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Endocrinopathies in Turkish Children with Thalassemia Major

Talasemi Majör Tanılı Çocuklarda Endokrin Problemler

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ABSTRACT

Aim: Endocrinopathies are common in patients with thalassemia major (TM) and affect their life quality. Our aim was to identify the frequency of growth retardation and endocrine complications in these patients.

Materials and Methods: Sixty-two patients aged 3-18 years with TM were evaluated retrospectively for height, weight, body mass index (BMI), and pubertal stage. Blood tests for endocrine function, and oral glucose tolerance test (OGTT) results were recorded.

Results: The mean age of 62 subjects (33 females/29 males) was 10.4±3.9 years. The frequency of ≤-2 standard deviation scores was 37.1% for height, 33.9% for weight and 11.3% for BMI. Short stature, being underweight, and low BMI were significantly more prevalent in children over 7 years old (p<0.001). Delayed puberty/hypogonadism was present in 37% of 19 adolescents. Thirteen percent of the subjects had vitamin D deficiency (<10 ng/mL), hyperparathyroidism was observed in 29% of the subjects, while subclinical hypothyroidism (thyroid-stimulating hormone 5-10 IU/mL) was determined in 3 (5.5%) of the 55 subjects. In OGTT, impaired fasting glucose was seen in 7 subjects (14.5%), impaired glucose tolerance in 3 (6.3%), diabetes mellitus in 1 (2.1%), and hypoglycemia at 120-min was observed in 5 subjects (10.4%). Overall, 67.7% of the 62 subjects had height standard deviation score ≤-2 and/or at least one endocrinopathy.

Conclusion: Growth retardation and endocrine problems are still a serious problem in TM patients, and develop particularly in those older than 7 years. Additionally, attention must be paid to hypoglycemia in these patients as well as diabetes.

Keywords: Thalassemia major, growth retardation, endocrinopathies, hypoglycemia

ÖZ

Amaç: Talasemi majörlü (TM) çocuklarda endokrinopatiler halen yaygın bir sorun olup hayat kalitesini önemli bir ölçüde etkilemektedir. Bu çalışmada TM'li çocuklarda büyüme geriliği ve endokrin komplikasyon sıklığının belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Yaşları 3-18 arasında olan 62 TM hastası boy, kilo, vücut kitle indeksi (VKİ) ve puberte açısından retrospektif olarak değerlendirildi. Hastaların yapılan endokrin testleri ve oral glukoz tolerans testi (OGTT) sonuçları kaydedildi.

Bulgular: Altmış iki (33 kız/29 erkek) hastanın ortalama yaşı 10,4±3,9 yıl idi. Hastaların %37,1'inin boyu, %33,9'unun kilosu ve %11,3'ünün VKİ'si ≤-2 standart sapma puanı idi. Kısa boy, düşük kilo ve düşük VKİ anlamlı olarak 7 yaş sonrasında görülmekteydi (p<0,001). Gecikmiş puberte/hipogonadizm ise 19 adölesanın %37'sinde saptandı. Hastaların %13'ünde vitamin D eksikliği (<10 ng/mL), %29'unda ise hiperparatiroidi görüldü. Subklinik hipotiroidi (tiroid stimüle edici hormon 5-10 IU/mL) ise 55 hastanın 3'ünde (%5,5) mevcuttu. OGTT sonuçlarına göre, bozulmuş açlık glukozu 7 (%14,5), bozulmuş glukoz toleransı 3 (%6,3), diabetes mellitus 1 (%2,1) ve 2. saatte hipoglisemi 5 (%10,4) hastada saptandı. Toplamda 62 hastanın %67,7'sinde boy kısalığı ve/veya en az bir endokrinopati mevcuttu.

Sonuç: Büyüme geriliği ve endokrin problemler halen ciddi bir sorun olup özellikle 7 yaş sonrasında ortaya çıkmaktadır. Ayrıca TM'li hastalarda diyabet kadar hipoglisemi açısından da dikkatli olunmalıdır.

