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Evaluation of Glucose Metabolism, Thyroid Function, Growth and Development Pattern and Calcium Status in Patients with Thalassemia Major

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Abstract: Thalassemia major is a genetic disorder. Blood transfusion is critical for survival in these patients. Over the course of the past two and three decade's hypertransfusion therapy in these patients has increased significant improvement in life expectancy and quality of life. Unfortunately, this type of therapy increased the frequency of complication due to iron overloud. In the past endocrine abnormalities were very common in beta-thalassemia patients but it is more common now. The aim of this study was evaluation of prevalence of endocrine disturbances in patients with thalassemia major greater than 10 years old. Fifty six patients with thalassemia major greater than 10 years enrolled. Physicians collected demographic data and history of therapies as well as menstrual history in female. Patients have been 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 test were performed. Serum level of calcium, phosphorous, thyroid stimulating hormone, free thyroxin, luteinizing hormone and follicular stimulating hormone, estradiol in girls and testosterone in boys were measured. Fifty six patients with thalassemia major 10-27 years old were evaluated. In this study prevalence of diabetes mellitus, impaired fasting glucose and impaired glucose tolerance test were 8.9, 28.6 and 7.1%, respectively. Short stature (SDS= -2) was seen in 70 of boys and 73% of girls. Hypocalcaemia and primary overt hypothyroidism were present in 41 and 16%, respectively. 14.3% of our patients have not any endocrine abnormalities. 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

INTRODUCTION

The major hemoglobin in 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 absent production of one or more globin chains, thus disrupting this ratio (Bens and Schwartz, 1990). Erythrocyte transfusion therapy is associated with iron overload and possible iron-induced organ damage (John, 1999). Treatment with transfusion programs and chelating therapy has considerably prolonged survival in thalassemic patients. 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 (John, 1999). Despite intensive chelation therapy, hypogonadotropic hypogonadism, diabetes mellitus and hypothyroidism represent the most common endocrinopathies in thalassemic patients (Borgna-Pignatti *et al*., 2004).

MATERIALS AND METHODS

We studied a total of 65 patients with β-thalassemia major greater than 10 years, who were followed up and treated at the department pediatric and endocrinology

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and metabolism of sina hospital, with regard to the endocrine complications of the disease. Patients' evaluations for endocrine complications are performed each 3-6 months. Among these patients, nine of them were excluded from the study. Overall, 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 pretransfusional hemoglobin levels above 9 g dL^{-1}. The mean hemoglobin concentration was 9.7±0.4 g dL^{-1}. All thalassemic patients were subjected to an iron chelation program with subcutaneous desferrioxamine. All patients were active and self-dependent.

After enrolment, the subject's medical history was documented by a review of the 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 collected. A medical record review was also conducted by the research coordinator at the patient's centre, which included documentation of transfusion and chelation 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, 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. Serum ferritin levels were measured to monitor the effect of chelation therapy.

Medical records showed that gonadal status and thyroid functions and the presence of diabetes (or impaired glucose tolerance) were checked in all subjects. For females, hypogonadism was diagnosed by the presence of primary or secondary amenorrhea. Primary amenorrhea was regarded as present when the menarche had not appeared by the age of 15, or a lack of breast development by the time a girl had reached the age of 13 year. 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 4 mL), 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.

Evidence for growth failure: Height standard deviation score less than -2. Evidence for diabetes mellitus: Fasting glucose equal or greater than 126 mg dL^{-1} and/or post 2 h (75g glucose in patients greater than 30 kg and 1.75 g kg^{-1} in patients less than 30 kg) greater than 200 mg dL^{-1} and/or exogenous insulin administration and/or use of oral hypoglycemic medications. Evidence for impaired fasting glucose: Fasting glucose equal or greater than 100 mg dL^{-1} and less than 126 mg dL^{-1}. Evidence for impaired glucose tolerance test: 2 h serum glucose post (75 g glucose in patients greater than 30 kg and 1.75 g kg^{-1} in patients less than 30 kg) equal or greater than 140 mg dL^{-1} and less than 200 mg dL^{-1}. Evidence for primary overt hypothyroidism: free thyroxin less than normal and thyroid stimulating hormone greater than normal. Evidence for subclinical hypothyroidism: Free thyroxin normal and thyroid stimulating hormone greater than normal but less than 10 mu L^{-1}. Evidence of hypocalcaemia: serum calcium less than 8.5 mg dL^{-1} 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) with thalassemia major, aged 10-27 years (mean age: 15.62±4.44 years) were collected from a pediatric hematology clinic in Tabriz (Table 1).

