Assessment of hypothyroidism among adult patients suffering from beta thalassemia major

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Assessment of Hypothyroidism Among Adult Patients With Beta-thalassemia Major


Abstract

Background: Although patients with beta-thalassemia major (BTM) are properly treated with blood transfusions accompanied with iron chelation therapy, they experience serious complications such as hypothyroidism.

Aim: This work aims to assess hypothyroidism among adult patients with BTM and to find out its association with various parameters such as age, BMI, sex, hemoglobin, and serum ferritin levels.

Patients and methods: This cross-sectional study included 200 adult patients with BTM (males 115 and females 85; mean age 24.684 ± 5.30761 years; range, 18–43 years old). Statistical data analysis was performed using IBM SPSS software package, version 26.0.

Results: The overall frequency of hypothyroidism was 9.5%. The maximum frequency was 3.5% within the age group 27–less than 32 years, with serum ferritin level in the range of 2501–3500 ng/ml. Six (3%) of the patients had overt hypothyroidism, and 13 (6.5%) patients had subclinical hypothyroidism; normal values of thyroid hormone were found in 181 (90.5%) patients. No central hypothyroidism was found.

Conclusion: The most common subclass of thyroid dysfunction was subclinical hypothyroidism, which was more prevalent than overt hypothyroidism. Early assessment of hypothyroidism should be followed among adult patients with BTM, especially in the age group 27–less than 32 years.

Keywords: Beta-thalassemia major, Ferritin level, Hypothyroidism

1. Introduction

Currently, patients with thalassemia are clinically classified as either TDT or NTDT, where TDT stands for transfusion-dependent thalassemia and NTDT means nontransfusion-dependent thalassemia. Patients with TDT represent thalassemia major cases, whereas patients with NTDT represent thalassemia intermedia cases (Cappellini et al., 2014; Taher et al., 2013).

According to this differentiation, a patient with thalassemia (TDT or NTDT) needs a careful clinical evaluation using several clinical and hematological parameters, especially baseline hemoglobin (Hb) levels. Patients with TM require lifelong blood transfusions and iron chelation. Lifelong blood transfusion and chelation therapy are cornerstones in disease management. One of the complications of β-thalassemia is endocrine disorder (Swee, 2005; Bordbar et al., 2019; Suporn et al., 2019). Endocrine complications such as hypogonadism, short status, glucose intolerance, and diabetes mellitus are also reported (Toumba et al., 2007; Vincenzo et al., 2019a,b). Hypothyroidism is one of the endocrine complications among patients with beta-thalassemia major (BTM), where its incidence ranges widely from 13 to 60%, reflecting the severity of the disease (Jensen et al., 1997; Sharma et al., 2017; Ali et al., 2018; Valeria et al., 2013; Ankush and Hema, 2020; Vincenzo et al., 2019a,b; Vincenzo De et al., 2012).

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Low prevalence of primary hypothyroidism ranges from 4 to 10% (Sushil et al., 2017). High prevalence of primary hypothyroidism reaches to 29% (Mariotti et al., 1999; Vincenzo et al., 2019a,b). Some studies reported subclinical hypothyroidism as 13% and overt hypothyroidism as 4% (Athanasios et al., 2002). A retrospective study in Italian center showed that subclinical hypothyroidism was 72.2% (8/11) and overt hypothyroidism was 18.18% (2/11) (Vincenzo et al., 2016c).

The primary incentive of this work was the presence of little data and information concerning hypothyroidism among adult patients with BTM. Having knowledge about that endocrinopathy among such patients can increase the expectancy and improve their life through careful monitoring and proper management.

A correlation analysis with bivariate method was used to find out the correlation between hypothyroidism and variables such as serum ferritin level, Hb, sex, BMI, and age groups. A cross-sectional study was conducted. A total of 200 patients with BTM with age greater than or equal to 18 years were enrolled in the study. The data were collected from Zagazig University hospitals concerning patients with BTM.

