original article

A cross-sectional study of metabolic and endocrine complications in beta-thalassemia major

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BACKGROUND AND OBJECTIVES: Iron overload is a major problem in patients with beta-thalassemia major, and it has many structural and metabolic consequences. The aim of this study was evaluation of endocrine disturbances in patients with beta-thalassemia major who were older than 10 years of age.

PATIENTS AND METHODS: In this cross-sectional study, investigators collected demographic data and medical histories, as well as menstrual history in females, from the medical records of 56 patients with beta-thalassemia major. Patients were examined to determine their pubertal status and the standard deviation score for height for evaluation of short stature. For evaluation of glucose tolerance, a fasting blood glucose and oral glucose tolerance test were performed. Evidence for diabetes mellitus was based on American Diabetes Association and World Health Organization criteria. Serum levels of calcium, phosphorous, thyroid-stimulating hormone, free thyroxin, luteinizing hormone and follicular-stimulating hormone, and estradiol in girls and testosterone in boys were measured.

RESULTS: The mean and standard deviation for age in the 56 patients (36 males and 20 females) was 15.62±4.44 years. Diabetes mellitus was present in 5 patients (8.9%), impaired fasting glucose was found in 16 patients (28.6%) and an impaired glucose tolerance test was found in 4 patients (7.1%). Short stature (standard deviation score <-2) was seen in 25 (70%) boys and 14 (73%) girls. Impaired puberty was found in 40 patients (71%). Hypocalcaemia and primary overt hypothyroidism were present in 23 (41%) and 9 patients (16%), respectively. Only eight patients (14.3%) had no endocrine abnormalities.

CONCLUSION: Despite therapy with deferoxamine to treat iron overload, the risk of secondary endocrine dysfunction remained high. Hypogonadism was one of the most frequent endocrine complications. Impaired glucose tolerance, short stature, hypocalcemia, subclinical and overt hypothyroidism are also frequent.

Treatment with transfusion and chelating therapy has considerably prolonged survival in thalassemic patients.[1] However, as a result of hypertransfusion therapy and increased longevity, iron tissue toxicity has become more common, and contributes significantly to morbidity in these patients.[2] In recent years, several authors have reported a high incidence of endocrine abnormalities in children, adolescents and young adults suffering from thalassemia major.[3] Short stature and hypogonadism are extremely frequent in patients with thalassemia. In some reports, 49% of thalassemic patients had a height standard deviation score less than −2 and 83% of thalassemic patients had a height standard deviation score less than −1.[4] Borgna-Pignatti and co-workers evaluated 720 thalassemia major patients and reported 54.7% hypogonadism in their study.[3] Hypoparathyroidism is thought to be a rare complication, usually, but not always, accompanied by hypocalcemia.[5] Recently, abnormal cerebral CT findings have been reported in a high percentage of patients with thalassemia and hypoparathyroidism.[6] The prevalence of diabetes among thalassemia patients has been reported to range from 2.3% to 24%.[2,3,6,7] Thyroid dysfunction is known to occur frequently in thalassaemia major, but its prevalence and severity varies in different cohorts, and the long-term natural history is poorly described.[8] The aim of this study was evaluation of the prevalence of growth retardation, hypogonadism,

hypothyroidism, hypocalcaemia, diabetes mellitus, impaired fasting glucose and impaired glucose tolerance in patients with thalassemia major who were older than 10 years of age.

PATIENTS AND METHODS

In this cross-sectional study we evaluated endocrine complications of the disease in all beta-thalassemia major patients older than 10 years of age (65 patients) who were followed up and treated at the Department Pediatric and Endocrinology and Metabolism of Sina Hospital, Tabriz, Iran. Nine patients were excluded due to incomplete data so the study population consisted of 56 patients. All patients had been maintained on a regular transfusion program (every 15-25 days) with the aim of maintaining pre-transfusion hemoglobin levels above 9 g/dL. The duration of blood transfusion was 13.16±4.65 years. The mean hemoglobin concentration was 9.7±0.4 g/dL. All thalassemic patients had been taking desferrioxamine with doses of 59±38 g/month for 11.3±2.6 years. All patients were active and self-dependent.