Five patients (8.9%) had diabetes mellitus and all of them diagnosed after age of 14. The mean 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 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 of them diagnosed with oral glucose tolerance test and fasting blood glucose were normal in these patients. Family histories of diabetes mellitus were negative in diabetic patients and anti glutamic acid decarboxylase were negative in all of them. Sixteen patients (28.6%) had impaired fasting glucose with mean age 16.2±3.3 years. Four patients (7.1%) had impaired glucose tolerance test with mean age 18.5±3.4 years. In the statistical analysis, several risk factors were detected. Age and duration of blood transfusion were risk factors of diabetes mellitus with p-value of 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 any risk was detected for impaired glucose tolerance test (Table 2).

Table 1: Demographic and biochemical characteristic of 56 patients with talassemia

Parameters	Min.	Max.	SD±Mean
Age (year)	10	27	15.62±4.44
SDS Height	-1	-5.4	2.35±0.94
LH mIu mL^{-1}	0.3	11	3.54±3.05
FSH mIu mL^{-1}	1	9.9	3.74±2.73
Testosterone ng mL^{-1}	0.1	6.9	1.65±2.16
Esteradiol pg mL^{-1}	2	60	12.88±19.57
TSH mu L^{-1}	0.9	100	8.94±19.58
FT4 ng dL	0.1	1.5	0.96±0.33
Ca mg dL	6	10	8.94±1.11
p mg dL	4	7.2	5.21±0.8
Alk. Ph. U L^{-1}	50	620	341±179
Iron µg dL^{-1}	89	600	199±72
TIBC µg dL^{-1}	136	530	231±61
Ferritin µg mL^{-1}	863	66.9	2888±948

Table 2: Comparison between beta-thalassemia patients with normal and abnormal glucose tolerance

Parameters	Normal 31 persons	IGT 4 persons	IFG 16 persons	DM 5 persons
(Year) Age	14.4±4.4	18.5±3.4	16.2±3.3	19.8*±4.3
Blood transfusion U/Month	1.8±0.54	2.3±1.06	2.4*±0.76	1.7±0.81
Desferal gr/Monthl	53±25	54±12	63±13	65±42
Iron µg dL^{-1}	198±83	201±11.08	210±56	175±20.9
TIBC µg dL^{-1}	235±68	226±12.84	230±50	210±55.5
Ferritin µg mL^{-1}	2780±989	3526±1186	2985±882	2927±943
FBS mg dL^{-1}	85±7	109±13.12	109±7.4	94±18
mg dL OGTT	106±12	159±19.6	130±42.5	266±16
Duration of blood transfusion (year)	12.2±4.6	15.8±5.02	13.4±3.43	17*±4.2
Duration of Desfera (year)	10.2±3.9	11.1±2.17	12.1±3.2	14.7±2.5

P-value <0.05* Comparison with normal group Mean±SD

Table 3: Biochemical characteristic of boys and girls with hypogonadism

Parameters	Age (Year)	FSH mIu mL^{-1}	LH mIu mL^{-1}	Testosterone ng mL^{-1} Esteradiol pg mL^{-1}
Boys	19.58±3.33	2.63±2.06	2.77±2.68	0.74±0.34
Girls	17.75±4.33	3.87±2.94	3.75±3.3	5.07±2.1

Mean±SD

Table 4: Biochemical characteristic of patients with hypothyroidism

Parameters	(Year) Age	FT4 ng dL^{-1}	TSH mu L^{-1}
Subclinical Hypothyroidism	17.33±4.22	0.85±0.12	6.41±1.35
Overt hypothyroidism	13.11±2.42	0.33±0.14	42.2±30.85

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. Lake of puberty changes was the most common endocrine complication in this study. Eleven female were greater than 13 years and only 3 of them (27%) with mean age of (18.71±3.9) had regular menses. Twenty male were greater than 14 years and 6 of them (30%) with mean age of (19.27±2.41) 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 (Table 3). No any cases of primary hypogonadism were detected.

Primary hypothyroidism was present in 16% of patients with mean age (17.33±4.22). Subclinical hypothyroidism (normal free thyroxin and high thyroid stimulating hormone) was observed in 10.7% of patients (Table 4). No any 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.

