Vitamin D Deficiency in Children with Beta Thalassemia Major and Intermedia

Beta Talasemi Major ve İntermedialı Çocuklarda Vitamin D Eksikliği

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ABSTRACT Objective: Beta thalassemia major and intermedia patients show a tendency to osteoporosis and pathologic fractures. Vitamin D deficiency increases osteoporosis and its consequences. The aim of this study was to retrospectively determine the frequency of vitamin D deficiency and insufficiency in children with thalassemia major and intermedia who applied to our Pediatric Hematology department. **Material and Metods:** Our 42 patients with thalassemia major and intermedia were retrieved from hospital automation records. Blood samples had been taken before transfusion between January to June 2012. Age, gender, serum levels of ferritin, liver enzymes, calcium, phosphorus, alkaline phosphatase, 25-OH vitamin D, and parathormone were recorded. 25-OH vitamin D levels were measured using HPLC. Laboratory normal values for Vitamin D were 30-80 ng/ml. **Results:** Median vitamin D levels was 12.80 (1.43-47.04). Values were below 10 ng/mL (severe vitamin D deficiency) in 15 cases (36%), between 10 and 20 ng/mL (vitamin D deficiency) in 18 cases (43%), between 20 and 30 ng/mL (vitamin D insufficiency) in 6 cases (14%) and above 30 ng/mL (normal vitamin D level) in 3 cases (7%). No patients had clinical and radiologic findings of rickets. There was no difference in vitamin D level by gender and age. Patients with vitamin D deficiency or insufficiency received 1200 U per day of vitamin D_3 supplementation. **Conclusion:** This is the first report from Turkey about vitamin D levels in thalassemia. Majority of our thalassemia patients (93%) had low vitamin D levels. We advise routine check of vitamin D level and vitamin D supplementation in thalassemia patients.vitamin D supplementation in thalassemia patients.

Key Words: Vitamin D deficiency; beta-thalassemia; child

ÖZET Amaç: Beta talasemia major ve intermedialı hastalar osteoporoz ve patolojik kırıklara eğilimlidir. Vitamin D eksikliği osteoporoz ve sonuçlarını arttırır. Bu çalışmada amacımız, çocuk hematoloji bölümünde izlenen talasemi major ve intermedialı çocuklarda vitamin D eksikliği ve yetersizliği sıklığını geriye dönük olarak belirlemektir. **Gereç ve Yöntemler:** Hastane kayıtlarından 42 talasemi major ve intermedialı hastanın kaydına ulaşıldı. Kan örnekleri Ocak-Haziran 2012 tarihleri arasında transfüzyon öncesinde alındı. Yaş, cinsiyet, serum ferritin, karaciğer enzimleri, kalsiyum, fosfor, alkalen fosfataz, 25-OH vitamin D ve parathormon düzeyleri kaydedildi. 25-OH vitamin D düzeyleri HPLC ile ölçüldü. Normal vitamin D düzeyi 30-80 ng/mL idi. **Bulgular:** Hastaların ortanca vitamin D seviyesi 12,80 (1,43-47,04) ng/mL idi. Hastalar ölçülen vitamin D seyiyelerine göre gruplandırıldı. Hastaların 15 (%36)'inde vitamin D düzeyi 10 ng/ml'nin altında (ağır vitamin D eksikliği), 18 (%43)'inde 10 ile 20 ng/mL arasında (vitamin D eksikliği), 6 (%14)'sında 20-30 ng/mL arasında (vitamin D yetersizliği) ve 3 (%7)'ünde 30 ng/mL üstünde (normal) idi. Talasemili hastaların hiçbirinde riketsin belirgin klinik ve radyolojik bulguları saptanmadı. Vitamin D seviyeleri cinsiyet ve yaş gruplarında farklı değildi. Vitamin D seviyeleri eksik veya yetersiz olan hastalara 1200 U/gün vitamin D_3 verildi. **Sonuç:** Bu makale Türkiye'deki talasemi hastalarında vitamin D seviyeleri ile ilgili ilk makaledir. Bizim talasemili hastalarımızın büyük çoğunluğunda (%93) vitamin D seviyesi düşüktü. Bu sonuçların ışığında biz, talasemili hastalarda düzenli vitamin D seviyesi kontrolünü ve vitamin D profilaksisi almalarını öneriyoruz.

