Prevalence of endocrine complications in β-thalassaemia major in the Islamic Republic of Iran

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معدل انتشار المضاعفات الصمَّاويَّة في الثلاسيميا – بيتا الكبرى في جمهورية إيران الإسلامية

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الخلاصة: للتعرُّف على معدل انتشار خلل وظائف الغدد الصماء لدى الإيرانيِّين المصابين بالثلاسيميا، أجرينا تقييماً للوظائف الدرقية والدُّريقية والبنكرياسية والكظرية لدى 150 من هؤلاء المرضى الذين تتراوح أعمارهم بين 10–22 عاماً، في وحدة طب الأطفال في جامعة شيراز للعلوم الطبية. وقد لوحظ قصور الدرقية البدئي في 6٪ من المرضى الذين تبلغ أعمارهم (14.6 + 1.9) عاماً وقصور الكظر في مريض واحد. إن المعدل المرتفع للخلل في وظائف الغدد الدرقية الذي لوحظ في دراستنا قد يعود إلى سوء مكافحة وتدبير المرض في باكورة الحياة، حيث ينتج تخرُّب النسج الذي لا يمكن شفاؤه بسبب الحِمْل الزائد من الحديد. وتؤكِّد نتائجنا على أهمية المتابعة النظامية للمرضى المصابين بالثلاسيميا – بيتا الكبرى لضمان الكشف الباكر والتدبير العلاجي للمضاعفات المرافقة.

ABSTRACT To identify the prevalence of endocrine dysfunction in Iranians with β-thalassaemia, we assessed thyroid, parathyroid, pancreatic and adrenal function in 150 β-thalassaemic patients aged 10–22 years at the Paediatrics Unit, Shiraz University of Medical Sciences. Primary hypothyroidism was found in 6.0% of patients (mean age: 14.6 ± 1.9 years), hypoparathyroidism in 7.3% (14.5 ± 3.2 years), type 1 diabetes mellitus in 7.3% (13.9 ± 2.8 years) and adrenal insufficiency in 1 patient. 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 β-thalassaemia major for early detection and management of associated complications.

Prévalence des complications endocriniennes dans la β-thalassémie majeure en République islamique d'Iran

RESUME Afin de déterminer la prévalence des dysfonctionnements endocriniens chez les Iraniens atteints de β-thalassémie, nous avons évalué la fonction thyroïdienne, parathyroïdienne, pancréatique et surrénale chez 150 patients atteints de β-thalassémie, âgés de 10 à 22 ans, au Service pédiatrique de l'Université des Sciences médicales de Chiraz. On a trouvé une hyperthyroïdie primaire chez 6,0 % des patients (âge moyen : 14,6 ± 1,9 ans), une hypoparathyroïdie chez 7,3 % (14,5 ± 3,2 ans), un diabète sucré de type 1 chez 7,3 % (13,9 ± 2,8 ans) et une insuffisance surrénale chez 1 patient. La fréquence relativement élevée du dysfonctionnement endocrinien notée dans notre étude peut résulter d'un mauvais contrôle et d'une mauvaise prise en charge de la maladie dans les premiers mois de la vie lorsque des lésions tissulaires irréversibles se produisent du fait d'une surcharge en fer. Ces résultats soulignent l'importance d'un suivi régulier des patients atteints de β-thalassémie majeure pour le dépistage précoce et la prise en charge des complications qui y sont associées.

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Introduction

Endocrine disorders are well-described in patients with β-thalassaemia major [*1–3*]. They are among the most common consequences of the disease worldwide, affecting patients' quality of life and causing considerable morbidity and mortality. Although data from developing countries are scant, investigations elsewhere have documented evidence of hypothalamic–pituitary dysfunction [*4,5*], hypothyroidism [*6*], hypoparathyroidism [*7*], adrenal insufficiency [*8*] and pancreatic dysfunction [*9*].

Endocrine problems in β-thalassaemia could result from a variety of factors, with most studies suggesting that chronic iron overloading secondary to hypertransfusion therapy is the major cause of the observed abnormalities [*2,10*]. Iron overload as a consequence of blood transfusion is the primary therapeutic complication in thalassaemia major [*1,6*]. The use of iron-chelating drugs has been shown to delay the development of iron-induced damage of cardiac and liver tissues, resulting in improved survival [*1,11*]. The ability of desferrioxamine to prevent damage to endocrine functions is less clear [*1*].

As little information is available about the endocrine complications of thalassaemia in the Islamic Republic of Iran, this study aimed to evaluate the prevalence of endocrine system disorders in patients with β-thalassaemia major.

Methods

We studied 150 patients aged 10–22 years with β-thalassaemia major attending the Paediatrics Unit, Shiraz University of Medical Sciences. A medical history was taken and complete physical examination carried out for each case. Age, sex, weight and height were recorded.