DISCUSSION

Before the institution of regular blood transfusion, patients with ß-thalassemia major died during the first few years of life from congestive heart failure or other complications resulting from chronic anemia (Raiola *et al*., 2003). Transfusion and iron-chelation therapy have prolonged and improved the quality of life in patients with this disease. The improvement was mainly due to the decrease in mortality from heart failure. Such a treatment, however, leads to chronic iron overload and frequently to endocrine complications (Borgna-Pignatti *et al*., 2004). Primary and secondary characteristics of sexual development are usually delayed for both boys and girls (Chern *et al*., 2003). Menarche is frequently delayed, breast development is often poor and patients are frequently oligomenorrheic or amenorrheic, even if menarche occurs. Boys frequently develop no or sparse facial and body hair and tend to have decreased libido, even if sperm production does occur. While there is increasing evidence that hypogonadism may be primarily due to iron overload (Chern *et al*., 2003; Fung *et al*., 2006). Impaired puberty, which occurred in approximately 71% of our patients, was the most common endocrine abnormality. Hypogonadism was presents in 72.72 of girls and 70% of boys without significant differences. In this study no any secondary hypogonadism were seen. Impaired puberty seems to be more prevalent in our study compared to study of Italian working group (Anonymous, 1995). In a longitudinal study, prevalence of hypogonadism has been reported to be as much as 75 in girls and 62% in boys (Filosa *et al*., 2006). 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 (De Sanctis *et al*., 2004). In another study, De Sanctis *et al*. (2006) and co-workers evaluated 3817 beta thalassaemia major patients. Thirty-six percent of patients were over the age of 16 years. They found lack of pubertal changes (40.5%) in their study. Moayeri and Oloomi (2006) researches were found hypogonadism

(69%) in 158 patients, aged 10-20 years (82 females and 76 males) with thalassemia major. They found a low serum level of gonadotropins (FSH and LH) in over 14-year-old patients with impaired puberty, which indicated that hypogonadotropic hypogonadism is responsible for this complication. Borgna-Pignatti *et al.* (2004) evaluated 720 thalassemia major and reported 54.7% hypogonadism in their study. Shamshirsaz *et al.* (2003) 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. In Italian working group on 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 (Anonymous, 1995). Soliman *et al.* (1999) reported in thalassaemic patients between the ages of 13 and 21 years a complete lack of pubescent changes was present in 73 of boys and 42% of girls. Seventy-four percent of the thalassaemic girls had primary amenorrhea. Chern *et al.* (2003) examined 29 patients with thalassemia major aged 15 years or older and reported prevalence of hypogonadotropic hypogonadism was 72%. 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 chelation therapy is instituted early in life (Theodoridis *et al.*, 1998). Normal stature is thus rarely attained, even in well-managed patients. Mostafavi *et al.* (2005) examined 44 patients, 8.5-25 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 *et al.* (1999) reported in thalassaemic patients between the ages of 13 and 21 years, 49% of thalassaemic patients had height standard deviation score less than -2 and 83% of thalassaemic patients had height standard deviation score less than -1. Moayeri and Oloomi (2006) reported high prevalence of short stature (62%). Results of growth hormone provocative tests and serum insulin-like growth factor-1 levels in short stature patients showed a reduced growth hormone response in 38 and low insulin-like growth factor-1 levels in 42% of thalassemic patients (Theodoridis *et al.*, 1998). Although, 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 GH insufficiency or primary hypothyroidism (Low and Growth, 1997). Abnormal body proportions with truncal shortening are commonly seen and could be due to the disease itself, iron toxicity, delay in puberty or toxic effects of desferrioxamine (Low and Growth, 1997). The absence of a pubertal growth spurt during spontaneous or induced puberty is detrimental to the achievement of a normal final adult height. Low serum insulin-like growth factor-1 and normal growth hormone reserve in short thalassaemic children imply that a state of relative growth hormone resistance exists (Theodoridis *et al.*, 1998). The rise in insulin-like growth factor-1 and improvement in growth with growth hormone therapy suggest that this growth hormone resistance is only partial (Theodoridis *et al.*, 1998). Although, the results of short-term growth hormone therapy are encouraging, the impact of treatment on final height of non-growth hormone deficient short thalassaemic children remains uncertain. For example De Sanctis *et al.* (2006) reported short stature was present in 31.1 of males and 30.5% of females and the prevalence of growth hormone deficiency was 7.9 in males and 8.8% in females.

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 (EL-Hazmi *et al.*, 1994). Interestingly, the early lesion appears to be related more to insulin resistance than to defective insulin production. The latter is a complication that occurs only during the late stages of development of hemosiderosis. More effective iron chelation appears to improve glucose intolerance (Farmaki *et al.*, 2006). Prevalence of diabetes has been reported to range from 2.3-24% and risk factors for diabetes in patients with ß-thalassemia major have been suggested to include age, increased amount of blood transfusion, serum ferritin level, compliance with iron-chelation therapy, family history of diabetes and pubertal status (Khalifa *et al.*, 2004). Before our study, the prevalence and risk factors for abnormal glucose tolerance in patients with blood-transfused ß-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% (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) in an oral glucose tolerance test. Fasting blood glucose was normal in all of them and diabetes mellitus was diagnosed only in oral glucose tolerance test. This finding is important because fasting blood glucose is not enough test for diagnosis and screening of patents with thalassemia major. In a study of 142 chronically transfused patients with beta thalassemia

