Evaluation of Endocrine Disorders in Patients with Thalassemia Major

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Thalassemia major is a genetic disorder and blood transfusion is critical for survival in these patients. Over the course of the past three decades, hypertransfusion therapy in these patients has shown significant increase in life expectancy and quality of life. Unfortunately this type of therapy also increased the frequency of complications due to iron overload. The aim of this study was to evaluate the prevalence of endocrine disturbances in patients, aged over 10 years, with thalassemia major.

Materials and Methods: Fifty six patients, aged over 10 years, with thalassemia major were enrolled. Physicians collected demographic data and history of therapies as well as menstrual histories in females. Patients were examined to determine their pubertal status and SDS of height for evaluation of short stature. For evaluation of glucose tolerance, fasting blood glucose and oral glucose tolerance tests were performed. Serum levels were measured for calcium, phosphorous, thyroid stimulating hormone, free thyroxin, luteinizing hormone, follicular stimulating hormone, and estradiol and testosterone in girls and boys respectively.

Results: Fifty-six patients with thalassemia major, aged between 10-27 years, were evaluated. In this study prevalences of diabetes mellitus, impaired fasting glucose and impaired glucose tolerance tests were 8.9%, 28.6% and 7.1% respectively. Short stature (SDS ≤-2) was seen in 70% of boys and in 73% of girls. Hypocalcaemia and primary overt hypothyroidism were present in 41% and 16% respectively; 14.3% of our patients had no endocrine abnormalities.

Conclusion: Despite recent therapy with Desferal in the management of beta-thalassemia major, the risk of secondary endocrine dysfunction remains high. Hypogonadism is one of the most frequent endocrine complications. Endocrine evaluation in patients with thalassemia major must be carried out regularly especially in those patients over the age of 10 years, in Tabriz.

Key Words: Thalassemia major, Hypocalcaemia, Hypogonadism, Hypothyroidism, Diabetes mellitus, Impaired glucose tolerance test, Impaired fasting glucose, Endocrine disorders, Growth retard

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Introduction

The major hemoglobin in normal adults is hemoglobin A, a tetramer consisting of one pair of alpha chains and one pair of beta chains. In normal subjects, globin chain synthesis is very tightly controlled, such that the ratio of production of alpha to non-alpha chains is 1.00±0.05. Thalassemia refers to a spectrum of diseases characterized by reduced, or lack of, production of one or more globin chains, thus disrupting this ratio.1 Erythrocyte transfusion therapy is associated with iron overload and possible iron-induced
organ damage. Treatment with transfusion programs and chelating therapy has considerably prolonged survival in thalassemic patients. However, as a result of hyper transfusion therapy and increased longevity, iron tissue toxicity has become more common, and contributes significantly to morbidity in these patients. Despite intensive chelating therapy, hypogonadotropic hypogonadism, diabetes mellitus, and hypothyroidism represent the most common endocrinopathies in thalassemic patients.

**Materials and Methods**

We studied a total of 65 patients, aged over 10 years, with β-thalassemia major, followed up and treated at the Departments of Pediatrics and Endocrinology and Metabolism of Sina Hospital, with regard to the endocrine complications of the disease. Patients were evaluated for endocrine complications intervals at 3-6 months; 9 were excluded from the study, and the study population consisted of 56 patients. All patients had been on a regular transfusion program (every 15–25 days) with the aim of maintaining pre-transfusion hemoglobin levels above 9 g/dL. The mean hemoglobin concentration was 9.7±0.4 g/dL. All thalassemic patients, subjected to an iron chelating program with subcutaneous desferrioxamine, were active and self-dependent.

After enrollment, the subject’s medical history was documented by a review of previous medical records. The subject interview questionnaire included items on demographics, medical and surgical history (e.g. splenectomy), family history of endocrine complications and medication usage. For female subjects, menstruation history was also abstained. A medical record review was also conducted by the research coordinator at the patient’s centre, which included documentation of transfusion and chelating history and recent endocrine laboratory values. Each subject’s height was obtained at the baseline visit.