Anahtar Kelimeler: Talasemi majör, büyüme geriliği, endokrinopati, hipoglisemi

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Introduction

Thalassemia is the most common genetic blood disease, and patients with thalassemia major (TM) require regular blood transfusions. Iron chelation therapy is also essential for these patients in order to prevent morbidity and mortality. Although the main cause of death in TM is cardiac failure, endocrine complications are the most important problems affecting the quality of life in these patients.

Chelation therapy in order to reduce iron overload is provided with deferasirox, desferrioxamine or deferiprone (1). Few studies have compared each chelator with their combinations in terms of reducing iron overload and endocrine complications (2). So, there are no recommendations concerning the superiority of one over the other in the prevention of endocrine complications.

Although patients with TM take regular chelation therapy, the prevalence of endocrine problems is reported as high as 60% in some studies (3). Limited data are available concerning oral chelation therapy in preventing or improving endocrine disorders (4-6).

This study was planned to evaluate the growth and development status in children diagnosed with TM, and to investigate the prevalence of endocrine problems.

Materials and Methods

The 62 patients aged 3-18 years with TM that were followed-up at the Diyarbakır Child Health Hospital, Pediatric Hematology Unit, Diyarbakır, Turkey, between January and December 2015 were evaluated retrospectively.

During hematological follow-up, patients received blood transfusions every 3-4 weeks to maintain a pre-transfusion hemoglobin level of >9 g/dL. Iron chelation therapy, (deferasirox 20-40 mg/kg/d, desferrioxamine 25-60 mg/kg/d or deferiprone 50-75 mg/kg/d) was administered when ferritin level was >1000 ng/mL.

The patients' height, weight, body mass index [BMI weight (kg)/height (m^2)], pubertal stage and chelation therapy status were recorded. Basal cortisol (8:30-10:00 a.m.), adrenocorticotropic hormone (ACTH), Ca, P, alkaline phosphatase, parathyroid hormone (PTH), 25 hydroxyvitamin (OH) D_3, thyroid-stimulating hormone (TSH), sT4, HbA1c levels, and oral glucose tolerance test (OGTT, 1.75 gr/kg glucose-max 75 gr, and 0-120/min glucose and insulin) results were also evaluated. OGTT results were classified according to the criteria (7) of the International Society for Pediatric and Adolescent Diabetes.

Bone mineral density (BMD) was measured using a dual energy X-ray absorptiometer (DEXA). The L2-4 Z-scores and BMD values of the patients who had undergone DEXA measurement were recorded, and age and sex-adjusted data were calculated.

The study was approved by the Gazi Yaşargil Training and Research Hospital Local Ethics Committee and the patients or their parents provided informed consent for the study.

Statistical Analysis

SPSS v.18 software was used for statistical analysis. Data were analyzed as mean ± standard deviation or percentages. Chi-square and t-tests were used to compare mean values.

Results

The mean age of the 62 subjects (33 females/29 males) included in the study was 10.4±3.9 years. All the subjects received blood transfusion and took chelation therapy consisting of deferasirox (92%), desferrioxamine (3.2%), deferiprone (3.2%), and deferasirox and desferrioxamine (1.6%). Forty-two patients (67.7%) had height standard deviation scores (SDS) ≤-2 and/or at least one endocrinopathy.

The mean height, weight and BMI, SDS were -1.63±1.26, -1.44±1.31 and -0.70±1.07 respectively. The frequency of ≤-2 SDS was 37% for height, 34% for weight, and 11% for BMI. Short stature, being underweight, and low BMI were significantly more prevalent in children older than 7 years of age (p<0.001) (Table I). Delayed puberty/hypogonadism was present in 7 (37%) of the 19 adolescents aged ≥13 years old, and all of these patients also had short stature (≤-2 SDS). The growth hormone (GH) stimulation test was performed on 6 of the 23 patients of short stature, and one patient (peak GH: 3.4 and 4.7 µg/L) was administered GH therapy. The mean ferritin level was 1963±2185 mg/dL, however 12 patients had levels >2000 mg/dL. Ferritin levels were not significantly correlated with short stature, being underweight or low BMI (p=0.35, p=0.40, and p=0.32, respectively).