The aim of this study was to assess thyroid dysfunction among adult patients with BTM and to see whether that endocrine disorder is associated with a certain age group and to determine other variables associated with that endocrinopathy.

2. Patients and methods

A total of 200 adult patients from Zagazig University Hospitals, Egypt, with confirmed diagnosis of BTM were enrolled in the study. The patients' data from 2016 to 2019 were considered. Patients more than or equal to 18 years old were enrolled in this work. Patients less than 18 years old and patients with hemolytic anemia other than BTM were excluded.

The study protocol was approved by the Institutional Review Board (IRB), Faculty of Medicine, Zagazig University, Egypt (Approval IRB #: 5895-8-3-2020).

The patients were classified according to age into the following groups: first group, 18—less than 22 years old; second group, 22—less than 27 years old; third group, 27—less than 32 years old; and fourth group, more than or equal to 32 years old. Hypothyroidism was classified as overt hypothyroidism [thyroid-stimulated hormone (TSH) > 5 μIU/ml and serum free thyroxine (FT4) low], subclinical hypothyroidism (normal FT4 with TSH>5 μIU/ml), or central hypothyroidism (FT4 low with low or normal TSH) (Bordbar et al., 2019). Serum ferritin levels were categorized as follows: first range, 0–1500 ng/ml; second range, 1501–2500 ng/ml; third range, 2501–3500 ng/ml; and fourth ferritin level range, more than 3500 ng/ml.

2.1. Statistical analysis

Data were analyzed by IBM SPSS Statistics for Windows, version 26.0. (IBM Corp., Armonk, New York, USA). Descriptive data are presented as mean, SD, and percentages. Analysis of variance test was used to compare quantitative variables among three or more groups. The associated variables with hypothyroidism were investigated. In this work, we suggested the correlated factors as age groups, ferritin level, BMI, sex, and Hb. Pearson correlation and bivariate analysis were used to detect the correlation between hypothyroidism and the suggested parameters. A two-tailed P value less than 0.05 was considered to be statistically significant.

3. Results

A total of 200 patients with BTM with a mean age of 24.6840 ± 5.30761 years were enrolled in this study. There were 115 males and 85 females. The general and clinical characteristics of the sample are shown in Table 1. The mean serum ferritin level was 3909.02 ± 1935.72465 ng/ml. Overall, 49 (24.5%) patients had serum ferritin levels from 2501 to 3500 ng/ml and 96 (48%) patients had serum ferritin levels more than 3500 ng/ml, that is, 145 (72.5%) patients had extremely high ferritin levels, being higher than 2500 ng/ml (Table 2). This reflects poor compliance with iron chelation therapy. Moreover, this information indicates that our patients with BTM needed a new regimen for iron chelation. Hypothyroidism had overall distribution of 9.5% among patients with BTM (Table 3). This result was approximately near to the results of other research studies (Zervas et al., 2002; Filosa et al., 2006). The maximum frequency was 3.5%, which found in the age group 27–less than 32 years.

Thyroid dysfunctions were classified as follows: overt hypothyroidism was found in six patients (3% of the total patients), whereas 13 (6.5%) patients had subclinical hypothyroidism. Central hypothyroidism was not found. Normal values of thyroid hormone were found in 181 (90.5%) patients (Fig. 1).

Fig. 2 shows the distribution of hypothyroidism according to ferritin level. The top most frequencies of that endocrine disorder were 3 and 6%, which had ferritin levels of 2501–3500 ng/ml and more than 3500 ng/ml, respectively.
Table 4 shows the hormone profile of hypothyroidism among patients with BTM. In overt class of hypothyroidism, the group with hypothyroidism (indicated in Table 4 with ‘yes’) was compared with the group without thyroid disorder (indicated in Table 4 with ‘no’). It was found that there were higher TSH levels and lower FT4 levels in hypothyroidism compared with the group with normal thyroid function (mean TSH was 7.071500 ± 1.3668357 and mean of FT4 was 0.388667 ± 0.1452373, with P = 0.024 and 0.032, respectively). In subclinical class of hypothyroidism, it showed higher levels of TSH and normal values of FT4 (mean TSH was 7.576923 ± 1.407157 and mean of FT4 was 1.071615 ± 0.2093134, with P values were 0.022 and 0.323, respectively.

