Research Article / Araştırma Makalesi

Endocrine Complications in Pediatric Beta-Thalassemia Major Patients: A Single-Center Experience

Pediatrik Beta Talasemi Major Hastalarında Endokrin Komplikasyonlar: Tek Merkez Deneyimi

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Abstract

Background: Our aim was to identify risk factors and clinical correlates of endocrine complications in β-thalassemia major (BTM) patients.
Materials and methods: This was a retrospective study carried out in the pediatric hematology and pediatric endocrinology departments of a tertiary healthcare institution with the medical data of 249 children with BTM (108 females, 43.4%; 141 males, 56.6%) with a median age of 7.17 (2 -17.8) years. Baseline descriptive, clinical features including endocrine complications and laboratory data were noted. Correlation between the presence of endocrine complications and demographic, clinical, and laboratory variables were sought. The effects of age, gender, race, height, weight, and splenectomy on endocrine complications were evaluated separately in each complication group.
Results: Vitamin D deficiency/insufficiency is the most common endocrine complication (41.7%). According to Turkish children, Syrian children had also significantly lower vitamin D concentration (p=0.001). At least one endocrinopathy was reported in the majority of BTM patients (67.9%). Accordingly, pubertal status (p=0.014) and Syrian nationality (p=0.007) had significant impacts on TSH levels. Syrian children and those with delayed puberty had greater likelihood for subclinical or evident hypothyroidism. The likelihood of suffering from at least one endocrine complication was higher in older children (p=0.042) and those with Syrian nationality (p=0.025)
Conclusion: Disorders of endocrine and metabolic nature are common in children with BTM. Early detection and protocol-based multidisciplinary management of these disorders constitute the most suitable strategies to increase patients' quality of life. Surveillance, early detection and treatment, and collaborative follow-up with a multidisciplinary team are the key points in the reduction of the severity and frequency of endocrine complications as well as optimization of therapeutic outcomes.

Key Words: Beta thalasemia major; endocrin; complications; treatment

Öz

Amaç: β-talasemi major (BTM) hastalarında endokrin komplikasyonların risk faktörlerini ve klinik korelasyonlarını araştırmayı amaçladık.
Materyal ve Metod: Bu retrospektif çalışma, ortanca yaşı 7.17 olan BTM'li 249 çocuğun (108 kadın, %43.4; 141 erkek, %56.6) tıbbi kayıtlarından elde edilen veriler kullanılarak üçüncü basamak bir bakım merkezinin pediatrik hematoloji ve pediatrik endokrinoloji bölümlerinde gerçekleştirildi. (2-17.83 yaş). Demografik veriler, endokrin komplikasyonları ve laboratuvar verilerini içeren klinik özellikler kaydedildi. Endokrin komplikasyonlarının varlığı ile demografik, klinik ve laboratuvar değişkenleri arasındaki ilişki araştırıldı. Yaş, cinsiyet, ırk, boy, kilo ve splenektominin endokrin komplikasyonlar üzerindeki etkileri her komplikasyon grubunda ayrı ayrı değerlendirildi.
Bulgular: D vitamini eksikliği/yetersizliği en sık görülen endokrin komplikasyon olarak bulundu (%41,7). Suriyeli çocuklarda D vitamini düzeyi istatistiksel anlamlı derecede daha düşüktü. Puberte durumu ve Suriye uyruklu olma TSH düzeyleri üzerinde istatistiksel olarak anlamlı etkiye sahip olarak bulundu (p değerleri sırasıyla; p=0,001, p=0.007) . Suriyeli çocuklar ve ergenlik gecikmesi olanlarda, subklinik veya belirgin hipotiroidizm daha fazla saptandı. En az bir endokrin komplikasyon görülme olasılığı ileri yaşta ve Suriye uyruklu olanlarda daha yüksekti (p değerleri sırasıyla; p=0.042, p=0.025).
Sonuç: BTM'li çocuklarda endokrin ve metabolik bozukluklar çok yaygındır. Bu bozuklukların erken tespiti ve standart protokollerle multidisipliner yönetimi, bu hastalara daha iyi bir yaşam kalitesi sağlamak için en uygun stratejidir. Düzenli sürveyans, erken tanı, tedavi ve multidisipliner bir ekibin işbirliği ile takip, endokrin komplikasyonların şiddetinin ve sıklığının azaltılmasının yanı sıra terapötik sonuçların optimizasyonunda kilit noktalardır.