12 years of age and an average serum ferritin 2000 mg L^{-1}, diabetes mellitus were noted in 13% of them (Farmaki *et al*., 2006). Ethnic variations are frequently reported on prevalence and complications of diabetes mellitus in beta-thalassemia patients. Ramachandran *et al.* (2001) reported prevalence of 12.1 and 14% for diabetes mellitus and impaired glucose tolerance, respectively, in India . 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.* (2006) in Italy, whereas, lower prevalence was found in Saudi thalassemic patients (6% for diabetes mellitus) compared to other ethnic groups (EL-Hazmi *et al*., 1994). 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 the chronic iron overload (Karahanyan *et al*., 1994; Chern *et al*., 2001). Monge *et al.* (2001) 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 (Cario *et al*., 2003). It is still unclear whether diabetes in ß-thalassemia major is related to genetic factors (Khalifa *et al*., 2004). 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, amounts of blood transfusion and duration of blood transfusion. The mechanism of abnormal glucose homeostasis in patients with ß-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 (Karahanyan *et al*., 1994; Chern *et al*., 2001). Insulin resistance may come from iron deposition in both 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 (Cario *et al*., 2003).

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 the guidelines of the American Diabetes Association for the diagnosis of abnormal glucose tolerance in thalassemic patients.

Hypoparathyroidism is thought to be a rarer complication, usually, but not always, accompanied by hypocalcemia (De Sanctis *et al*., 1992). 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 (De Sanctis *et al*., 1992). In our study prevalence of hypocalcaemia was 41 and 60% of patients with hypocalcaemia had hyperphosphatemia at same time. Mostafavi *et al.* (2005) reported hypocalcaemia in 22.7% of thalassemic patients and hyperphosphatemia in 70% of them were noted. Garofalo *et al.* (1998) reported hypocalcaemia was present in 16.6% of thalassemic patients Garofalo. Gulati *et al.* (2000) reported hypoparathyroidism was present in 33 patients (17 males and 16 females), with a prevalence of 13.5% in the study population. Although, parathormone was not measured in this study but regarded to other studies, hypocalcaemia is less likely to hypoparathyroidism. For this reason we can say there are several etiologies for hypocalcaemia such as nutritional cause. In our study 60% of patients with hypocalcaemia had hyperphosphatemia at same time. So, 76.7% of thalassemic patients had an increased alkaline phosphatase, which is due to vitamin D defitiency. 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 (Pantelakis, 1994). Some studies reported a high prevalence of primary hypothyroidism, reaching up to 17-18%, (Landau *et al*., 1993; Agarwal *et al*., 1992; Margo *et al*., 1990) while others reported low prevalence of 0-9% (Depaz *et al*., 1985; Phenekos *et al*., 1984; Senanayake *et al*., 1999). It is important to note that even in the 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 patients' ages (in some study patients age were from 2 years) and difference treatment protocols, including differing transfusion rates and chelation therapies. In the past, chelation therapies was not performed correctly and hypothyroidism was more common than today's. In study by Garofalo *et al.* (1998) at 1992 prevalence of primary hypothyroidism was reported 19.4%. Subclinical hypoparathyroidism in our study observed in 10.7%.

Eight patients in our study (14.5%) had not any endocrine complication and all of them were under 14 years. Although, there were not any endocrine abnormality in this group, but we must tested regularly for screening of endocrine diseases. We couldn't found any correlation between desferal and endocrine abnormality, but in Italian working group Anonymous (1995) and Karimifar *et al.* (2003) studies, these correlations were significant. We hadn't information about desferal in past several years and some patients discontinued for several mounts in the past. High prevalence of endocrine abnormalities was reported by several authors. They demonstrated that these abnormalities were related to iron overload. The histological studies of different endocrine glands supported this hypothesis (John, 1999). These findings yield the importance of iron overload in development of endocrine disorders. No any correlation was found between ferritin and endocrine abnormalities in our study but in study by Chern *et al.* (2001) serum ferritin was a risk factor for glucose intolerance. In contrast, there are some other reports which have suggested no relation between the level of ferritin and other endocrinopathies. Deferoxamine has been used as a chelating agent in an attempt to prevent the complications of tissue damage by iron deposition. Early introduction of the chelating agent to combat iron overload in vulnerable organs leads to improve life expectancy. Compliance to chelation therapy was poor in 48% of patients. Since, iron overload seem to be the most important factors responsible for endocrine complications, adequate compliance to chelation therapy is imperative.

CONCLUSION

Our study has demonstrated several points. Endocrine evaluation in thalassaemic patients must be carried out regularly, especially in those patients over the age of 10 years with iron overload and poor compliance with chelation therapy. Hence, it is to be hoped endocrine complications will be less common in the future, for patients who have started chelation therapy during the first year 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 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 beta-thalassaemia major for early detection and management of associated complications.

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