Using Pearson’s correlation analysis with bivariate method, it was found that there was a statistically significant correlation between hypothyroidism and age groups (P = 0.002) and no correlation with each of the following evaluated parameters: BMI, sex, Hb, and ferritin levels, as shown in Table 5.

Most of researchers reported that there was no correlation between thyroid disorder and serum ferritin levels (Bordbar et al., 2019; Sushil et al., 2017; Tutar et al., 1995; Magro et al., 1990; Senanayake et al., 1999; Pitrolo et al., 1995), but few others found a relation (Handan and Ilkay, 2019). However, this may be due to the iron chelation protocols taken before the time of diagnosis. In our patients, screening should be done carefully and especially for the age group 27–less than 32 years old, regardless of serum ferritin levels.

4. Discussion

The aim of this study was to evaluate the distribution of hypothyroidism among adult patients with BTM and to find out the association between this endocrine disorder with parameters such as age,
sex, BMI, serum ferritin levels, and Hb level. Attaining the knowledge about this endocrine disorder is of great importance for the management of the disease.

Table 6 shows that the prevalence of hypothyroidism among patients with BTM in many studies and in different communities. A study reported that the prevalence of hypothyroidism was 10.7% among 713 patients with BTM (Bordbar et al., 2019), whereas others showed that the prevalence was 10%, with a sample size of 276 cases (Thuret et al., 2010). Some researchers reported the prevalence as 16.8% with a sample size of 77 cases (Gamberini et al., 2008).

In our work, the overall prevalence was 9.5% of 200 patients, which was low compared with the aforementioned studies. The maximum frequency of hypothyroidism was 3.5% within the age group 27—less than 32 years old with serum ferritin level in the range of 2501—3500 ng/ml. Six (3%) of the patients had overt hypothyroidism and 13 (6.5%) patients had subclinical hypothyroidism; normal values of thyroid hormone were found in 181 (90.5%). No central hypothyroidism was found. Moreover, a comparative study was done in a recent work (Handan and Ilkay, 2019), where the patients with BTM were more than or equal to 18 years old.

Comparative study of distribution of hypothyroidism with previous studies:

Hypothyroidism among our patients with BTM had a prevalence of 9.5%, which was approximately near to the results of other works such as the studies

![Fig. 2. Frequency of hypothyroidism with serum ferritin levels.](image)

Table 4. Hormone profile of hypothyroidism among patients with β-thalassemia major.

<table>
<thead>
<tr>
<th>Hypothyroidism</th>
<th>Count</th>
<th>Mean</th>
<th>SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt TSH (mU/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>181</td>
<td>3.1123</td>
<td>1.1435</td>
<td>0.024</td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>7.0215</td>
<td>1.3668</td>
<td>0.001</td>
</tr>
<tr>
<td>FT4 (ng/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>181</td>
<td>0.9215</td>
<td>0.1242</td>
<td>0.032</td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>0.3887</td>
<td>0.1452</td>
<td>0.001</td>
</tr>
<tr>
<td>Subclinical TSH (mU/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>181</td>
<td>3.1123</td>
<td>1.1435</td>
<td>0.022</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>7.8769</td>
<td>1.4006</td>
<td>0.001</td>
</tr>
<tr>
<td>FT4 (ng/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>181</td>
<td>0.9215</td>
<td>0.1242</td>
<td>0.323</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>1.0716</td>
<td>0.2093</td>
<td>0.001</td>
</tr>
</tbody>
</table>

FT4, serum free thyroxine; TSH, thyroid-stimulated hormone.

