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Effect of iron overload on endocrinopathies in patients with beta-thalassaemia major and intermedia

Wpływ przeładowania żelazem na występowanie endokrynopatii u chorych na beta-talasemię *major* i *intermedia*

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Abstract

Introduction: Iron overload is a major problem in patients with β-thalassemia major, and it has many structural and metabolic consequences. In this study, we aimed to consider the prevalence of endocrine abnormalities in patients with β-thalassemia major and thalassemia intermedia.

Materials and methods: We ordered following tests for consideration endocrine abnormalities: fasting plasma glucose, oral glucose tolerance, iron, total iron binding capacity, ferritin, thyroid-stimulating hormone (TSH), free thyroxin (fT4), free triiodothyronine (fT3), parathyroid hormone levels.

Results: According to our study including 70 patients with thalassemia major, 7 (10%) had diabetes, 5 (7.1%) had impaired glucose tolerance, 9 (12.8%) had hypothyroidism, 2 (2.8%) had hypoparathyroidism, 2 (2.8%) had hyperparathyroidism. Of 22 patients with thalassemia intermedia, 1 (4.5%) had diabetes.

Conclusions: These findings reinforce the importance of regular follow-up of patients with β-thalassemia major and thalassemia intermedia for early detection and management of associated complications. In this way, the prevalence of endocrine abnormalities can be decreased in future. **(Endokrynol Pol 2012; 63 (4): 260–263)**

Key words: *iron overload, endocrine abnormalities, thalassemia major, thalassemia intermedia*

Streszczenie

Wstęp: Przeładowanie żelazem jest częstym problemem u osób chorujących na beta-talasemię major, związanym z wieloma strukturalnymi i metabolicznymi następstwami. Niniejsze badanie przeprowadzono w celu oceny częstości zaburzeń metabolicznych u pacjentów z *β*-talasemią *major* i *intermedia*.

Materiały i metody: Przeprowadzono następujące badania pozwalające ocenić zaburzenia gospodarki hormonalnej: glikemia na czczo, doustny test tolerancji glukozy, stężenie żelaza, całkowita zdolność wiązania żelaza, stężenia ferrytyny, tyreotropiny (TSH), wolnej tyroksyny (fT4), wolnej trijodotyroniny (fT3) i parathormonu.

Wyniki: Spośród 70 chorych z talasemią *major* włączonych do niniejszego badania u 7 (10%) osób stwierdzono cukrzycę, u 5 (7,1%) nieprawidłową tolerancję glukozy, u 9 (12,8%) niedoczynność tarczycy, a u 2 (2,8%) nadczynność tarczycy. W grupie 22 chorych z talasemią *intermedia* 1 (4,5%) osoba chorowała na cukrzycę.

Wnioski: Uzyskane wyniki potwierdzają znaczenie regularnych badań u chorych na beta-talasemię *major* i *intermedia*, co umożliwia wczesne wykrycie i rozpoczęcie leczenia związanych z tą chorobą powikłań. Takie postępowanie może się przyczynić do zmniejszenia częstości zaburzeń hormonalnych w przyszłości. **(Endokrynol Pol 2012; 63 (4): 260–263)**

Słowa kluczowe: *przeładowanie żelazem, zaburzenia hormonalne, talasemia* major, *talasemia* intermedia

Introduction

Trace elements are necessary for the regular functioning of the human body [1]. A deficiency of a trace element results in problems with bodily functions [2, 3]. Similarly, an excess of a trace element leads to important problems. Beta-thalassaemia is a disease in which iron overload and iron deposition in tissues is a common and devastating problem if proper precautions are not taken. Beta-thalassaemia represents a group of recessively inherited haemoglobin disorders characterised by reduced synthesis of β-globulin chain. About 3% of the world's population carries β-thalassaemia genes. The homozygous state results in severe anaemia, which needs regular blood transfusion. Treatment with transfusion and chelating therapy has considerably prolonged survival in thalassaemic patients [4]. Treatment consists of multiple blood transfusions, a complication of which is iron overload. At the same time, there has

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been an increase in the frequency of complications of this therapy caused by iron overload [5, 6].

Iron overload has for a long time been considered to be the major cause of endocrine abnormalities of β-thalassaemia, and this is supported by histological studies of different endocrine glands [7–9]. The precise mechanism whereby iron overload causes tissue damage is not completely understood, although there is evidence of free radical formation and lipid peroxidation resulting in mitochondrial lysosomal damage. In recent years, several authors have reported a high incidence of endocrine abnormalities in children, adolescents and young adults suffering from thalassaemia major [9–11].

In this study, we wanted to consider the prevalence of endocrine abnormalities in patients with β-thalassaemia major and thalassaemia intermedia.