Anahtar Kelimeler: Beta talasemi major; endokrin; komplikasyonlar; tedavi

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Introduction

β-thalassemia major (BTM), the most prevalent hereditary anemia, is characterized by reduction or absence of β-globin chain synthesis. Patients with BTM require blood transfusions regularly, every 2 to 4 weeks. In order to prevent mortality and morbidity, iron chelation therapy is essential (1). In cases where chelation therapy is inadequate or not given, iron accumulation develops in critical organs, such as the heart, liver and endocrine glands, which cause dysfunctions. Also, annual transfusion amount, splenectomy, serum ferritin level and type of iron chelation are primary contributors to the secondary effects aimed at establishing iron values. Cardiac failure has been established to be the leading cause of death; however, the most important problem affecting quality of life is endocrine complications (2-3).

The existence of these endocrine disorders may be facilitated by factors including genetic factors, hepatic dysfunction, hypoxia, age at the onset of chelation treatment, and chronic anemia. There are heterogeneous data of endocrine comlication's prevalence, age at onset, severity, presentation, and severity in BTM (4-6). Common endocrine complications in thalassemia patients can be listed as short stature, delayed puberty and hypogonadism, sexual dysfunction, bone diseases such as osteoporosis, diabetes, hypothyroidism and hypoparathyroidism (4-7).

Our aim was to evaluate risk factors of endocrine complications and to detect clinical correlates of these complications in BTM patients. Thereby, we hope our data may aid in the early recognition of endocrine complications and orientation of the clinical approach based on the health needs of patients and to avoid the occurrence of more severe metabolic and pathological consequences.

Materials and Methods

Study design

The present study was designed as a retrospective research carried out in the pediatric hematology and pediatric endocrinology departments of our tertiary healthcare institution, with inclusion of data from 2016 to 2018. Before beginning data collection, Harran University ethics review board approved the study (Date:05/07/2018/; no:18/07/31). Written informed consent for scientific use of data was provided by all parents or legal guardians of patients. Medical records and the electronic database of the hospital were reviewed to obtain the data of 249 children (108 females, 43.4%; 141 males, 56.6%) diagnosed with BTM. Exclusion criteria were: incomplete data or diagnosis of thalassemia intermedia.

BTM diagnoses had been made by hemoglobin electrophoresis and genetic testing, following suspicion due to clinical and laboratory findings (hemoglobin electrophoresis and DNA testing). After diagnosis, hemoglobin levels of 9-9.5 mg/dl were maintained by administration of regular blood transfusions with 3 to 4 week intervals. Iron chelation therapy usually starts after two years (or 10 to 15 transfusions) or when two consecutive measurements of serum ferritin demonstrate levels exceeding 1000 µg/L. We started deferasirox as the initial iron chelating agent in patients with ferritin levels of ≥1000 µg/L. All physical examinations and follow-up had been performed by the same clinician.

Measurements of weight and height were performed using a Harpenden stadiometer and a calibrated digital scale, respectively. Children with a height measurement lower than 2 SDs (standard deviations) relative to Turkish age-matched and sex-matched populations were defined to have short stature (4). The staging of puberty was evaluated with respect to Tanner's criteria, and testicular volume was measured with Prader's orchidometer (4). In girls, puberty delay was defined according to breast development (lack thereof by age 13), while delayed puberty was defined according to testis volume (< 4 ml by age 14) (4).

Basic serum biochemical features such as fasting plasma glucose, oral glucose tolerance, fasting calcium, phosphorus, alkaline phosphatase, thyroid-stimulating hormone, free triiodothyronine (fT3), free thyroxine (fT4), follicle-stimulating hormone (FSH), vitamin D, calcitonin, parathormone (PTH), and luteinizing hormone (LH) were recorded in all patients. Serum testosterone levels were assessed in boys, while serum estradiol levels were evaluated in girls. The measurement of serum ferritin had been performed regularly in order to assess the impact of chelation. Serum calcium level was adjusted for serum albumin, and serum phosphorus was adjusted for age.

BMI was measured and calculated using the standard formula, and categorized into four groups based on conventional WHO classification (8). Hypoparathyroidism was identified when low serum PTH, increased serum phosphate and low serum calcium concentration (9). Hypothyroidism was classified into three groups as follows: Primary overt hypothyroidism , subclinical hypothyroidism and central hypothyroidism (10).

Vitamin D concentration was determined by measurement of 25(OH)D, and the threshold for sufficient 25(OH)D was accepted as >20 ng/mL (50 nmol/L). Deficiency was diagnosed in patients with 25(OH)D concentrations of <12 ng/mL (<30 nmol/L), while insufficiency was diagnosed between 12 and 20 ng/mL (30-50 nmol/L) (11).

Oral glucose tolerance tests were performed, interpreted and classified according to the guidelines put forth by the International Society for Pediatric and Adolescent Diabetes (12).

All samples were collected early in the morning after overnight fasting.