Basic serum biochemical parameters, including fasting calcium, phosphorus, alkaline phosphatase, total iron binding capacity, iron, ferritin thyroid stimulating hormone, free thyroxin, luteinizing hormone and follicular stimulating hormone were obtained for all patients. In male patients, serum testosterone and, in female patients, serum estradiol was obtained.

Medical records were used to check the gonadal status thyroid functions, and the presence of diabetes (or impaired glucose tolerance). For females, hypogonadism was diagnosed by the presence of primary or secondary amenorrhea. Primary amenorrhea was regarded as being present when menarche had not begun by the age of 15, or a lack of breast development by the time a girl had reached the age of 13. Secondary amenorrhea was defined as the absence of menstruation for a 6-month period at any time after menarche. In males, hypogonadism was considered to be indicated by the absence of testicular enlargement in boys (less than 4ml), as measured by Prader’s orchidometer, by the age of 14, and by the measurement of low serum testosterone in adults. In patients with diabetes, anti glutamic acid decarboxylase was measured.

The following criteria were used to ascertain abnormalities as given below:

- Height standard deviation score less than 2 for growth retardation, fasting glucose equal or greater than 126 mg/dL and/or post 2 hours (75 gram glucose in patients greater than 30 kg and 1.75 gram/kg in patients less than 30 kg) greater than 200 mg/dL and/or exogenous insulin administration and/or use of oral hypoglycemic medications for diabetes, fasting glucose equal or greater than 100 mg/dl and less than 126 mg/dL for impaired fasting glucose, two hours serum glucose post (75 gram glucose in patients greater than 30 kg and 1.75 gram/kg in patients less than 30 kg) equal or greater than 140 mg/dl and less than 200 mg/dL for impaired glucose tolerance test, free thyroxin less than normal and thyroid stimulating hormone greater than
normal for primary overt hypothyroidism, free thyroxin normal and thyroid stimulating hormone greater than normal but less than 10 mu/L for subclinical hypothyroidism and serum calcium less than 8.5 mg/dL of hypocalcaemia and hyperphosphatemia was correlated with ages.

Data were analyzed by using SPSS software version 14. Numerical data are presented as mean±standard deviation. p<0.05 was considered significant. Differences in continuous variables were analyzed using Student’s t-tests and differences in categorical variables using Pearson chi-squared tests.

Results
Clinical data of 56 patients (20 females and 36 males), aged 10-27 years (mean age: 15.62±4.44 years), with thalassemia major, are shown in Table 1.

Table 1. Demographic and biochemical characteristics of 56 thalassemia patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SD±Mean</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>15.62±4.44</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>SDS Height</td>
<td>20.35±0.94</td>
<td>1</td>
<td>5.4</td>
</tr>
<tr>
<td>LH (mu/mL)</td>
<td>3.54±3.05</td>
<td>0.3</td>
<td>11</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>3.74±2.73</td>
<td>1</td>
<td>9.9</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>1.65±2.16</td>
<td>0.1</td>
<td>6.9</td>
</tr>
<tr>
<td>Esteradiol (pg/mL)</td>
<td>12.88±19.87</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>TSH (mu/L)</td>
<td>8.94±19.58</td>
<td>0.9</td>
<td>100</td>
</tr>
<tr>
<td>FT₄ (ng/dL)</td>
<td>0.96±0.33</td>
<td>0.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>8.94±11.11</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>p (mg/dL)</td>
<td>5.21±0.8</td>
<td>4</td>
<td>7.2</td>
</tr>
<tr>
<td>Alk. Ph. (U/L)</td>
<td>341±179</td>
<td>50</td>
<td>620</td>
</tr>
<tr>
<td>Iron (µg/dL)</td>
<td>199±72</td>
<td>89</td>
<td>600</td>
</tr>
<tr>
<td>TIBC (µg/dL)</td>
<td>231±61</td>
<td>136</td>
<td>530</td>
</tr>
<tr>
<td>Ferritin (µg/mL)</td>
<td>2888±948</td>
<td>863</td>
<td>6619</td>
</tr>
</tbody>
</table>