Material and methods

In th s study, we evaluated endocrine complications of the disease in all β-thalassaemia major and intermedia patients aged 11 and above (92 patients) who were followed up and treated at the Thalassaemia Centre of the Education and Research Hospital, Antalya, Turkey. All patients had been maintained on a regular transfusion programme (every 15–30 days) with the aim of maintaining pre-transfusion haemoglobin levels above 9 g/dL. We ordered the following tests for the consideration of endocrine abnormalities: fasting plasma glucose, oral glucose tolerance, iron, total iron binding capacity, ferritin, thyroid-stimulating hormone (TSH), free thyroxin (fT4), free triiodothyronine (fT3), and parathyroid hormone levels. Blood glucose, iron, and total iron binding capacity (TIBC) were measured by photometry assay (Aeroset Abbott Diagnostics). Ferritin, TSH, fT4, fT3 and PTH levels were determined by immunoassay (Beckmann Unicel DxI 800). Evidence for diabetes mellitus was based on American Diabetes Association and World Health Organisation criteria. The presence of a low fT4 level and a high TSH level was accepted as evidence for the existence of primary overt hypothyroidism.

SPSS 10.0.1 software was used for statistical analysis. All data are presented as mean ± standard deviation (SD). The t test was used, setting $p < 0.05$ for significance.

Results

Of 92 patients with β-thalassaemia, 22 (23.9%) had thalassaemia intermedia and 70 (77.1%) had thalassaemia major. Of patients with thalassaemia intermedia, 13 (59.1%) were male and nine (40.9%) were female. Of patients with thalassaemia major, 45 (64.2%) were male and 25 (35.8%) were female. In all, 58 (63.1%) were male and 34 (36.9%) were female.

In patients with thalassaemia intermedia, the mean ± SD age was 37.54 ± 11.8 years, the mean ± SD glucose level was 87.22 ± 14.25 mg/dL, the mean ± SD iron level was 195 ± 29 µg/dL, the mean ± SD TIBC level was 235 ± 38 µg/dL, the mean ± SD ferritin level was 957 ± 218 ng/mL, the mean ± SD TSH level was 1.83 ± 0.83 UI/mL, the mean ± SD fT3 level was 2.78 ± 0.28 pg/mL, the mean ± SD fT4 level was 0.73 ± 0.09 pg/mL, and the mean ± SD PTH level was 47.48 ± 21.07 pg/mL (Table I).

In patients with thalassaemia major, the mean ± SD age was 18.66 ± 6.48 years, the mean ± SD glucose level was 112.47 ± 71.93 mg/dL, the mean ± SD iron level was 235 ± 45 µg/dL, the mean ± SD TIBC level was 240 ± 37 µg/dL, the mean ± SD ferritin level was 2,350 ± 450 ng/mL, the mean ± SD TSH level

Table I. *Demographic and biochemical characteristics of 22 patients with thalassaemia intermedia*
Tabela I. *Demograficzna i biochemiczna charakterystyka 22 chorych na talasemię* **intermedia**

Parameters	Minimum	Maximum	Mean ± SD	Reference range
Age (years)	11	55	37.54 ± 11.8	–
Glucose [mg/dL]	69	133	87.22 ± 14.25	70–110
TSH [UI/mL]	0.54	3.4	1.83 ± 0.83	0.34–5.6
fT4 [pg/mL]	0.56	0.88	0.73 ± 0.09	0.54–1.12
fT3 [pg/mL]	2.14	3.45	2.78 ± 0.28	2.5–3.9
PTH [pg/mL]	17.8	81.7	47.48 ± 21.07	15–88
Ferritin [ng/mL]	285	1,750	957 ± 218	11–306
Iron [µg/dL]	104	295	195 ± 29	25–156
TIBC [µg/dL]	117	387	235 ± 38	250–450

TSH — thyroid-stimulating hormone; fT4 — free thyroxin; fT3 — free triiodothyronine; PTH — parathyroid hormone; TIBC — total iron binding capacity

Table II. *Demographic and biochemical characteristics of 70 patients with thalassaemia major*
Tabela II. *Demograficzna i biochemiczna charakterystyka 70 chorych na talasemię* **major**

Parameters	Minimum	Maximum	Mean ± SD	Reference range
Age (years)	10	34	18.66 ± 6.48	–
Glucose [mg/dL]	66	510	112.47 ± 71.93	70–110
TSH [UI/mL]	0.04	100	4.73 ± 13.45	0.34–5.6
fT4 [pg/mL]	0.56	0.88	0.67 ± 0.14	0.54–1.12
fT3 [pg/mL]	1.47	3.66	2.86 ± 0.38	2.5–3.9
PTH [pg/mL]	2	95.4	40.8 ± 19.32	15–88
Ferritin [ng/mL]	930	4,500	2,350 ± 450	11–306
Iron [μg/dL]	95	590	235 ± 45	25–156
TIBC [μg/dL]	114	478	240 ± 37	250–450

TSH — thyroid-stimulating hormone; fT4 — free thyroxin; fT3 — free triiodothyronine; PTH — parathyroid hormone; TIBC — total iron binding capacity

was 4.73 ± 13.45 UI/mL, the mean ± SD fT3 level was 2.86 ± 0.38 pg/mL, the mean ± SD fT4 level was 0.67 ± 0.14 pg/mL, and the mean ± SD PTH level was 40.8 ± 19.32 pg/mL (Table II).