After enrollment, the medical records of the patients were reviewed for demographic data, medical and surgical history (e.g. splenectomy), family history of endocrine complications and medication usage. For female subjects, menstruation history was collected. The research coordinator at the patient's centre conducted a medical record review, 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 plasma glucose, oral glucose tolerance, fasting calcium, phosphorus, alkaline phosphatase, total iron binding capacity, iron, thyroid-stimulating hormone, free thyroxin, luteinizing hormone and follicular-stimulating hormone were obtained for all patients. Serum testosterone was obtained in male patients and serum estradiol in female patients. Serum ferritin levels were measured to monitor the effect of chelating therapy. Serum calcium was adjusted for serum albumin. Serum phosphorus was adjusted for age.

For females, hypogonadism was diagnosed by the presence of primary or secondary amenorrhea. The absence of menses by age 16 has been used traditionally to define primary amenorrhea.[4,5] Secondary amenorrhea was defined as the absence of menstruation for a 3- to 6-month period at any time after menarche. In males, hypogonadism was considered the absence of testicular enlargement in boys (less than 4 mL), as measured by a Prader's orchidometer, by the age of 14 years, and by the measurement of low serum testosterone in adults.[5] In patients with diabetes, anti-glutamic acid decarboxylase was measured.

Evidence for growth failure was a height standard deviation score less than −2. Evidence for diabetes mellitus was based on American Diabetes Association and World Health Organization criteria.[7] Glucose tolerance was classified into three categories based on the fasting plasma glucose: (1) fasting plasma glucose <100 mg/dL was considered normal; (2) fasting plasma glucose of 100-<126 mg/dL was defined as impaired fasting glucose; and (3) a fasting plasma glucose ≥126 mg/dL warranted the diagnosis of diabetes. Based on the oral glucose load, impaired glucose tolerance was defined as a plasma glucose level between 140 and <200 mg/dL and diabetes was defined as a glucose level ≥200 mg/dL 2 hours after a 75-g oral glucose load. Individuals with impaired fasting glucose and/or impaired glucose tolerance were recently designated as pre-diabetic by the American Diabetes Association.[7] In patients with diabetes, anti-glutamic acid decarboxylase was measured.

Evidence for the existence of primary overt hypothyroidism was when free thyroxin was less than normal and thyroid-stimulating hormone was greater than normal. Evidence for subclinical hypothyroidism was when free thyroxin was normal and thyroid-stimulating hormone was greater than normal.[8] Evidence of hypocalcaemia was serum calcium less than 8.5 mg/dL. Phosphate level was adjusted for age. Calcium, phosphorus and hemoglobin were determined by automated routine procedures. Immediately after the blood samples were taken, calcium was measured with an ion-selective electrode (9180 model; AVL Medical Instruments, Basel, Switzerland). Ferritin was measured by a two-site immunoluminometric assay (Byk-Sangtec Diagnostica; Dietzenbach, Germany). TIBC was measured by the magnesium carbonate precipitating method (Darman Kave). Thyroid-stimulating hormone, free thyroxin, luteinizing hormone, and follicular-stimulating hormone, testosterone, esteradiol were measured by an electrochemiluminescence immunoassay (Elecsys Roche Diagnostics, Mannheim, Germany). Blood glucose and alkaline phosphatase were determined by photometry assay (Pars Azmun, Iran). ALT and AST were measured by the IFCC method (Pars Azmun, Iran). Albumin was measured by the Bromcrozal Green method (Pars Azmun, Iran). Iron was measured by the Freen method (Pars Azmun, Iran). All samples were drawn in the morning and in a fasting state.

Data were analyzed using SPSS software version 14. All data are presented as mean±standard deviation and values of $P<.05$ were considered statistically

significant. Differences in continuous variables were analyzed by the *t* test.

