table (1): Description of disease history among thalassemic cases.

Variables (n=70)	**Minimum**	**Maximum**	**Mean**	**±SD**
Onset of disease (months)	4	36	11.4	7.2
Duration of transfusion (years)	3	15.5	8.5	3.5
Intervals of transfusion (weeks)	3	6	4.5	0.9
Cases management (n=34)				
Duration of chelating treatment (months)	4	48	19	11.6
Age of splenectomy (years)	4	8	5.8	1

Table (2): Comparisons of routine investigations among different study groups.

Variables	**Cases (n= 70)**		**Control (n= 70)**		***p*-value**	**Sig.**
	Mean	**±SD**	**Mean**	**±SD**		
Complete blood count						
Hb%	**7**	0.7	10.5	1.4	**<0.001**	**HS**
PLT	**336.6**	95.4	370.3	82	**0.03**	**S**
TLC	**9.2**	2.3	7.9	1.7	**<0.001**	**HS**
Thyroid hormone profile						
fT3	3.4	0.5	3.2	0.8	0.1	NS
fT4	**1.02**	0.2	1.5	1.8	**0.02**	**S**
TSH	3.1	1.5	2.7	1.1	**0.04**	**S**
Other investigations						
Serum ferritin	**2128.3**	1962.8	96.9	61.2	**<0.001**	**HS**

Table (3): Comparisons of TSH level among different study groups.

TSH	**Cases (n= 70)**		**Control (n= 70)**		***p*-value**	**Sig.**
	No.	**%**	**No.**	**%**		
Normal	66	94.3%	70	100%	0.1	NS
High	4	**5.7%**	0	0%		

Table (4): Comparisons of serum ferritin level between patients using and not using chelating agents.

Variables	**No- chelating (n=36)**		**Chelating (n=34)**		***p*-value**	**Sig.**
	Mean	**±SD**	**Mean**	**±SD**		
Thyroid hormone profile						
fT3	3.6	0.4	3.7	0.6	0.9	NS
fT4	0.96	0.1	**1.1**	0.3	**0.03**	**S**
TSH	2.9	1.5	3.3	1.6	0.4	NS
Other investigations						
Serum ferritin	2243.1	2013.5	2006.7	1930.2	0.6	NS

Table (5): Comparisons of thyroid hormone profile among different chelating groups.

Chelating types	**fT3**	**fT4**	**TSH**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**
Deferoxamine(n=8)	3.5±0.8	1±0.1	3.6±1.4
Deferasirox(n=11)	3.4±0.5	1.1±0.2	3.2±1.9
Deferiprone(n=13)	3.4±0.3	1.2±0.3	2.8±1.1
DFP +DFO (n=2)	2.5±0.7	**0.6±0.4**	5.8±1.8
***p*-value**	0.1	**0.02**	0.08
Sig.	NS	**S**	NS

Table (6): Correlation between serum Ferritin level and thyroid hormones profile and disease history (age, duration of transfusion) among thalassemic patients.

Variables	Serum Ferritin level		
	R	*p*-value	Sig.
Thyroid hormones profile			
fT3	-0.10	0.7	NS
fT4	-0.14	0.2	NS
TSH	**0.43**	**<0.001**	**HS**
Disease history			
Age(years)	**0.29**	**0.02**	**S**
Duration of transfusion (years)	**0.35**	**0.003**	**HS**

Table (7): Correlation between TSH level with study variables among thalassemic patients.

Variables	TSH level		
	R	*p*-value	Sig.
Age(years)	**0.37**	**<0.001**	**HS**
Intervals between f transfusions (weeks)	**-0.28**	**0.01**	**S**
Duration of transfusion (years	**0.44**	**<0.001**	**HS**

4. Discussion

Clinically overt manifestations of hypothyroidism occur late in life and most of the studies available are done on adults. Only a very few pediatric studies are available. In Egypt, cost of chelation precludes ideal therapy for majority of the patients and the compliance with transfusion is often not optimal. Therefore there is a possibility that there may be high prevalence of hypothyroidism in thalassemic children, we therefore planned the present study with the aim to assess thyroid function in children suffering from β-thalassemia major with iron overload and to evaluate its relation, if any, with serum ferritin level.