Outcome measures

Baseline descriptive data involved age, pubertal status, nationality, sex, weight, height, stature, physical examination findings for organomegaly, and history for splenectomy. Clinical and laboratory features under investigation involved thyroid dysfunction, glucose intolerance, serum levels of fer-

ritin, thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), calcium, phosphorus, alkaline phosphatase, vitamin D, parathormone (PTH), calcitonin, FSH, LH, testosterone, and estradiol.

Statistical analysis

All statistical analyses were subject to a significance threshold of $p < 0.05$ (two-tailed), and were conducted on the SPSS version 21.0 software (IBM, NY, USA). Quantitative variables were summarized with eithe the mean and SD or median and minimum-maximum values, while categorical variables were summarized with absolute and relative frequencies. Normally distributed data were presented as mean±SD, non-normally distributed data were presented as median (min-max). Normality of distribution of quantitative variables were performed with the Kolmogorov-Smirnov test (with Lilliefor's correction). Two independent groups were compared with either the T-test or the Mann-Whitney U test. The comparisons of 3 or more groups were performed with one way analysis of variance or the Kruskal-Wallis test. In case of significant differences in initial ≥3-group comparisons, pairwise corrections were performed. The relationship between categorical variables was sought with chi-square tests. Logistic regression was performed to determine parameters independently associated with dependent variables with two subtypes. The association between quantitative variables was investigated using Pearson or Spearman correlation coefficients.

Results

Our series consisted of 249 patients (108 females, 43.4%; 141 males, 56.6%) with a median age of 7.17 years (2 -17.8 years). The demographic features of the study population are presented in Table 1.

The clinical and laboratory features of our series are summarized in Table 2.

The majority of BTM patients (n=169, 67.9%) had at least 1 endocrine complication(s). Mean ferritin level was 1633 ng/ml (667-8276) and 2795ng/ml (491-12468) in Turkish and Syrian children respectively, demonstrating significantly higher levels among Syrian children.

The frequency of endocrinopathies in the subjects with thalassemia are given in Table 3.

The effects of age, gender, race, height, weight, and splenectomy on endocrine complications were evaluated separately in each complication group.

The investigation of the impacts of variables on thyroid hormone levels revealed that Syrian patients had higher likelihood for subclinical hypothyroidism, but this was not statistically significant. Accordingly, pubertal status (p=0.014) and nationality (p=0.007) had significant impacts on TSH levels. Syrian children and those with delayed puberty had greater likelihood for subclinical or evident hypothyroidism.

Syrian patients had significantly lower vitamin D concentration (p=0.001). Analysis of our data indicated that serum PTH levels were affected significantly by nationality (p=0.037) and sex (p=0.006). Secondary hyperparathyroidism was more frequent in Syrian patients and females .

The likelihood of suffering from at least one endocrine complication was higher in older children (p=0.042) and those with Syrian nationality (p=0.025) (Table 4).

Table 1. Demographic features of our study population (n=249)

		n (%)
Age (months)		86.0 (24 – 214)
Age (years)		7.2 (2 – 17.8)
Nationality	Turkish Syrian	172 (69.1) 77 (30.9)
Sex	Female Male	108 (43.4) 141 (56.6)
Weight (kg)		21.0 (9 – 69)
Weight (percentile)		7.5 (0 – 100)
Weight (z)		1.46 (0.02 – 41.0)
Height (cm)		117.0 (78 – 178)
Height (percentile)		11.0 (0.0 – 100.0)
Height (z)		1.32 (0.02 – 7.73)

Table 2. Clinical and laboratory features of our series (n=249)

		n (%)
Splenectomy	No Yes	218 (87.6) 31 (12.4)
Physical examination	Normal Organomegaly	120 (48.2) 129 (51.8)
Ferritin (ng/ml)		1813.0 (359 – 12468)
TSH (mU/L)		2.67 (0.63 – 46.80)
fT3		3.76 ± 0.53
fT4		0.87 ± 0.17
Ca		9.39 ± 0.49
P		5.22 ± 1.02
ALP (IU/L)		191.0 (72.0 – 941.0)
Vitamin D (ng/ml)		33.61 ± 13.88
PTH level (pg/ml)		38.4 (0.10 – 224.0)
Calcitonin (pg/ml)		2.64 (2.0 – 30.40)
FSH		1.98 (0.14 – 9.20)
LH (IU/L)		0.38 (0.01 – 9.04)
Testosterone (ng/dl)		0.08 (0.0 – 7.20)
Estradiol (pg/ml)		6.55 (0.0 – 132.20)
No. of endocrine complications, n(%)	None ≥ 1 complications	80 (32.1) 169 (67.9)

TSH: thyroid stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine; Ca: calcium; P: phosphorus; ALP: alkaline phosphatase; PTH: parathormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone

Table 3. The frequency of endocrinopathies in the subjects with thalassemia (n=249)

	Number of the subjects n, (%)	
Thyroid function	Subclinical Primary hypothyroidism	38 (15.3) 3 (1.2)
Pubertal status	Delayed	18 (7.2)
Stature	Short	63 (25.3)
Vitamin D level	Deficient Insufficient	50 (20) 55 (22.1)
PTH status	Secondary hyperPTHism HypoPTHism	43 (17.3) 4 (1.6)
İmparied Glucose tolerance	Yes	4 (16)

As shown in Table 5, correlation analysis between various variables demonstrated significant but weak relationships between ferritin level and age ($r=0.371$;$p<0.001$), weight (z) ($r=0.226$; $p=0.001$), height (percentile) ($r=-0.176$; $p=0.013$), and height (z) ($r=0.337$; $p<0.001$). The relationships between fT3 and all variables under investigation were negligible. The

associations between fT4 and age (r=-0.265; p<0.001), weight (g) (r=-0.272; p<0.001) and height (cm) (r=0.31; p<0.001) were statistically significant, but still negligible. Serum calcium levels displayed a remarkable association with age (r=-0.211; p<0.001), weight (g) (r=-0.176; p=0.006), height (cm) (r=-0.183; p=0.004), height (percentile) (r=0.154; r=0.031), and height (z) (r=-0.208; p=0.003). However, these associations were also negligible. A weak positive relationship was detected between calcitonin and age (r=-0.345; p<0.001), weight (g) (r=-0.343; p<0.001) and height (cm) (r=-0.375; p<0.001). The relationship between age and FSH was negligible, whereas a moderate and positive relationship was noted between FSH and weight (g) and height (cm). Moderate and positive relationships were observed between testosterone and age (r=0.461; p<0.001), weight (g) (r=0.537; p<0.001) and height (cm) (r=0.516; p<0.001). Similarly, there were moderate and positive relationships between estradiol and age (r=0.523; p<0.001), weight (g) (r=0.569;p<0.001), and height (cm) (r=0.535; p<0.001).

Table 4. Analysis of the impact of variables on the presence of endocrine complications (*: statistically significant).

		Presence of endocrine complications		
		None (n=80)	**≥1 (n=169)**	p-value
Age (months)		79.5 [25 - 200]	93.0 [24 - 214]	***0.042****
Age (years)		6.6 [2 – 16.7]	7.8 [2.0 – 17.8]	***0.042****
Pubertal status	Normal Delayed	71 (36.6) 0 (0.0)	123 (63.4) 18 (100.0)	***0.002****
Nationality	Turkish Syrian	63 (36.6) 17 (22.1)	109 (63.4) 60 (77.9)	***0.025****
Sex	Female Male	35 (32.4) 45 (31.9)	73 (67.6) 96 (68.1)	0.934
Weight (kg)		20.0 [9 - 58]	21.0 [10 - 69]	0.233
Weight (percentile)		16.0 [0.0 – 93.0]	6.0 [0.0 – 100]	0.061
Weight (z)		1.22 [0.05 – 41.0]	1.59 [0.02 – 8.38]	0.950
Height (cm)		116.0 [85 - 178]	117.5 [78 - 168]	0.502
Height (percentile)		17.0 [3.0 - 95]	5.0 [0.0 – 100.0]	0.120
Height (z)		0.97 [0.05 – 1.95]	1.68 [0.02 – 7.73]	***<0.001****
Stature	Normal Short	59 (44.0) 0 (0.0)	75 (56.0) 63 (100.0)	***<0.001****
Splenectomy	No Yes	72 (34.0) 5 (16.1)	140 (66.0) 26 (83.9)	0.053
Physical examination	Normal Organomegaly	38 (33.0) 40 (31.0)	77 (67.0) 89 (69.0)	0.734

Table 5. Analysis of the relationship between quantitative variables in BTM patients (*: statistically significant).