RESULTS

The clinical data of 56 patients (20 females and 36 males) with thalassemia major ranged in age from 10 to 27 years (mean, 15.62±4.44 years) (Table 1). Five patients (8.9%) had diabetes mellitus, all diagnosed after the age of 14 years. The mean and standard deviation for age at the time of diagnosis was 19.8±4.3 years. No significant difference was seen between males and females in the prevalence of diabetes mellitus. Serum ferritin levels in thalassemic patients with diabetes and those without diabetes were not significantly different (Table 2). Two patients had diabetes mellitus previously and 3 of them diagnosed with the oral glucose test while fasting blood glucose were normal in these patients. Family histories of diabetes mellitus were negative in diabetic patients and anti-glutamic acid decarboxylase was negative in all five patients. Sixteen patients (28.6%) had impaired fasting glucose with a mean and standard deviation for age of 16.2±3.3 years. Four patients (7.1%) had an impaired glucose tolerance test with a mean and standard deviation for age of 18.5±3.4 years. Age and duration of blood transfusion were risk factors for diabetes mellitus with *P* values of .0026 and .042, respectively. The amount of blood transfusion was a risk factor for impaired fasting glucose with a *P* value of .002 (Table 2). We found no risk factors for the impaired glucose tolerance test.

Growth failure was commonly observed. Short stature was seen in 29 patients (52%) with a standard deviation score of height less than −2 and in 10 patients (17.85%) with a standard deviation score of height less than −3. Lack of pubertal changes were the most common endocrine complication in this study. Eleven females were older than 13 years of age and only 3 of them (27%) (mean age, 18.71±3.9 years) had regular menses. Twenty males were older than 14 years of age and only 6 (30%) (mean age, 19.27±2.41 years) had criteria of puberty. Overall, 22 patients (71%) had hypogonadism in our study. Luteinizing hormone, follicular-stimulating hormone and testosterone in boys and estradiol in girls were lower than normal. No cases of primary hypogonadism were detected. Overt primary hypothyroidism was present in 16% of patients (mean age, 17.33±4.22 years). Subclinical hypothyroidism was observed in 10.7% of patients. No cases of second-

Table 1. Demographic and biochemical characteristics of 56 patients with beta-thalassemia major.

Parameters	Minimum	Maximum	Mean±SD	Reference range
Age (years)	10	27	15.62±4.44	-
SD score for height	-1	-5.4	-2.35±0.94	-
LH (mIU/mL)	0.3	11	3.54±3.05	2-15
FSH (mIU/mL)	1	9.9	3.74±2.73	3-20
Testosterone (ng/mL)[a]	0.1	6.9	1.65±2.16	2.7-10.7
Esteradiol (pg/mL)[b]	2	60	12.88±19.57	20-443
TSH (mIU/L)	0.9	100	8.94±19.58	0.5-4
FT4 (ng/dL)	0.1	1.5	0.96±0.33	0.8-1.9
Calcium (mg/dL)	6	10	8.94±1.11	9-10.5
Phosphorous (mg/dL)	4	7.2	5.21±0.8	3-4.5
Alkaline phosphates (U/L)	50	620	341±179	30-320
Iron (µg/dL)	89	600	199±72	30-160
TIBC (µg/dL)	136	530	231±62	228-428
Ferritin (µg/dL)	863	6619	2888±948	30-300

[a]35 males, [b]20 females. LH: luteinizing hormone, FSH: follicle-stimulating hormone, TSH: thyroid-stimulating hormone; FTH: free thyroxine, TIBC: total iron binding capacity.

Table 2. Beta-thalessemia patients with normal and abnormal glucose tolerance.