The age of patients with thalassaemia major was significantly low ($p < 0.05$). The serum ferritin level of patients with thalassaemia major was significantly high ($p < 0.05$). The serum PTH level was significantly higher in patients with thalassaemia intermedia ($p < 0.05$). There were no significant differences regarding serum glucose, iron, TIBC, TSH, fT3, or fT4 levels between patients with thalassaemia major and intermedia ($p > 0.05$).

According to the data, of 70 patients with thalassaemia major, seven (10%) had diabetes, nine (12.8%) had hypothyroidism, five (7.1%) had impaired glucose tolerance, two (2.8%) had hypoparathyroidism, and two (2.8%) had hyperparathyroidism. Of 22 patients with thalassaemia intermedia, one (4.5%) had diabetes.

Serum iron, iron binding capacity, and ferritin levels of patients with diabetes and hypothyroidism were not significantly different from those patients who had no diabetes and hypothyroidism ($p > 0.05$).

Discussion

Endocrine and metabolic abnormalities are quite common in patients with β-thalassaemia. Abnormal glucose tolerance is an important endocrine abnormality in these patients. Glucose intolerance usually develops in adolescence, even though baseline blood glucose levels are frequently normal. Diabetes mellitus later in life is also a frequent complication, mainly due to iron overload, chronic liver disease and genetic predisposition.

The prevalence of diabetes has been reported as ranging from 2.3% to 24.1% in b-thalassaemia [12, 13]. We found that the prevalence of impaired glucose tolerance was 7.1% and diabetes was 10% in patients with β-thalassaemia major. The prevalance of diabetes was 4.5% in patients withβ-thalassaemia intermedia. Ethnic variations are frequently reported in the prevalance and complications of diabetes mellitus in these patients. Ong et al. reported a prevalance of 8% diabetes mellitus in Malay and Chinese patients [14]. Najafipour et al. found that prevalance of impaired glucose tolerance was 7.1% and diabetes was 8.9% in Iran [9]. Jaruratanasirikul et al. reported prevalence of impaired glucose metabolism of 12.5% in patients in Thailand [15].

Although the early literature suggested that the high prevalence of diabetes mellitus in patients with thalassaemia was due to direct impairment of insulin excretory function by chronic iron overload [16], Monge et al. demonstrated evidence of immune system activation against pancreatic β-cells in β-thalassaemia patients [17]. They proposed that pancreatic iron deposition may contribute to selective β-cell damage [18].

Iron overload causes deposition of iron in the thyroid gland, with consequent fibrosis of the glandular parenchyma, and progressive thyroid dysfunction going through different degrees of severity up to overt hypothyroidism [6]. Thyroid dysfunction is known to occur frequently in thalassaemia major, but its prevelance and severity varies in different cohorts, and long-term natural history is poorly understood. In our study, we found that 12.8% had hypothyroidism. Zervas et al. reported that 4% had hypothyroidism, and 12.5% had subclinical hypothyroidism [19]. Karamifar et al. showed that 6% of patients had hypothyroidism [20]. De Sanctis et al. reported that 21.6% were discharged with a diagnosis of hypothyroidism of different degrees of severity [21].

Gamberini et al. studied 273 patients with thalassaemia major followed from diagnosis in the Ferrara Centre and divided into three cohorts according to the

year of their birth. Over time, the prevalence of hypothyroidism, diabetes mellitus and hypoparathyroidism increased to 24.4%, 14.7%, and 6.7%, respectively, at the time of the study. Incidences peaked in the early 1980s, and declined in the following years (primary hypothyroidism from 6.5% in 1981 to 0.9% in 2007; DM from 3.9% in 1986 to 0.8% in 2007; hypoparathyroidism from 2.4% in 1984 to 0% in 2007 and correlated with the decrease in annual mean serum ferritin levels in all patients. The main risk factors associated with endocrine complications were high serum ferritin levels, poor compliance with desferioxamine (DFO) therapy, early onset of transfusion therapy (only for hypogonadism) and splenectomy (only for hypothyroidism). Serum ferritin levels of approximately 2,000 ng/mL were found to correlate with hypogonadism, and 3,000 ng/mL for hypothyroidism, hypoparathyroidism and DM. They showed that in the last 30 years in the Ferrara Centre the incidences of hypothyroidism, diabetes mellitus, and hypoparathyroidism declined, and pubertal development in males with thalassaemia major improved in patients on DFO treatment born after 1976. The efficacy of alternative chelation regimens with deferiprone or deferasirox to monotherapy with desferioxamine remains to be established [22].

These findings reinforce the importance of the regular follow-up of patients with β-thalassaemia major and thalassaemia intermedia for early detection and management of associated complications. In this way, the future prevalence of endocrine abnormalities can be lessened.

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