Serum ferritin concentrations were determined by the ELISA method (Ferritin EIA kit, Padtan, Iran). Blood samples were taken from patients at least 2 weeks after the last blood transfusion. Thyroxin (T_4), cortisol and parathyroid hormone (PTH) levels were measured by radioimmunoassay (RIA) (RIA kit, Kavoshyar Iran, Teheran; hPTH kit, Biosource Europe, Belgium; cortisol kit, Orion Diagnostica, Finland). Thyroid-stimulating hormone (TSH) was measured by immunoradiometric assay (IRMA) (IRMA kit, Kavoshyar Iran, Teheran) with standard commercial reagents used in the endocrine laboratory of Nemazee Hospital. Serum cortisol was measured at 08.00 hours after overnight fasting and the adrenocorticotropic hormone (ACTH) stimulation test performed if serum cortisol was below 10 μg/dL [*13*]. Serum calcium and phosphorus levels were determined using the end-point colorimetry method. Blood sugar, liver function tests, hepatitis B surface antigen and anti-hepatitis C virus antibody were measured twice per year (Paramax, California, USA). Fasting blood sugar levels were measured by the glucose-oxidase method.

The definitions of endocrine problems were as follows.

- Hypothyroidism: TSH level > 3.8 μU/mL (normal range: 0.3–3.8 μU/mL) and T_4 level < 4.5 μg/dL (normal range: 4.5–12.0 μg/dL).
- Hypoparathyroidism: serum calcium < 8.0 mg/dL, serum phosphorus > 6.5 mg/dL and serum PTH level < 13 pg/mL (normal range: 13–66 pg/mL), or if a normal PTH level was inappropriate for the low calcium level.
- Type 1 diabetes mellitus: fasting blood sugar > 126 mg/dL [*12*] on 2 separate occasions.

- Adrenal insufficiency: serum cortisol level < 10 μg/dL and clinical manifestations.

Statistical analysis was carried out by Fisher exact test and Student *t*-test.

Results

Of the 150 β-thalassaemia major patients enrolled in the study, 84 (56.0%) were males and 66 (44.0%) were females (age range 10–22 years; mean 14.4 ± 2.8 years). The mean height was 138.8 ± 10.7 cm in boys and 136.6 ± 10.4 cm in girls. Short stature (height below the third percentile for age) was recorded for 59.0% of the girls and 51.1% of the boys. The mean weight was 33.4 ± 7.5 kg. In 43.3% of patients, weight was below the third percentile for age.

Patients were receiving blood transfusions to maintain pre-transfusion haemoglobin concentrations > 9.5 g/dL. The mean age at the start of blood transfusion therapy was 1.9 ± 2.2 years (range 1–11 years).

Subcutaneous desferrioxamine therapy had been started in patients aged over 3 years who had a serum ferritin concentration > 1000 μg/L. At the time of this study, 90.0% of patients were receiving desferrioxamine by pump (40–50 mg/kg/day, 5 nights/week). The mean age at the start of desferrioxamine was 7.1 ± 4.0 years, with 63.3% of patients having received desferrioxamine at age over 6 years. The mean serum ferritin levels of the patients was 3365 + 2172 μg/L and 50.0% of patients had a serum ferritin level > 3000 μg/L.

A total of 4.0% of patients were positive for hepatitis B surface antigen and 21.3% for hepatitis C virus antibodies.

Table 1 shows the characteristics of the β-thalassaemia major patients with endocrine complications. Primary hypothyroidism, defined as raised TSH and lowered T_4 levels, was present in 9 (6.0%) of the patients (4 boys and 5 girls), all of whom had no clinical signs of hypothyroidism. The mean age at diagnosis of hypothyroid patients was 14.6 ± 1.9 years (range 12–16 years). There was no difference in the incidence of hypothyroidism between boys and girls. A TSH level > 15 μU/mL was present in 11.1% of patients. The mean serum ferritin level in patients with and without primary hypothyroidism was 2751 ± 2791 μg/L and 3300 ± 2120 μg/L respec-

Table 1 **Characteristics of 150 β-thalassaemia patients with endocrine complications**

Variable	Primary hypothyroidism	Hypo-parathyroidism	Type 1 diabetes
All cases [No.(%)]	9 (6.0)	11 (7.3)	11 (7.3)
Males (No.)	4	4	6
Females (No.)	5	7	5
Mean ± *s* age at diagnosis (years)	14.6 ± 1.9	14.5 ± 3.2	13.9 ± 2.8
Mean ± *s* age at start of desferrioxamine therapy (years)	9.8 ± 2.8	7.8 ± 4.2	6.8 ± 4.9
Mean ± *s* serum ferritin level (μg/L)	2751 ± 2791	2424 ± 2236	3800 ± 2088

s = standard deviation.

tively (P = 0.56). The mean age at which the subjects first received desferrioxamine was 9.8 ± 2.8 years.