Five patients (8.9%) had diabetes mellitus, all diagnosed after the age of 14 (mean age at the time of diagnosis 19.8±4.3 years). No significant difference was seen between males and females in the prevalence of diabetes mellitus. Serum ferritin level in thalassemic patients with diabetes and those without diabetes was not significantly different (Table 2). Two of patients had diabetes mellitus previously and 3 were diagnosed with oral glucose tolerance tests; fasting blood glucose levels were normal in these patients. Family histories of diabetes mellitus were negative in diabetic patients and anti glutamic acid decarboxylase evaluations were negative in all. Sixteen patients (28.6%), mean age 16.2±3.3 years, had impaired fasting glucose; four patients (7.1%), mean age 18.5±3.4 years, had impaired glucose tolerance tests. Statistical analysis revealed several risk factors. Age and duration of blood transfusion were risk factors of diabetes mellitus, P values 0.0026 and 0.042 respectively. Amount of blood transfusion was a risk factor of impaired fasting glucose with P. value of 0.002. No risk was detected for impaired glucose tolerance test (Table 2).
Table 2. Comparison between beta-thalassemia patients with normal and abnormal glucose tolerance

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal (31 persons)</th>
<th>IGT (4 persons)</th>
<th>IFG (16 persons)</th>
<th>DM (5 persons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>14.4±4.4</td>
<td>18.5±3.4</td>
<td>16.2±3.3</td>
<td>19.8±4.3*</td>
</tr>
<tr>
<td>Blood transfusion (U/Month)</td>
<td>1.8±0.54</td>
<td>2.3±1.06</td>
<td>2.4±0.76*</td>
<td>1.7±0.81</td>
</tr>
<tr>
<td>Desferal (gr/Month)</td>
<td>53±25</td>
<td>54±12</td>
<td>63±13</td>
<td>65±42</td>
</tr>
<tr>
<td>Iron (µg/dL)</td>
<td>198±83</td>
<td>201±11.08</td>
<td>210±56</td>
<td>175±20.9</td>
</tr>
<tr>
<td>Ferritin (µg/mL)</td>
<td>2780±989</td>
<td>3526±1186</td>
<td>2985±882</td>
<td>2927±943</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>85±7</td>
<td>109±13.12</td>
<td>109±7.4</td>
<td>94±18</td>
</tr>
<tr>
<td>OGTT (mg/dL)</td>
<td>106±12</td>
<td>159±19.6</td>
<td>130±42.5</td>
<td>266±16</td>
</tr>
<tr>
<td>Duration of blood transfusion (year)</td>
<td>12.2±4.6</td>
<td>15.8±5.02</td>
<td>13.4±3.43</td>
<td>17±4.2*</td>
</tr>
<tr>
<td>Duration of Desferal (year)</td>
<td>10.2±3.9</td>
<td>11.1±2.17</td>
<td>12.1±3.2</td>
<td>14.7±2.5</td>
</tr>
</tbody>
</table>

* P<0.05 Compared with normal group, † Mean±SD

Growth failure was commonly observed. Short stature was seen in 29 patients (52%) with standard deviation score of height, less than -2 and in 10 patients (17.85%) with standard deviation score of height less than -3. Lack of puberty changes was the most common endocrine complication in this study. Eleven females were aged over 13 years and only 3 of them (27%) with a mean age of (18.71±3.9) had regular menses. Of twenty males, aged over 14 years, 6 (30%) with a mean age of (19.27±2.41) had the criteria for puberty. Overall, 22 patients (71%) had hypogonadism in our study. Luteinizing hormone, follicular stimulating hormone and testosterone in boys and estradiol in girls were below normal (Table 3); no cases of primary hypogonadism were detected.

Table 3. Biochemical characteristics of boys and girls with hypogonadism

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Age (years)</th>
<th>FSH (mIU/mL)</th>
<th>LH (mIU/mL)</th>
<th>Testosterone (ng/mL)</th>
<th>Estradiol (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>19.58±3.33*</td>
<td>2.63±2.06</td>
<td>2.77±2.68</td>
<td>0.74±0.34</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>17.75±4.33</td>
<td>3.87±2.94</td>
<td>3.75±3.30</td>
<td></td>
<td>5.07±2.1</td>
</tr>
</tbody>
</table>

* Mean±SD

Primary hypothyroidism was present in 16% of patients with mean age (17.33±4.22). Sub clinical hypothyroidism (normal free thyroxin and high thyroid stimulating hormone) was observed in 10.7% of patients (Table 4). No cases of secondary hypothyroidism were detected.