		Age (months)	Weight (kg)	Weight (percentile)	Weight (z)	Height (cm)	Height (percentile)	Height (z)
Ferritin	r	0.371	0.349	0.038	0.226	0.310	-0.176	0.337
	p	***<0.001****	***<0.001****	0.581	***0.001****	***<0.001****	***0.013****	***<0.001****
TSH	r	0.086	0.102	0.001	0.074	0.036	0.011	0.109
	p	0.177	0.111	0.988	0.293	0.578	0.875	0.128
fT3	r	-0.250	-0.214	0.220	-0.203	-0.209	0.191	-0.169
	p	***<0.001****	***0.001****	***0.001****	***0.004****	***0.001****	***0.007****	***0.018****
fT4	r	-0.265	-0.272	0.069	-0.037	-0.281	-0.010	0.064
	p	***<0.001****	***<0.001****	0.327	0.596	***<0.001****	0.889	0.372
Ca	r	-0.211	-0.176	0.009	-0.179	-0.183	0.154	-0.208
	p	***0.001****	***0.006****	0.896	***0.011****	***0.004****	***0.031****	***0.003****
P	r	-0.022	-0.010	0.038	-0.028	-0.067	-0.031	0.048
	p	0.727	0.872	0.588	0.689	0.303	0.668	0.506
ALP	r	0.003	0.056	0.041	-0.091	0.023	-0.033	-0.037
	p	0.957	0.384	0.559	0.199	0.721	0.648	0.606
Vitamin D	r	-0.012	-0.008	-0.016	-0.076	0.027	-0.002	-0.049
	p	0.851	0.901	0.816	0.282	0.680	0.975	0.499
PTH	r	0.051	0.063	0.002	0.040	0.058	0.064	0.050
	p	0.431	0.334	0.979	0.576	0.376	0.378	0.492
Calcitonin	r	-0.345	-0.343	0.037	-0.049	-0.375	-0.011	0.105
	p	***<0.001****	***<0.001****	0.607	0.493	***<0.001****	0.883	0.151
FSH	r	0.246	0.314	0.033	0.083	0.179	0.045	-0.006
	p	***0.010****	***0.001****	0.758	0.437	0.067	0.685	0.960
LH	r	0.565	0.636	-0.044	0.095	0.563	-0.004	0.025
	p	***<0.001****	***<0.001****	0.531	0.180	***<0.001****	0.951	0.734
Testosterone	r	0.461	0.537	-0.145	0.090	0.516	-0.009	-0.017
	p	*<0.001**	*<0.001**	0.130	0.350	***<0.001****	0.926	0.861
Estradiol	r	0.523	0.569	-0.095	0.052	0.535	-0.050	-0.111
	p	***<0.001****	***<0.001****	0.372	0.628	***<0.001****	0.653	0.315

TSH: thyroid stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine; Ca: calcium; P: phosphorus; ALP: alkaline phosphatase; PTH: parathormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone

Discussion

Among all hemoglobinopathies, BTM is most frequently associated with endocrine complications. This is due to frequent transfusions for therapeutic purposes, even in cases in which chelation therapy is initiated in the early period. Even in cases where chelation therapy is started in the early stages of the disease, the effects of the accumulated iron load in the body on the endocrine system can be observed (13-15). Studies investigating the clinical features of patients with endocrine complications and their prevalence / risk factors have demonstrated that the following factors are of particular importance: age, genotype, annual number of red blood cell transfusions, chelation therapy compliance, ferritin concentration, and iron accumulation in endocrine organs (16). Even in beta thalassemia major patients receiving regular chelation therapy, it has been reported that endocrine complications are seen at a high rate of up to 60% (17) . We found that 67.9% of our patients had experienced at least a single endocrinopathy, which is in line with previous reports. In Syrian patients, endocrine complications was statistically significantly higher than Turkish patients (p=0.023). We believe these findings may be associated with irregular follow-up and irregular chelation treatment after migration to Turkey. Also, age was a consistent risk factor.

Endocrinopathies in BTM patients are believed to be associated with chronic anemia, hypoxia, chronic liver disease, viral infections, and iron overload (18). Common endocrine complications are; short stature, delayed puberty, bone disorders like osteoporosis, diabetes, hypothyroidism and hypoparathyroidism (19). Although the prevalence of vitamin D deficiency has decreased over the years in Turkey, it still poses a significant problem in transfusion-dependent thalassemia patients. Işık et al. reported vitamin D deficiency or insufficiency in 78% of the patients (20). The Middle East region, including our country, is one of the regions where vitamin D deficiency is most common worldwide. The prevalence of vitamin D deficiency in this region ranges from 30% to 90%, considering the desired 25-OH-vitamin D level of 20 ng/ml. These insufficient levels may be associated with reduced sun exposure. (conservative dressing culture and/or avoiding exposure to hot sunny weather) (21).

This study determined vitamin D deficiency/insufficiency similar to the rates in the literature and showed it as the most common endocrine problem (41.7%). Vitamin D deficiency can cause hypocalcemia and is a leading cause of bone-related pathologies in patients with BTM. Although vitamin D deficiency is suggested to demonstrate increased frequency with age in the literature, no relationship was found with older age in the current study (22). Short stature is reportedly present in 30-60% of patients (23). The difference in prevalence of short stature short stature in patients living in various countries is explained by the fact that genetic susceptibility to the toxic effects of iron overload in endocrine gland and serum ferritin (24). The present findings demonstrate an incidence of 32% for short stature.