Parameters	Normal glucose tolerance (n=31)	Impaired glucose tolerance (n=4)	Impaired fasting glucose (n=16)	Diabetes mellitus (n=5)
Age (years)	14.4±4.4	18.5±3.4	16.2±3.3	19.8±4.3
Blood transfusion (U/mo)	1.8±0.54	2.3±1.06	2.4±0.76[a]	1.7±0.81
Deferoxamine (g/month)	53±25	54±12	63±13	65±42
Iron (µg/dL)	198±83	201±11.08	210±56	175±20.9
TIBC (µg/dL)	235±68	226±12.84	230±50	210±5.5
Ferritin (µg/mL)	2780±989	3526±1186	2985±882	2927±943
FPG (mg/dL)	85±7	109±13.12	109±7.4	94±18
2 h. post 75-g glucose (mg/dL)	106±12	159±19.6	130±42.5	266±16
Duration of blood transfusion (years)	12.2±4.6	15.8±5.02	13.4±3.43	17±4.2[a]
Duration of deferoxamine (years)	10.2±3.9	11.1±2.17	12.1±3.2	14.7±2.5

Data are mean±SD, [a]*P*<.05 compared with normal group. TIBC: total iron-binding capacity, FPG: fasting plasma glucose.

ary hypothyroidism were detected. The mean serum calcium level was 7.87±0.81 mg/dL. The serum calcium level was lower than normal in 23 patients (41%). Fourteen (25%) patients had hyperphosphatemia and 31 patients (56%) had elevated alkaline phosphatase.

DISCUSSION

Impaired puberty, which occurred in approximately 71% of our patients, was the most common endocrine abnormality. Hypogonadism was present in 73% of girls and 70% of boys without significant differences. In this study, none of our patients was found to have primary hypogonadism. Delayed puberty seemed to be more prevalent in our study compared to the study of an Italian working group.[7] In a longitudinal study, the prevalence of hypogonadism has been reported to be as much as 75% in girls and 62% in boys.[8] 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 centers in Italy, found delayed puberty in 18.4% of boys and 17.7% of girls.[9-11] Shamshirsaz and co-workers evaluated 258 adolescent homozygous beta-thalassemia patients in Tehran.[12] 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. Soliman and co-workers reported a complete lack of pubertal changes in 73% of boys and 42% of girls with thalassemia between the ages of 13 and 21 years.[13] Seventy-four percent of the thalassemic girls had primary amenorrhea.

The second most common endocrine dysfunction in this study was short stature (51.8%). Growth retardation is frequently profound in these children, which 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 chelation therapy is instituted early in life.[14] 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 that height in 90.9% of patients was under the fifth percentile (standard deviation score of height less than −2).[15] Although a delay in onset of puberty is a common cause of growth failure in adolescent thalassaemic patients, growth retardation could also be due to iron overload, the toxic effects of desferrioxamine, or the development of other endocrinopathies such as growth hormone insufficiency or primary hypothyroidism.[16]

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.[17] Interestingly, the earliest abnormality appears to be related more to insulin resistance than to defective insulin production. More effective iron-chelating strategy appears to improve glucose intolerance.[18] The prevalence of diabetes has been reported to range from 2.3% to 24%, and it has been suggested risk factors for diabetes in patients with beta-thalassemia major include age, increased amount of blood transfusion, serum ferritin level, compliance with