Mean serum calcium level was (7.87±0.81). Serum calcium level was lower than normal in 41% of patients. Fourteen (25%) of patients had hyper phosphatemia and 56% of them had hyper alkaline phosphatase.

Table 4. Biochemical characteristics of patients with hypothyroidism

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Age (years)</th>
<th>FT4 (ng/dL)</th>
<th>TSH (mu/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical hypothyroidism</td>
<td>17.33±4.22*</td>
<td>0.85±0.12</td>
<td>6.41±1.35</td>
</tr>
<tr>
<td>Overt hypothyroidism</td>
<td>13.11±2.42</td>
<td>0.33±0.14</td>
<td>42.2±30.85</td>
</tr>
</tbody>
</table>

* Mean±SD
Discussion

Before the institution of regular blood transfusion, patients with β-thalassemia major died within the first few years of life from congestive heart failure or other complications resulting from chronic anemia. Transfusion and iron-chelation therapy have prolonged and improved the quality of life in patients with this disease, the improvement being mainly due to the decrease in mortality from heart failure. Such a treatment, however, leads to chronic iron overload and frequently to endocrine complications. Primary and secondary characteristics of sexual development are usually delayed for both boys and girls. Menarche is frequently delayed, breast development is often poor, and patients are frequently oligomenorrheic or amenorrheic, even if menarche occurs. Boys frequently do not develop, or have sparse, facial and body hair and tend to have decreased libido, even if sperm production does occur.