Although the basic pathophysiology of BTM is based on anemia, iron overload, and iron toxicity, conventional treatments aim to control the main symptoms of anemia and iron overload (19, 25). Endocrine complications are reportedly more common in patients with elevated ferritin and splenectomy. On the assumption that patients with splenectomy are more exposed to free iron radicals, it is suggested that they are predisposed to endocrine injury (26). Unlike previous studies, we did not find a significant relationship between serum ferritin levels and endocrine complications in this study. Serum ferritin level reflects an indirect measure of iron load, with conflicting results in inflammation, liver dysfunction, and vitamin C deficiency (27, 28). We thought that this situation might be related to the type of chelation therapy and also serum ferritin tolerance may be another cause of this condition. In this study, serum ferritin levels were measured at a given time and their changes at different times were not determined. Also, there was no increase in the incidence of complications in patients who had undergone splenectomy. This situation may be related to the different distribution of iron and the varying sensitivity of organs to iron toxicity.

The high prevalence of endocrine complications in BTM patients may be related to poor disease control or failure of treatment in early life. In such a case, irreversible injury of tissues can occur due to iron overload; therefore, evidently showing the importance of regular follow-up in BTM, which can allow early detection of complications (7, 29). Vitamin D deficiency / insufficiency, parathyroid disorders and thyroid disorders were significantly more common among Syrian children. At the same time, ferritin concentrations and the rate of at least one endocrine complication were significantly higher compared to Turkish patients. Many patients included in this study were not followed up regularly in their home country before and during the war, and they did not receive chelation in a regular and appropriate dose. Also, after immigrating to our country, the language barrier further impacted sufficient treatment administration in these patients.

Hypoparathyroidism is reported in 3.6 to 22.5% of patients with BTM (30). If unrecognized or untreated, it may cause decreased bone density, fractures and bone pain, which are often detected in thalassemia, as well as severe hypocalcemia findings (31). In our study, hypoparathyroidism was found 1.6%, lower rate than the literature. However high PTH levels were detected 17.6% of patients, and 25-OHD levels were found to be low in all these patients, although they were taken during the summer months. Unless there is accompanying primary or tertiary hyperparathyroidism, it is known that vitamin D deficiency and elevated PTH usually indicate secondary hyperparathyroidism. The accumulation of iron in the liver is also thought to contribute to this condition (32).

Primary hypothyroidism was found in 1.2% of our patients,

which is relatively low compared to the literature. However, the onset of this disorder is generally in the second decade of life (33). Most of the patients of hypothyroidism were subclinical (16.6%); their periodic evaluation of the thyroid function was done to detect children of hypothyroidism who need thyroid replacement therapy. If annual surveillance of thyroid function was not performed, patients with subclinical hypothyroidism would not have been detected (34).

Subclinical/primary hypothyroidism was found to be more frequent in patients with delayed puberty. These findings are crucial for patient management since hypothyroidism can delay puberty due to the established effects of thyroid hormones on sexual development and reproductive function (35).

Many factors influence pubertal development, such as genetics, nutrition, chronic anemia, and systemic diseases. The main reasons for the failure of the hypothalamic-pituitary axis in BTM are iron accumulation and oxidative injury in the pituitary gland (36). In our group, delayed puberty was detected in 18 of the 249 (8.5%) patients. Although hypogonadism is one of the most common endocrine complications, the low number of patients with delayed puberty in our study was thought to be due to the younger age of the patients.

Our data revealed that demographic factors such as age, nationality, and pubertal status may affect endocrine and metabolic profiles in BTM patients. The complex interaction between clinical and laboratory parameters necessitates the implementation of further prospective, randomized, controlled, multicenter trials on larger series. Although the prevalence of endocrinopathies in BTM is well studied in developed countries, data from developing countries are limited.

Optimal treatment in BTM should focus on disease management and complication prevention. Occult and overt endocrine complications such as delayed puberty, hypothyroidism, glucose intolerance, hypoparathyroidism, osteoporosis, and osteopenia require the close collaboration of hematology, endocrinology, and other related specialist disciplines. A careful analysis of demographic characteristics, together with a complete physical examination and interpretation of laboratory results, is imperative to avoid missing accompanying endocrine complications. The chronic disease itself and the masking effects of other symptoms make it difficult to identify endocrine complications that may present with specific or subtle symptoms. Development of guidelines that outline the diagnostic and therapeutic strategy for BTM patients must be encouraged. We noted that immigrants displayed different features compared to those of local inhabitants. The changing epidemiological features and the diversity of clinical presentations should be remembered when determining appropriate diagnostic and therapeutic strategies (37).