Anahtar Kelimeler: D vitamini eksikliği; beta talasemi; çocuk

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Beta thalassemias are a group of autosomal inherited anemias caused by globin chain mutations affecting hemoglobin synthesis. These children exhibit severe anemia, massive hepatosplenomegaly and severe growth retardation.[1,2] Increased erythropoiesis due to hemolysis and ineffective erythropoiesis lead to extension of bone marrow area against the bone tissue. Osteoporosis, tendency to pathologic fractures and changes of skeletal appearance are still important findings of thalassemia patients.[1-12] After transfusion programs patients live longer, but regular transfusion leads to complications of chronic iron load including growth retardation, diabetes mellitus, delayed sexual maturation and congestive hearth failure. Conventional treatment of thalassemia is directed to eliminate main symptoms of anemia and iron overload.[1-5]

Vitamin D deficiency prevalence was reported to be high in thalassemia patients (2-87.5%).[13-29] There is an increased interest to the relation between thalassemia and vitamin D status recently. However, majority of publications were not an incidence report. They reported vitamin D levels in studies investigating another aspect of thalassemia disease. This may lead to a selection error for correct incidence.

Vitamin D deficiency leads several clinical and biochemical abnormalities in thalassemia patients such as osteoporosis, pathological fractures, muscle weakness, myelofibrosis, diabetes, hyperparathyroidism, and allergy.[30-32] Moreover, it might be responsible for different effects since a lot of cell species have vitamin D receptors. That is why measurement of vitamin D levels in patient with the diagnosis of thalassemia is important, and appropriate supplementation is necessary in case of deficiency.

The aim of this study was to determine the frequency of vitamin D deficiency and insufficiency in children with thalassemia major and intermedia who applied to our Pediatric Hematology department retrospectively.

MATERIAL AND METHODS

We retrospectively investigated vitamin D status in patients with thalassemia major and intermedia. The diagnosis of disease was established by clinic findings, hemoglobin electrophoresis and mutation analysis. The patients with thalassemia major were on a regime of regular blood transfusions every 2-3 weeks as well as folic acid supplementation. Iron chelation therapy with deferasirox was given with 20-30 mg/kg/day doses, and the dose was decreased to 15 mg/kg/day when ferritin level was below 1000 ng/ml.

The patients with thalassemia intermedia were not on a regime of regular blood transfusions. They received transfusions when hemoglobin levels were ≤7 g/dl and deferasirox when ferritin levels were ≥1000 ng/ml. None of the patients had received vitamin D supplementation before. No patient had clinical or radiologic findings of rickets.

Our 42 patients with thalassemia major and intermedia were retrieved from hospital automation records retrospectively. Blood samples were taken before transfusion between January to June 2012. Age, gender, serum levels of ferritin, alanine transaminase, aspartate transaminase, calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), 25-OH vitamin D, and parathormone (PTH) were recorded. The levels of 25-OH vitamin D were measured by HPLC. Laboratory normal values for Vitamin D were 30-80 ng/ml. 25-OH vitamin D level below 10 ng/mL was accepted as severe vitamin D deficiency. The values between 10 and 19.99 ng/mL were accepted as vitamin D deficiency and levels between 20 and 29.99 ng/mL was regarded as an insufficiency.[30]

Statistical analysis was made using SPSS version 13.0. The differences between the groups were compared using independent Mann-Whitney U test. Differences for genders were compared using Fisher exact test. The correlations between the groups was analyzed using Pearson coefficient of correlation test.

RESULTS

Twenty-three male and 19 female patients were included in the study. Thirty-four patients were thalassemia major (81%) and 8 (19%) were thalassemia intermedia. The median age was 9 years (7 month-21 year). Median vitamin D level was

12.8 (1.43-47.04) ng/ml. Vitamin D levels were below 10 ng/mL in 15cases (36%), between 10 and 19.99 ng/mL in 18 cases (43%), between 20 and 29.99 ng/mL in 6 cases (14%) and above 30 ng/mL in 3 cases (7%). Three patients with normal vitamin D levels show following properties: one case was seven- month- old, at initial transfusion period and had major form. The second case was 6- year-old and had major form. The third case was 21-year-old and had intermedia form of thalassemia.

We did not find significant differences in gender or age distribution of the patients. Table 1 shows vitamin D sufficiency status data of the patients. It shows mean and standard deviation (SD) values of Ca, P, ALP and median (minimum- maximum) values of PTH, ferritin and vitamin D levels. Laboratory normal ranges were as follows: Ca 8.1-10.7 mg/dl, P 2.3-4.7 mg/dl, ALP 95-280 U/L and PTH 15-65 pg/ml. Liver enzyme levels were normal in all patients.

Table 2 shows statistically significant differences in ferritin and alkaline phosphatase levels between thalassemia major and intermedia groups (p=0.001 and p=0.000, respectively). There are no differences for other parameters. In thalassemia major group, there is no correlation between vitamin D versus ferritin levels and age (p=0.059 and p=0.057).