The mean basal cortisol level was 10.6±4.5 µg/dL (n=50), while 10 (20%) patients had <7 µg/dL. Peak cortisol levels in the low dose ACTH test were higher than 18 µg/dL in 4 patients who had cortisol levels <5 µg/dL. Also, 25(OH) vitamin D_3 insufficiency (10-20 ng/mL) was determined in 21 (46%), and deficiency (<10 ng/L) in 6 (13%) patients. Hyperparathyroidism (PTH >65 ng/L) was observed in 16 (29%) patients, but accompanying low vitamin D_3 was detected in only 8 of them. BMD Z-scores were below -2 SDS in 12 (48%) of the 25 patients in whom DEXA was able to be measured. BMD Z-score was calculated according to

Table I. The mean age, height, weight, body mass index and ferritin levels of the subjects

	All subjects	<7 years	≥7 years	p*
n	62	15	47	
Age	10.37±3.93	4.75±1.28	12.16±2.52	
Height SDS	-1.63±1.26	-0.76±0.93	-1.91±1.23	<0.001
Weight SDS	-1.43±1.31	-0.21±0.96	-1.82±1.16	<0.001
BMI SDS	-0.70±1.07	0.31±0.82	-1.03±0.93	<0.001
Ferritin (mg/dL)	1963±2185	1362±703	2274±2609	0.10

*Subjects between <7 and ≥7 years old
BMI: Body mass index, SDS: Standard deviation scores

their sex and bone age, and 4 patients were evaluated as osteopenic (Z-score -1>-<-2), and 1 as osteoporotic (Z-score -2.19). Subclinical hypothyroidism (TSH 5-10 IU/mL) was determined in 3 (5.5%) of the 55 patients, and low sT4 was not observed in any (Table II).

Table II. The frequency of endocrinopathies in the subjects with thalassemia

	Number of the subjects	%
Growth retardation	23/62	37
Adrenal insufficiency	0/50	0
Hypothyroidism		
Overt	0/55	0
Subclinical	3/55	5.5
Vitamin D insufficiency	21/46	46
Vitamin D deficiency	6/46	13
Hyperparathyroidism	16/55	29
Osteoporosis	1/25	4
OGTT		
IFG	7/48	14.5
IGT	3/48	6.3
DM	1/48	2.1
Hypoglycemia	5/48	10.4

OGTT: Oral glucose tolerance test, IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, DM: Diabetes mellitus

When the OGTT results were analyzed, impaired fasting glucose was determined in 7 patients (14.5%), impaired glucose tolerance (IGT) in 3 (6.3%), diabetes mellitus in 1 (2.1%) patient. Hypoglycemia values were <60 mg/dL at 120-min in 5 patients (10.4%). The mean fasting glucose and insulin levels were 90±9.9 mg/dL and 4.8±2.8 mUI/mL respectively. The glucose and insulin levels at 120-min in OGTT were 100.3±33 mg/dL and 13±11.9 mIU/mL respectively. 4/5 subjects with hypoglycemia had higher than 2 mIU/mL insulin levels at 120-min in OGTT. The subjects' mean HbA1c values were 6.7±0.6%, and this value was even more elevated when individuals with abnormal OGTT were excluded.

Discussion

In this retrospective study, quite a high number (67.7%) of transfusion-dependent thalassemia subjects were of short stature and/or had endocrinopathy. These results are comparable to other studies. Also, growth retardation was seen especially in subjects over 7 years old.