The retrospective design and single-center data collection are the foremost limitations of this study. However, our study represents the highest number of cases from a single institution in our country. Extrapolation of our results to larger populations must be made cautiously.

Conclusion

In conclusion, endocrinopathies are very common in children with BTM. Early detection of these disorders and their multidisciplinary management with standardized protocols seem to be the most appropriate strategy to increase quality of life. Factors such as chronic iron overload, inadequate compliance with chelation therapy, and chronic liver disease are factors that increase the occurrence of clinical sequelae. Reducing endocrine complications and optimizing therapeutic results; regular surveillance, early diagnosis, treatment, follow-up with the cooperation of a multidisciplinary team are the most important points. Decreased severity of endocrine complications would allow an easier and more effective treatment of BTM.

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References

1. He LN, Chen W, Yang Y, Xie YJ, Xiong ZY, Chen DY, et al. Elevated Prevalence of Abnormal Glucose Metabolism and Other Endocrine Disorders in Patients with β-Thalassemia Major: A Meta-Analysis. Biomed Res Int. 2019; 18:6573497.
2. Taher AT, Saliba AN. Iron overload in thalassemia: different organs at different rates. Am Soc Hematol Educ Progr. 2017; ;(1):265-71.
3. De Sanctis V, Soliman AT, Canatan D, Tzoulis P, Daar S, Di Maio S. et al. An ICET-A survey on occult and emerging endocrine complications in patients with 13- thalassemia major: Conclusions and recommendations. Acta Biomed. 2018;89(4):481-89
4. Altincik A, Akin M. Prevalence of Endocrinopathies in Turkish Children With β-Thalassemia Major: A Single-Center Study. J Pediatr Hematol Oncol. 2016; ;38(5):389-93.
5. Shamshirsaz AA, Bekheirnia MR, Kamgar M, Pourzahedgilani N, Bouzari N, Habibzadeh M,et al. Metabolic and endocrinologic complications in beta-thalassemia major: a multicenter study in Tehran. BMC Endocr Disord. 2003;12;(1):4-9.
6. Isik P, Yarali N, Tavil B, Demirel F, Karacam GB, Sac RU, et al. Endocrinopathies in Turkish children with Beta thalassemia major: results from a single center study. Pediatr Hematol Oncol. 2014;31(7):607-15.
7. Saffari F, Mahyar A, Jalilolgadr S. Endocrine and metabolic disorders in β-thalassemiamajor patients. Caspian J Intern Med. 2012;3(3):466-72.