Table 5. Association between overt or subclinical hypothyroidism and various variables.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>BMI</th>
<th>Sex</th>
<th>Hb</th>
<th>Ferritin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson correlation</td>
<td>0.220**</td>
<td>0.118</td>
<td>−0.106</td>
<td>−0.03</td>
</tr>
<tr>
<td>Overt (FT4&lt;12 ng/dl, TSH&gt;5 mU/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significance (2-tailed)</td>
<td>0.002</td>
<td>0.097</td>
<td>0.135</td>
<td>0.680</td>
</tr>
<tr>
<td>Subclinical (FT4 = normal, TSH &gt;5 mU/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

FT4, serum free thyroxine; Hb, hemoglobin; TSH, thyroid-stimulated hormone.
Sig. (2-tailed): **statistically significant, P value less than 0.01.
by Bordbar et al. (2019) and Thuret et al. (2010). Age groups were correlated with hypothyroidism, whereas other parameters, including sex, serum ferritin, BMI, and Hb, were not statistically significant. This endocrine disorder needs more in-depth studies to find out the associated parameters and the most critical risk factors among patients with BTM with that endocrinopathy. Some scientists claim that age, splenectomy, serum ferritin and duration of transfusion and splenectomy might be associated with that endocrine disorder, whereas others found no relation (Kolnagou et al., 2013).

Table 6 shows more details concerning the prevalence of this endocrinopathy with other studies.

In our study, the overall prevalence of hypothyroidism was 9.5%, whereas in another report was 22.6%. Therefore, the ratio between the prevalence reported in our study and the prevalence that study was found to be 1 : 2.379.

Overt hypothyroidism in our study was 3%, whereas that found in latter work was 14.6%, and subclinical hypothyroidism was found to be 6.5% but the subclinical hypothyroidism in the previous mentioned report was 6.4%. From this comparison, we concluded that similar percentage value was found in subclinical hypothyroidism in both works (i.e. approximate ratio 1 : 1), but the ratio between overt hypothyroidism in our study to that of the other report was 1 : 4.866. No central hypothyroidism was found in our study, but in the other report was one case, that is, 1/62 = 1.6%.

A correlation analysis with bivariate method showed that there was a statistically significant correlation between hypothyroidism and age groups ($P = 0.002$), and there was no correlation with each of the following variables: serum ferritin level ($P = 0.403$), Hb ($P = 0.68$), sex ($P = 0.135$), and BMI ($P = 0.097$).

Most reports revealed that there were no associations between thyroid disorder and serum ferritin levels (Sushil et al., 2017; Tutar et al., 1995; Magro et al., 1990; Senanayake et al., 1999; Pitrilo et al., 1995), but few others found a relation (Handan and Ilkay, 2019). More in-depth research should be done. However, our results revealed that patients should be monitored carefully, especially the age group 27–less than 32 years old, which had the most prevalent hypothyroidism regardless of ferritin levels.

### 4.1. Conclusion

Hypothyroidism had an overall distribution of 9.5% among patients with BTM. The frequencies of overt and subclinical endocrine disorders were 3 and 6%, which had ferritin levels of 2501–3500 ng/ml and more than 3500 ng/ml, respectively. There was a statistically significant correlation between hypothyroidism and age groups, whereas parameters such as ferritin, BMI, and Hb had no association. Careful monitoring should be done, especially for the age group 27–less than 32 years. More in-depth research must be carried out to detect the association between hypothyroidism and other parameters.

### Consent statement

The study protocol was approved by the Institutional Review Board (IRB) Faculty of Medicine, Zagazig University, Egypt (Approval IRB #: 5895-8-3-2020). The data are accessed confidentially by the authors. The information was not specific to certain patients and the work was cross-sectional study. The patient informed consent was waived for this research.

### Conflicts of interest

The authors report no conflicts of interest in this work.

### References