In our study, the frequency of subclinical hypothyroidism represents 5.7% (4 children) of thalassemic patients. They had elevated TSH levels and normal levels of T3&T4 with no clinical manifestation.

Similar results was found by ***Toumba et al. (2007***) who demonstrated hypothyroidism in 6% of thalssemic patients in Cyprus**[9],** also in Tehran the prevalence was 7.7% **[8]**. Whereas in Italy and France higher frequency 22% and 10% were noticed by ***De Sanctis et al., (2008*)[10]** and ***Thuret et al., (2010***) (11) respectively. On the other hand, ***Sharma and Aggarwal., (2014*)[12]** found lower prevalence.

Variations in these results may be due to different methods used for measuring thyroid hormone status, the different ages of the studied patients, difference in treatment protocols including different transfusion rates and chelation therapies. The lowest prevalence of hypothyroidism in our study compared to the other studies may be attributed to the fact that high percentage of our patients group were below the age of 10 years.

Many mechanisms responsible for thyroid dysfunction in thalassemic patients have been suggested, however the exact mechanism is not known. It has been demonstrated that thyroid abnormalities in these patients are related to iron overload. The precise mechanism for which is not completely understood. High concentrations of labile plasma iron and labile cell iron are considered responsible in the formation of free radicals and the production of reactive oxygen species (ROS) which may lead to cell and organ damage. Organ siderosis (liver, cardiac and skeletal muscle, kidney) may affect specific receptors, which regulate thyroid hormone action and convert T4 to the bioactive T3 **[13].** Our finding showed that no associations between the use of iron chelating agents and T3, TSH level and serum ferritin level (p value >0.05).Whereas the mean level of T4 was higher among patients using iron chelating agents. Our data about the regular use of chelating drugs relying on parent's reports so these data may be not accurate to confirm the efficacy of chelating agents.

Our study showed significant higher level of serum ferritin level in hypothyroid group as compared to euthyroid group (p value <0.001). Similar results were detected by ***Pirinccioglu et al., (2011*)[14]**. Our finding disagrees with ***Thuret et al., (2010*) [11], *Eschragi et al., (2011*)[15]** and ***Jaruratanasirikul et al., (2007*)[16]** as they found that incidence of hypothyroidism not related to high level of serum

ferritin level. These finding suggest possibility that spot serum ferritin sample may not be sufficient alone to determine the implication of chronic iron exposure in developing thyroid dysfunction.

There is no doubt that iron overload has important role in thyroid and other endocrinal dysfunction in thalassemic patients, the non-significant difference in ferritin levels between hypothyroid and euthyroid group suggests that the damage of endocrine glands caused by chronic hypoxia due to prolonged anemia may be associated factor responsible for thyroid dysfunction.

Our work showed significant positive association (p-value <0.001) between TSH level and both age, and duration of transfusion, whereas negative correlation was reported between TSH and frequency of transfusion among thalassemic patients. Similar results have been detected by ***Jaipuria et al., (2014)*****[17].** This may indicate that frequency and amount of blood transfusion may be more important parameter to predict the development of thyroid dysfunctions rather than absolute value of serum ferritin**.**

In the current study, hypothyroidism was more obvious in older age. Similar finding has been observed by ***Thuret et al., (2010)*** **[11]** who found significant increase in number of case of hypothyroidism with advancing age. Also we detected positive association of serum ferritin and TSH level and duration of transfusion (p value < 0.005) (table). This is inevitable since the older patients would have longer blood transfusion period as well as more transfusion requirement and hence chelation therapy is recommended to reduce iron overload and thyroid dysfunction due to iron overload.

Conclusion

We detected by this study that 5.7% of our thalassemic children suffer from hypothyroidism. Also there is positive correlation between age of patients, frequency of blood transfusion and developing iron overload and consequently hypothyroidism. For subjects who use iron chelating agents. they still suffer from iron overload and under risk of developing hypothyroidism, so they need closer and more regular follow up. So we recommend regular and early follow up of thalassmic patients for early detection and prevention of complication to achieve good life style of these patients.

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