8. Lim JU, Lee JH, Kim JS, Hwang YI, Kim T-H, Lim SY et al Comparison of World Health Organization and AsiaPacifc body mass index classifcations in COPD patients. Int J Chronic Obstr Pulm Dis.2017;12:2465-75.
9. De Sanctis V, Elsedfy H, Soliman AT, Elhakim IZ, Soliman NA, Elalaily R et al. Endocrine profle of β-thalassemia major patients followed from childhood to advanced adulthood in a tertiary care center. Indian J Endocrinol Metab. 2016; 20(4):451-59.
10. Haghpanah S, Jelodari S, Karamifar H, Saki F, Rahimi R, De VS et al. The frequency of hypothyroidism and its relationship with HCV positivity in patients with thalassemia major in southern Iran. Acta Bio Medica Atenei Parmensis. 2018; 89(1):55–60.
11. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. J Clin Endocrinol Metab. 2016;101(2):394-415.
12. Craig ME, Jefferies C, Dabelea D, Balde N, Seth A, Donaghue KC. ISPAD Clinical Practice Consensus Guidelines 2014 Compendium: Type 2 diabetes in the child and adolescent. Pediatr Diabetes 2015;16:392.
13. Al-Elq AH, Al-Saeed HH. Endocrinopathies in patients with thalassemias. Saudi Med J. 2004;25(10):1347-51.
14. Chirico V, Rigoli L, Lacquaniti A, Salpietro V, Piraino B, Amorini M, et al. Endocrinopathies, metabolic disorders, and iron overload in major and intermedia thalassemia: serum ferritin as diagnostic and predictive marker associated with liver and cardiac T2* MRI assessment. Eur J Haematol. 2015;94(5):404-12.
15. Mohammadian S, Bazrafshan HR, Sadeghi-Nejad A. Endocrine gland abnormalities in thalassemia major: a brief review. J Pediatr Endocrinol Metab. 2003;16(7):957-64.
16. De Sanctis V, Soliman AT, Elsedfy H, Pepe A, Kattamis C, El Kholy M, et al. Diabetes and Glucose Metabolism in Thalassemia Major: An Update. Expert Rev Hematol. 2016;9(4):401-08.
17. Haliloğlu B, Tüysüz G, Küpesiz F. Endocrinopathies in Turkish Children with Thalassemia Major. J Pediatr Res 2017;4(4):216-19.
18. Oerter KE, Kamp GA, Munson PJ, Nienhuis AW, Cassorla FG, Manasco PK. Multiple hormone deficiencies in children with hemochromatosis. J Clin Endocrinol Metab. 1993;76(2):357-61.
19. Aydinok Y, Darcan S, Polat A, Kavakli K, Nigli G, Coker M, et al. Endocrine complications in patients with beta-thalassemia major. J Trop Pediatr. 2002;48(1):50-54.
20. Isik P, Yarali N, Tavil B, Demirel F, Karacam GB, Sac RU, et al. Endocrinopathies in Turkish children with Beta thalassemia major: results from a single center study. Pediatr Hematol Oncol. 2014;31(7):607-15.
21. Bassil D, Rahme M, Hoteit M, Fuleihan Gel-H. Hypovitaminosis D in the Middle East and North Africa: Prevalence, risk factors and impact on outcomes. Dermatoendocrinol. 2013;5(2):274-98.
22. Soliman A, De Sanctis V, Yassin M. Vitamin d status in thalassemia major: an update. Mediterr J Hematol Infect Dis. 2013;5(1):e2013057.
23. Arab-Zozani M, Kheyrandish S, Rastgar A, Miri-Moghaddam E. A Systematic Review and Meta-Analysis of Stature Growth Complications in β-thalassemia Major Patients. Ann Glob Health. 2021;87(1):48.
24. Taher AT, Weatherall DJ, Cappellini MD. Thalassaemia. Lancet. 20 ;391(10116):155-67.
25. Toumba M, Sergis A, Kanaris C, Skordis N. Endocrine complications in patients with Thalassaemia Major. Pediatr Endocrinol Rev. 2007;5(2):642-48.
26. Skordis N, Michaelidou M, Savva SC, Ioannou Y, Rousounides A, Kleanthous M,et al. The impact of genotype on endocrine complications in thalassaemia major. Eur J Haematol. 2006;77(2):150-56.
27. Belhoul KM, Bakir ML, Saned MS, Kadhim AM, Musallam KM, Taher AT. Serum ferritin levels and endocrinopathy in medically treated patients with β thalassemia major. Ann Hematol. 2012;91(7):1107-14.
28. Rathaur VK, Imran A, Pathania M. Growth pattern in thalassemic children and their correlation with serum ferritin. J Family Med Prim Care. 2020;9(2):1166-69.
29. Esposito BP, Breuer W, Sirankapracha P, Pootrakul P, Hershko C, Cabantchik ZI. Labile plasma iron in iron overload: redox activity and susceptibility to chelation. Blood. 2003;102(7):2670-77.
30. Carsote M, Vasiliu C, Trandafir AI, Albu SE, Dumitrascu MC, Popa A, et al. New Entity-Thalassemic Endocrine Disease: Major Beta-Thalassemia and Endocrine Involvement. Diagnostics (Basel). 2022;12(8):1921.
31. Majid H, Jafri L, Ahmed S, Talati J, Moiz B, Khan AH. Unique classification of parathyroid dysfunction in patients with transfusion dependent thalassemia major using Nomogram-A cross sectional study. Ann Med Surg . 2019; 11(45):22-26.
32. Tangngam H, Mahachoklertwattana P, Poomthavorn P, Chuansumrit A, Sirachainan N, Chailurkit L, Khlairit P. Under-recognized Hypoparathyroidism in Thalassemia. J Clin Res Pediatr Endocrinol. 2018;10(4):324-30
33. Hussein SZ. Evaluation of thyroid hormones and ferritin level in patients with β-thalassemia. Med Pharm Rep. 2022;95(2):152-57.
34. Upadya SH, Rukmini MS, Sundararajan S, Baliga BS, Kamath N. Thyroid Function in Chronically Transfused Children with Beta Thalassemia Major: A Cross-Sectional Hospital Based Study. Int J Pediatr. 2018;16:9071213.
35. Dhouib NG, Ben Khaled M, Ouederni M, Besbes H, Kouki R, Mellouli F, et al. Growth and Endocrine Function in Tunisian Thalassemia Major Patients. Mediterr J Hematol Infect Dis. 2018;10(1):e2018031.
36. Manne N, Dr Gupta BK, Yadav SK, Singhal S, A Dubey. Prevalence of hypothyroıdısm, delayed puberty and dıabetes mellıtus ın patıents of β-thalassemıa major. International Journal of Medical and Biomedical Studies. 2020;4(3): 14-18.
37. Srisukh S, Ongphiphadhanakul B, Bunnag P. Hypogonadism in thalassemia major patients. J Clin Transl Endocrinol. 2016;16(5):42-45.