Growth retardation in patients with TM may develop due to various causes. The factors affecting growth include chronic anemia and hypoxia, chronic malnutrition, micronutrient deficiencies such as zinc, hypersplenism, hepatic involvement, delayed puberty, and GH deficiency (8). Approximately 37-40% of the adolescents with thalassemia are of short stature, and this problem is around 64-70% in developing countries. In Turkey, the prevalence of short stature has been reported as 25-40% (3,9), and we had 37.1% in this study. Several studies have shown low insulin-like growth factor 1 (IGF1) levels in patients with thalassemia and short stature, but GH deficiency has been determined in only 20-50% of these patients (3,10). Low IGF1 levels without GH deficiency suggest a possible association with chronic anemia, malnutrition or GH neurosecretory dysfunction (11). The GH stimulation test could only be performed in 6 cases in our study, and GH deficiency was determined in 1 (16.6%) of these subjects.

Approximately 50-60% of TM patients had at least one endocrine dysfunction, and the prevalence increased with age (1,3,9). The frequency was 67.7% in the present study, and growth retardation was seen especially in the older than 7-year-old subjects. However, no relation was determined between these findings and ferritin levels. In several previous studies there was no statistically significant relationship between ferritin levels and endocrinopathies (3,12). From this we can derive that serum ferritin levels may also increase with infection, inflammation and hepatic function disorders, and are also an indirect measure of iron overload. Calculation of iron overload with hepatic and cardiac T2- magnetic resonance imaging reflects iron deposition (13) more accurately.

Delayed adolescence and hypogonadism are one of the most common endocrine problems in adolescents with TM. The prevalence ranges between 40% and 50% (3,14). They may be caused by chronic malnutrition and iron deposition-related pituitary dysfunction. Incomparable with previous findings, delayed adolescence/hypogonadism was determined as 37% in our study.

The prevalence of hypothyroidism in these patients was 6-16%, the majority of the cases being subclinical. Overt hypothyroidism is quite rare (3,14). Similar to the literature, the prevalence of hypothyroidism was 5.5%, and no overt hypothyroidism was observed in this study. Hypoparathyroidism can develop in up to 10% of the patients with TM (15). Although it was not observed in our patients, we detected a secondary hyperparathyroidism associated with vitamin D deficiency. Whereas the prevalence of vitamin D deficiency in Turkey is decreasing, it still presents a significant problem in patients with thalassemia. Isik et al. (9) reported vitamin D deficiency or insufficiency in 78% of their patients, the comparable level in our study being 59%. However, it was not the cause of osteoporosis or osteopenia in any patient.

Abnormalities in glucose metabolism in patients with thalassemia generally appear in the second decade. The cause is insulin resistance, followed by insulin deficiency

associated with iron overload in the pancreas. The prevalence of diabetes and IGT in these patients ranges between 8% and 11% (3,14). Our study showed a similar frequency to that observed in these studies (8.4%). In addition, thalassemic patients tend to have more hypoglycemia when compared to Type I and Type II diabetes. In a recent study, severe hypoglycemia was common (56%) in thalassemic patients with diabetes who were treated with insulin (16). In our study, hypoglycemia in OGTT unexpectedly came up in 10.4% of the patients who had no diabetes. This present study suggested that hypoglycemia is not only seen in thalassemic patients with diabetes, but also in normoglycemic thalassemic patients. Hemosiderosis impairing glucagon secretion, and low liver glycogen storage due to hepatic fibrosis are possible mechanisms (16). Insulin resistance and delayed insulin secretion due to hemosiderosis could be other possible mechanisms of hypoglycemia, as seen in patients with cystic fibrosis (17).

Study Limitations

The higher number of the patients could give the frequencies of rare endocrine problems in patients with thalassemia.

Conclusion

This study emphasizes that growth retardation and endocrine problems are still a serious problem in patients with thalassemia, and become apparent particularly after age 7. So, close endocrinological monitoring is required from the time of diagnosis. In addition, hypoglycemia should be taken into consideration alongside diabetes in these patients.

Ethics

Ethics Committee Approval: The study was approved by the Gazi Yaşargil Training and Research Hospital Local Ethics Committee.

Informed Consent: The patients or their parents provided informed consent for the study.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.H., G.T., F.T., Concept: B.H., G.T., Design: B.H., Data Collection or Processing: B.H., G.T., Analysis or Interpretation: B.H., Literature Search: B.H., Writing: B.H.

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