There is increasing evidence that hypogonadism may be primarily due to iron overload. Impaired puberty, which occurred in approximately 71% of our patients, was the most common endocrine abnormality. Hypogonadism was present in 72.72% of girls and 70% of boys without significant differences. In this study, no secondary hypogonadism was seen. Impaired puberty seems to be more prevalent in our study compared to the study of an Italian working group. In a longitudinal study, prevalence of hypogonadism has been reported to be as much as 75% in girls and 62% in boys. De Sanctis and co-workers, in a study group of 238 patients, aged 2-17 years, with beta-thalassaemia major, regularly followed in 13 pediatric and hematological Italian centers, found delayed puberty in 18.4% of boys and 17.7% of girls. In another study, De Sanctis and co-workers evaluated 3817 beta thalassaemia major patients of whom thirty-six per cent of patients were over the age of 16 years; a lack of pubertal changes (40.5%) was observed in their study. Moayeri and co-workers found hypogonadism (69%) in 158 patients, aged 10-20 years (82 females and 76 males) with thalassemia major. They found a low serum levels of gonadotropins in patients over 14-year-old with impaired puberty, indicating that hypogonadotropic hypogonadism was responsible for this complication. Borgna–Pignatti and co–workers evaluated 720 thalassemia major and reported 54.7% hypogonadism in their study. Shamshirsaz and co–workers evaluated 258 adolescent, homozygous, beta-thalassemia patients in Tehran; impaired puberty, which occurred in approximately 77% of their patients, was the most common endocrine abnormality and hypogonadism was seen in 22.9% of boys and 12.2% of girls in their study. An Italian working group studying 1861 patients, showed that failure of puberty was the major clinical endocrine problem and was present in 51% of boys and 47% of girls, all over the age of 15 years. Soliman and co–workers reported in thalassaemic patients, between the ages of 13 and 21 years, there was a complete lack of pubescent changes in 73 percent of boys and 42 percent of girls. Of the thalassaemic girls, 74% had primary amenorrhea. Chern and co–workers examined 29 patients with thalassemia major, aged 15 years or older, and reported a 72% prevalence of hypogonadotropic hypogonadism. The second common endocrine dysfunction in this study was short stature (51.78%). Growth retardation is frequently profound in these children. This reflects, in part, the diversion of caloric resources for erythropoiesis, along with the effects of anemia, since hypertransfusion frequently restores normal growth rates. However, the adolescent growth spurt is often delayed, even in children who are hypertransfused, unless intensive iron chelating therapy is instituted early in life. Normal stature is thus rarely attained, even in well–managed patients. Mostafavi and co–workers examined 44 patients, 8.5 to 25 years old, with thalassemia major and reported height of 90.9% of patients was under the fifth percentile (standard deviation score of height less than -2). Soliman and co–workers
Abnormal carbohydrate metabolism is another major endocrine abnormality encountered in these children. Glucose intolerance usually develops during the second decade of life, even though baseline blood sugar levels are frequently normal. Interestingly, the early lesion appears to be related to insulin resistance rather than to defective insulin production. The latter is a complication that occurs only during the late stages of development of hemosiderosis. More effective iron chelating appears to improve glucose intolerance. Prevalence of diabetes has been reported to range from 2.3 to 24%, and risk factors for diabetes in patients with \( \beta \)-thalassemia major have been suggested to include age, increased amount of blood transfusion, serum ferritin level, compliance with iron-chelating therapy, family history of diabetes, and pubertal status. Before our study, the prevalence and risk factors for abnormal glucose tolerance in patients with blood-transfused \( \beta \)-thalassemia in Tabriz were unknown, a gap that the present study was designed to fill. The prevalence of impaired fasting glucose in this study was 28.6% (16 patients), impaired glucose tolerance was 7.1% (4 patients), and diabetes was 8.9% (5 patients). Diabetes was previously diagnosed in 2 of them, and in the remaining 3 patients, during oral glucose tolerance tests. Fasting blood glucose was normal in all of them and diabetes mellitus was diagnosed only in oral glucose tolerance tests. This finding is important because fasting blood glucose is not enough for diagnosis and screening of patients with thalassemia major. In a study of 142 chronically transfused, 12 years of age patients with beta thalassemia and an average serum ferritin 2000 microg/L, 13% were found to have diabetes mellitus. Ethnic variations are frequently reported in the prevalence and complications of diabetes mellitus in beta-thalassemia patients. Ramachandran et al. reported a prevalence in India of 12.1% and 14% for diabetes mellitus and impaired glucose tolerance, respectively. Khalifa and co-workers reported the prevalence of diabetes was
10.4% (5 of 48) and impaired glucose tolerance was 14.6% (7 of 48). Similar results were reported by De sancitis et al. in Italy, whereas, a lower prevalence was found in Saudi thalassemic patients (6% for diabetes mellitus) compared to other ethnic groups. Early literature suggests that the high prevalence of diabetes mellitus in patients with thalassemia is due to direct impairment of insulin excretory function by the chronic iron overload. Monge et al. demonstrated an evidence of immune system activation against pancreatic beta cells in beta-thalassemia patients; they proposed that pancreatic iron deposition may, through oxidative damage, act as an environmental factor that triggers the autoimmune response which, in turn, contributes to selective beta-cell damage. It is still unclear whether diabetes in β-thalassemia major is related to genetic factors. We did not demonstrate that family history was a risk factor in our patient group. In our study, risk factors of impaired glucose metabolism were age of patients, and number and duration of blood transfusions. The mechanism of abnormal glucose homeostasis in patients with β-thalassemia major is still unknown but is attributed mainly to insulin deficiency resulting from the toxic effects of iron deposited in the pancreas and from insulin resistance. Insulin resistance may come from iron deposition in both the liver (where iron deposits may interfere with insulin’s ability to suppress hepatic glucose production) and muscle (where iron deposits may decrease glucose uptake because of muscle damage). Persistent insulin resistance along with a progressive reduction in circulating insulin levels may lead to glucose intolerance and overt diabetes. Early identification of thalassemic patients with impaired glucose tolerance has decreased presentations with diabetic ketoacidosis. As a result, physicians caring for patients with thalassemia major should be particularly alert to the possibility of diabetes. Because not all of the patients with thalassemia major could be correctly diagnosed by fasting glucose alone, we preferred to use oral glucose tolerance test rather than fasting blood glucose for the diagnosis of abnormal glucose tolerance in thalassemic patients.