Oral vitamin D_3 supplementation (1200 U/day) has been given to thalassemia patients with low vitamin D levels.

TABLE 1: The data of patients showing vitamin D sufficiency status.

		Vitamin D levels (ng/ml)				
	All of the patient n=42 (100%)	<10 (severe vitamin D deficiency) n=15 (36%)	10-19.99 (vitamin D deficiency) n=18 (43%)	20-29.99 (vitamin D insufficiency) n=6 (14%)	≥ 30 ng/ml (normal) n=3 (7%)	p
Gender	23 m/19 f	8 m/7 f	9 m/9 f	3 m/3 f	3 m	
Age (year)	9 years (7 month-21 year)	11.33	9.58	5.53	9.28	0.092
Ferritin (ng/ml)	1516 (129-7246)	2038.33	1845.67	1332.67	1388.33	0.600
Ca (mg/ml)	9.5 ± 0.5	9.37	9.71	9.60	9.87	0.181
P (mg/ml)	4.9 ± 0.8	4.86	5.02	4.94	4.76	0.933
ALP (U/L)	210.6 ± 99.5	200.53	241.61	185.67	124.67	0.155
PTH (pg/ml)	32.58 (12.56-139)	37.75	23.82	31.81	28.41	0.514
Vitamin D (ng/ml)	12.80 (1.43-47.04)	6.04	13.60	26.52	39.06	

m: Male; f: Female; Ca: Calcium; P: phosphorus; ALP: Alkaline phosphatase; PTH: parathormone.

TABLE 2: The comparison of beta thalassemia major and thalassemia intermedia patients.

Median (min-max)	Thalassemia Major	Thalassemia Intermedia	p
Count	n=34 (81%)	n=8 (19%)	-
Gender	19 male/15 female	4 male/4 female	1.000
Age (year)	8.8 (0.6-18.8)	10.4 (5.9-21.0)	0.106
Ferritin (ng/ml)	1764 (342-7246)	416.5 (129-1984)	0.001
Ca (mg/dl)	9.6 (8.0-11.0)	9.45 (9.0-10.0)	0.960
P (mg/dl)	5.6 (3.16-6.39)	4.86 (3.2-6.02)	0.582
ALP (U/L)	210 (108-570)	128.5 (80-145)	0.000
PTH (pg/ml)	33.2 (12.6-139)	23.5 (20.7-68.0)	0.330
Vitamin D (ng/ml)	13.2 (1.43-47.04)	7.01 (3.17-33.98)	0.275
Vitamin D deficiency	32/34 (94%)	7/8 (87.5%)	0.478

Ca: Calcium; P: Phosphorus; ALP: Alkaline phosphatase; PTH: parathormone.

DISCUSSION

Thalassemia major and intermedia are a lifelong diseases. After regular transfusions and iron chelation treatments, patients achieve a near to normal life expectation. However, these patients show many multisystem disorders due to transfusion side effects, such as iron deposition in parenchyma of organs, hepatitis, and expansion of hematopoiesis in bone and extramedullary area.[1] Vitamin D deficiency in thalassemia is not only an associated finding, but also an aggravating/elevating factor for the main complications of the disease.

TABLE 3: Vitamin D levels and demographic features of the previous reports regarding thalassemia patients.