Hypoparathyroidism was present in 11 (7.3%) of the patients (4 boys and 7 girls), with a mean age at diagnosis of 14.5 ± 3.2 years (age range 11–21 years). The mean serum ferritin level in hypoparathyroid patients was 2424 ± 2236 µg/L and in patients without hypoparathyroidism was 2570 ± 2350 µg/L (P = 0.60). They had received desferrioxamine from a mean age of 7.8 ± 4.2 years.

Adrenal insufficiency was found in only 1 patient (0.7%), a 17-year-old boy with a serum ferritin level of 6405 µg/L.

There were 11 patients (7.3%) with type 1 diabetes (6 boys and 5 girls). All were aged over 10 years; the mean age at diagnosis was 13.9 ± 2.8 years (range 11–18 years). There was no significant difference between males and females regarding the prevalence of type 1 diabetes. The mean age at the start of desferrioxamine chelation treatment was 6.8 ± 4.9 years. The mean serum ferritin levels were 3800 ± 2088 µg/L and 3320 ± 2182 µg/L in diabetic and non-diabetic patients, respectively (P = 0.49).

Discussion

Primary hypothyroidism was seen in 6.0%, hypoparathyroidism in 7.3%, type 1 diabetes in 7.3% and adrenal failure in 0.7% of β-thalassaemic patients, all of whom were aged over 10 years. There was no statistically significant relationship between the prevalence of endocrine dysfunction and serum ferritin levels. In a study by Sabato et al., the prevalence of primary hypothyroidism was 17.5% (patients aged 10 years or over), with no correlation found between hypothyroidism and serum ferritin levels [*6*]. Jensen et al. reported a 10% prevalence of hypothyroidism in thalassaemic patients aged 11–44 years and a positive association between serum ferritin level and the presence of thyroid dysfunction [*14*]. A study by De Sanctis et al. found a 4.5% prevalence of hypoparathyroidism in patients aged 11–24 years and no relationship between serum ferritin levels and hypoparathyroidism [*15*].

De Sanctis et al. reported the prevalence of type 1 diabetes to be approximately 6.5% in β-thalassaemia patients (all diagnosed at age over 10 years), with 92% of patients showing signs of liver disease [*16*]. The age range of our patients was similar to the above studies.

Gulati et al. reported hypocortisolism in 13% of patients (the youngest of whom was 5 years old), hypothyroidism in 2 adolescent patients and diabetes/impaired glucose tolerance in 3 patients, of whom 2 were post-pubertal [*8*].

Iron overload has for a long time been considered the major cause of the endocrine abnormalities of thalassaemia major [*7*], a finding supported by histological studies of different endocrine glands [*7,17*]. Our data, however, indicated no association between serum ferritin levels and endocrine dysfunction in β-thalassaemia patients. There are several reasons for this. Our study was cross-sectional, relying on the most recent measurement of serum ferritin level. We did not, therefore, obtain an accurate reflection of iron overload in previous years. Also, the serum ferritin level is not the only indicator of iron overload, and diseases such as hepatitis, liver disease and haemosiderosis may falsely increase the serum ferritin level. It is possible, therefore, that there are other factors responsible for organ damage, including: chronic anaemia [*7*]; increased collagen deposition secondary to increased activity of the iron-dependent protocollagen proline hydroxylase

enzyme, with subsequent disturbed microcirculation in the pancreas and parathyroid glands [*18*]; chronic liver disease secondary to iron overload; viral infections; and individual susceptibility to damage from iron overload [*15,19*]. According to our current study, 63.3% of patients received desferrioxamine from the age of 6 years, leading to a high prevalence of complications due to iron overload.

Our patients suffered from poor nutrition, irregular blood transfusion and irregular desferrioxamine therapy. Serum ferritin levels > 3000 µg/L were found in 50.0% of patients, and this may be due to irregular and under-treatment with desferrioxamine. The mean age of commencement of blood transfusion was around 2 years and the mean age of desferrioxamine therapy was around 7 years. Thus most patients had received blood transfusion for a mean duration of 5 years before the start of chelation therapy, which may have lead to increased frequency of endocrine complications. The weight of 43.3% of our patients was below the third percentile for age, and more than 50% were of short stature, indicating that a significant number of patients were undernourished.

We conclude that the high frequency of endocrine complications found in this study in the Islamic Republic of Iran supports the rationale for regular follow-up of β-thalassaemia patients to ensure early detection and timely treatment of associated complications.

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