Hypoparathyroidism, thought to be a more rare complication, is usually, but not always, accompanied by hypocalcemia. However, hypoparathyroidism may cause various neurological manifestations, including tetany, seizures, carpopedal spasms, and paresthesia, and little is known about these associated complications in thalassemic patients. In our study, prevalence of hypocalcaemia was 41% and 60% of patients with hypocalcaemia had hyperphosphatemia simultaneously. Mostafavi and co-workers reported hypocalcaemia in 22.7% of thalassemic patients and hyperphosphatemia in 70% of them. Garofalo and co-workers reported hypocalcaemia was present in 16.6% of thalassemic patients. Gulati and co-workers reported hypoparathyroidism was present in 33 patients (17 males and 16 females), with a prevalence of 13.5% in the study population. Although the parathyroid hormone was not measured in this study, but according to other studies, hypocalcaemia is less likely to occur in hypoparathyroidism. For this reason it can be said that there are several etiologies for hypocalcaemia, possibly a nutritional cause as well. In our study, 60% of patients with hypocalcaemia had hyperphosphatemia simultaneously; hence 76.7% of the thalassemic patients had an increased alkaline phosphatase, which is due to vitamin D deficiency. No symptomatic hypocalcaemia was noted in this study.

Hypothyroidism was a complication in 16% of our patients. Thyroid dysfunction has been reported in 13–60% of patients with thalassemia, but its severity is variable in different series. Some studies reported a high prevalence of primary hypothyroidism, reaching up to 17–18%, while others reported low prevalence of 0–9%. It is important to note that even in studies in which the prevalence of overt hypothyroidism as a complication of thalassemia major is

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relatively low, milder forms of thyroid dysfunction are much more common, though again there are wide variations in different reports. These discrepancies can be attributed to differences in patients’ ages (in some studies patients were aged 2 years and above) and different treatment protocols, including differing transfusion rates about desferal in the past several years.

High prevalences of endocrine abnormalities were reported by several authors, demonstrating that these abnormalities were related to iron overload, a hypothesis supported by histological studies of different endocrine glands. These findings emphasize the importance of iron overload in development of endocrine disorders. No correlation was found between ferritin and endocrine abnormalities in our study but in a study by Chern, serum ferritin was a risk factor for glucose intolerance. In contrast, there are some other reports suggesting that no relation exists between the level of ferritin and other endocrinopathies. Deferoxamine has been used as a chelating agent in an attempt to prevent the complications of chelating therapies. In the past, chelating therapies were not performed correctly and hypothyroidism was more common than it is today. In a 1992 study by Garofalo and co-workers, prevalence of primary hypothyroidism was reported 19.4%.

Subclinical hypothyroidism in our study was 10.7%. Eight patients in our study (14.5%), all aged under 14 years, had endocrine complications. Although there were no endocrine abnormalities in this group, but regular testing for screening of endocrine diseases was necessary. We found no correlation between desferal and endocrine abnormalities, but in the Italian working group and Karimifar studies, these correlations were significant. We found no tissue damage by iron deposition. Early introduction of the chelating agent to combat iron overload in vulnerable organs leads to improved life expectancy. Compliance with chelating therapy was poor in 48% of patients. Since iron overload seem to be the most important factor responsible for endocrine complications, adequate compliance to chelating therapy is imperative.

Our study has demonstrated several points. Endocrine evaluation in thalassemic patients must be carried out regularly, especially in those patients, over the age of 10 years with iron overload and poor compliance with chelating therapy. Hence, it is recommended that patients who have iron overload start chelating therapy during the first years of life. Because of the improved survival of thalassaemic patients, and the high incidence of multiple endocrine complications, it is important to carry out careful follow-up studies for the early detection of any other associated complications to facilitate precise treatment. The relatively high frequency of endocrine dysfunction found in our study may be a result of poor disease control in early life, when irreversible tissue damage occurs due to iron overload.

References


27. Gulati R, Bhatia V, Agarwal SS. Early onset of endocrine abnormalities in beta-