iron-chelating therapy, family history of diabetes and pubertal status.[2,3,6,7,19] Before our study, the prevalence and risk factors for abnormal glucose tolerance in patients with blood-transfused beta-thalassemia in Tabriz were unknown; the present study was designed to fill this gap. The prevalence of impaired fasting glucose in this study was 28.6%, impaired glucose tolerance was 7.1% and diabetes was 8.9%. Diabetes was previously diagnosed in two patients and in the remaining 3 patients with an oral glucose tolerance test. Fasting blood glucose was normal in all patients and diabetes mellitus was diagnosed only by the oral glucose tolerance test. This finding is important because fasting blood glucose is not enough for diagnosis and screening for diabetes with thalassemia major. In a study of 142 chronically transfused patients with beta-thalassemia mean 12 years of transfusion and an average serum ferritin of 2000 μg/L, diabetes mellitus was noted in 13%.[18] Ethnic variations are frequently reported in the prevalence and complications of diabetes mellitus in beta-thalassemia patients. Ramachandran et al reported a prevalence of 12.1% and 14% for diabetes mellitus and impaired glucose tolerance in beta-thalassemia, respectively, in India.[20] Although the early literature suggested that the high prevalence of diabetes mellitus in patients with thalassemia was due to direct impairment of insulin excretory function by chronic iron overload,[21,22] Monge et al[23] demonstrated 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.[24] We did not demonstrate that family history was a risk factor in our patient group. In our study, risk factors for impaired glucose metabolism were age, amounts of blood transfusion and duration of blood transfusion. Because not all of the patients with thalassemia major could be correctly diagnosed by fasting glucose alone, we preferred to use the oral glucose tolerance test rather than fasting blood glucose for the diagnosis of abnormal glucose tolerance in thalassemic patients.

Hypoparathyroidism is thought to be a rare complication that is usually but not always accompanied by hypocalcemia.[25] 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.[25] In our study, the prevalence of hypocalcaemia was 41% and 60% of patients with hypocalcaemia had hyperphosphatemia at the same time. Serum calcium was adjusted with serum albumin and pseudohypocalcium was excluded. We did not measure serum parathyroid hormone and therefore cannot be certain that our patients had hypoparathyroidism. Garofalo and co-workers reported that hypocalcemia was present in 16.6% of thalassemic patients.[26] Gulati and co-workers reported that hypoparathyroidism was present in 33 patients (17 males and 16 females), with a prevalence of 13.5% in the study population.[27] In our study, 60% of patients had hypocalcaemia with hyperphosphatemia at the same time. Thus, 76.7% of thalassemic patients had an increased alkaline phosphatase, which is due to vitamin D deficiency or liver disease but we did not separate them. Hypothyroidism was a complication in 16% of our patients. Thyroid dysfunction has been reported in 13% to 60% of patients with thalassemia, but its severity is variable in different series.[28] Some studies reported a high prevalence of primary hypothyroidism, reaching up to 17% to 18%,[29-31] while others reported a low prevalence of 0% to 9%.[32-34] It is important to note that even in studies in which the prevalence of overt hypothyroidism as a complication of thalassemia major is 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 patient ages (in some studies patient ages were from 2 years) and differences in treatment protocols, including differing transfusion rates with deferoxamine in the past several years. In addition, some patients discontinued deferoxamine during transfusion therapy for several months.

In the past, chelating therapy was often not performed correctly and hypothyroidism was more common than today. In the study by Garofalo and co-workers in 1992, prevalence of primary hypothyroidism was reported as 19.4%.[26] Subclinical and overt hypothyroidism was observed in 10.7% and 16%, respectively, of our patients. Eight patients in our study (14.5%) had no endocrine complications and all were under 14 years of age. Although there were no endocrine abnormalities in this group, physicians should test regularly to screen for endocrine diseases. Early introduction of a chelating agent to combat iron overload in vulnerable organs leads to improved life expectancy.[22] Compliance to chelating therapy was poor in 48% of our patients. The patients in our study used chelating therapy intermittently and started several months after birth. Since iron overload seemed to be the most important factor responsible for endocrine complications, adequate compliance with chelating therapy is imperative.

Our study has demonstrated several points. Endocrine evaluation in thalassaemic patients must be carried out regularly, especially in patients over the

age of 10 years with iron overload and poor compliance with chelating therapy. It is hoped that endocrine complications will be reduced in the future for patients who have started chelating therapy during the first year of life. Because of the improved survival of thalassemic 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 correct treatment. The relatively high frequency of endocrine dysfunction found in our study may be a result of poor disease control and management in early life when irreversible tissue damage occurs due to iron overload. These findings reinforce the importance of regular follow-up of patients with ß-thalassaemia major for early detection and management of associated complications.

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