Author, year (reference number)	Country	Patient number (f/m)	Age (year)	Vitamin D level range (ng/ml)	Vitamin D deficiency ratio	Method (normal range)
Tsitoura, 1978 [13]	Greece	36 (16/20)	5-15	12.8±9.9	NA	PBA (NA)
Aloia, 1982 [14]	USA	5	10-23	12,2± 8,2	5/5	NA
Zaino, 1985 [15]	USA	7	5-24	22,4±14,3	2/7	NA
Zamboni, 1986 [16]	NA	13	3-13	22±10,6	NA	NA
Dandona, 1987 [17]	UK	7 summer	18-28	28±12.1	NA	PBA (NA)
		15 winter	18-28	12.6±6.7	10/18	PBA (NA)
Rioja, 1990 [18]	NA	6 winter	Child	6.5±4.9	NA	NA
		9 summer		13.8±8.4	NA	NA
Moulas, 1997 [19]	Greece	15 summer	5- 10	30.1±2.7	NA	HPLC (NA)
		Winter	5- 10	18.0±1.8	NA	HPLC (NA)
		22 summer	11-23	20.1±2.1	NA (5/22 <7.5)	HPLC (NA)
		Winter	11-23	10.6±0.9	NA (1/22 <7.5)	HPLC (NA)
Pratico, 1998 [20]	Italy	113	2-40	NA	32/113 (28%)	NA
Angelopoulos, 2006 [21]	Greece	210	25.1±6.2	22±10.6	NA	RIA (20.2-45.2)
Napoli, 2006 [22]	Italy	90 T. Major (53/37)	21-48	20.3±0.7	68/90 (76.5%)	ELISA (30-60)
		33 T. Interm	21-56	20.9±2.3	28/33 (85%)	ELISA (30-60)
Wood, 2008 [23]	USA	24 (11/13)	1.4–25.8	42.7±21.2 nmol/l* (2.5–82.5)	13/24 <50 nmol/l* 23/24 <75 nmol/l.	NA
Vogiatzi, 2009 [24]	USA, Canada	279 230 T. Major 41T. Interm. (49% male)	24.4±11.6 (6.1-53.2) 26.3±16.2 (6.1-75.4)	11-19 year: 47±20 6-10 year: 62±21 20 years+: 58.4±31	T. Major 176 (76.5%) T. Interm. 36 (87.8%)	RIA (<75 *nmol/l)
Dimitriadou, 2010 [25]	Greece	62 (33/29)	9.25–38.45	53.08±43.35 (8.01-222.92)	37/62 (60%) <50 *nmol/l 7/62 (11%) 50-75 *nmol/l.	RIA
Noetzli, 2010 [26]	USA	54	25.7±8.4	61.8±25.8	26% <50 *nmol/l 7% <25 *nmol/l.	NA
El-Edel, 2010 [27]	Egypt	22 (12/10)	4.3-12.4	12.56±4.71 (5.2-22.1)	NA	ELISA
		20 (11/9)	13.1-23.8	9.77±1.45 (6.3-10.5)	NA	NA
Fung, 2011 [28]	USA	74	3.6-57.5	23.9 (5-68)	69-72%	CIA (30-80)
Yavropoulou, 2011 [29]	Greece	33 (20/13)	33.09±1.36	37±1.46	NA (30-120*nmol/l)	NA
Our study	Turkey	42 (19/23)	0.6-21	14.49±9.96 (1.43-47.04)	39/42 (93%)	HPLC (30-80)

*25-OH Vitamin D:1 ng/ml= 2.5nmol/l; PBA: Protein binding affinity; ELISA: Enzyme linked immunosorbent assay; NA: Not available; CIA: Chemiluminescent immunoassay.
T. major: Thalassemia major; T. Interm.: Thalassemia intermedia.

Another consequence of vitamin D deficiency is myelofibrosis.[32] This complication may be important for thalassemia patients even in mild state, because myelofibrosis narrows bone morrow pool and pushes myelopoiesis to extramedullary tissues.

Vitamin D deficiency has a high prevalence in thalassemia patients (5-87 %).[13-29] Table 3 shows vitamin D levels and demographic features of the previous reports regarding thalassemia patients.

Iron deposition may cause vitamin D deficiency due to hyperpigmentation and liver dysfunction in thalassemia patients. Dark-color skin decreases vitamin D conversion by sun light and increases the content of daily supplementation required. Moreover, liver dysfunction may decrease 25 -hydroxylation.[30,31] Our patients were using deferasirox in this period as iron chelator, and their skin colors were less dark than it was in the desferroxamine period. Liver enzyme levels were normal in all of our patients. Another cause might be low sunshine exposure due to overprotection by mothers.

Muscle weakness is a prominent feature of the clinical syndrome of severe vitamin D deficiency. Clinical findings in vitamin D-deficiency associated with myopathy include proximal muscle weakness, diffuse muscle pain and gait impairments such as a waddling way of walking.[33] Vitamin D deficiency is also associated with prolonged congestive heart failure and impaired insulin secretion.[34,35] These abnormalities affect inversely comfort and health quality of patients.

Another research reported that more infants, young children and adolescents are vitamin D deficient even though they show no outward symptoms of deficiency.[36] For this reason, the possibility of deficiency may be underscored and some complaints and findings may be attributed to other diseases. In thalassemia patients, these complaints and findings are found to be associated organ dysfunction findings of chronic disease.

This report is the first report from Turkey about vitamin D levels in thalassemia. In Turkey, which is a sunny country, very high ratio of vitamin D deficiency in thalassemia patients may be surprising. This may attract attention to vitamin D deficiency and supplementation politics in normal, other chronic diseases and thalassemias.

In conclusion, frequency of vitamin D deficiency and insufficiency in our patients with the diagnosis of thalassemia major and intermedia study group was found to be high. Vitamin D deficiency is associated with particular complications/organ dysfunctions which are also observed in thalassemia patients. For this reason, vitamin D deficiency may aggravate these organ dysfunctions. High dose vitamin D supplementation might be necessary in thalassemia patients. Dose should be increased until sufficient blood levels are obtained, and then it must be measured twice a year.

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