Original Investigation / Özgün Araştırma

Evaluation of Risk Factors for Scoliosis in Children with Thalassemia Major

Talasemi Majörlü Çocuklarda Skolyoz Risk Faktörlerinin Araştırılması

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ABSTRACT

Objective: Scoliosis in thalassemia patients develops secondary to various risk factors. Early diagnosis and treatment are important to prevent the pathologies and to decrease the morbidity and mortality. This study is to evaluate the associations of scoliosis with anthropometric features, hematological measures, and bone mineral density.

Methods: Health records of patients under 18 years old were screened for the following data: gender, age, height, weight, transfusion frequency, use of chelating agents and medication, the levels of hematocrite, ferritin, fasting blood glucose, alanine aminotransferase, aspartate aminotransferase, calcium, phosphorus, alkaline phosphatase, thyroid stimulating hormone, free thyroxin, intact parathyroid hormone and bone mineral density (BMD) of lumbar vertebrae and femur using dual-energy X-Ray absorptiometry (DXA). By evaluating spinal deformities with anterior-posterior and lateral X-rays, scoliosis angle was measured using Cobb method.

Results: Nineteen patients (6 females, 13 males) were included in the study. Scoliosis was detected in 7 patients (2 females, 5 males), 12 patients (4 females, 8 males) were normal. Of these patients, 36.84% had scoliosis angle over 5°, 15.79% had between 10°- 19°. The patients with scoliosis had lower levels of hematocrite (p=0.009), calcium (p=0.044) and lumbar BMD (p=0.001); however, ferritin (p=0.043), alkaline phosphatase (p=0.033) levels were higher. There were no significant differences between the groups regarding other laboratory and DXA values (p>0.05).

Conclusion: Scoliosis rate was higher in the children with TM compared to the normal population. It can be concluded that low levels of hematocrite, calcium, BMD and higher ferritin and alkaline phosphatase might be responsible in scoliosis.

Keywords: Thalassemia major, scoliosis, hematocrit, bone mineral density, rehabilitation

ÖZET

Amaç: Talasemili (TM) hastalarda çeşitli faktörlere bağlı olarak skolyoz gelişir. Erken tanı ve patolojilerin gelişmesini önlemeye yönelik tedaviler mortalite ve morbiditeyi azaltır. Bu çalışmada TM'li çocuk hastalarda skolyoz gelişiminin antropometrik özellikler, hematolojik değerler ve kemik mineral yoğunluğu ile ilişkisinin araştırılması amaçlandı.

Yöntemler: Hastanemizde takip edilen TM'li 18 yaş altı tüm çocuk hastaların dosyaları tarandı. Hastaların cinsiyet, yaş, boy, kilo, transfüzyon sıklığı, kullandığı şelatör ve ilaçlar, transfüzyon öncesi hematokrit, ferritin, açlık kan şekeri, alanin aminotrensferaz, aspartat aminotransferaz, kalsiyum, fosfor, alkalen fosfataz, tiroid stimulan hormon, serbest tiroksin hormon, intakt paratiroid hormon ve dual enerji X-ray absorbsiyometri

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(DXA) yöntemi kullanılarak lomber vertebra ve femurdan ölçülmüş kemik mineral yoğunluğu (KMY) değerleri kaydedildi. Ön-arka ve lateral vertebra grafileri spinal deformite yönünden incelenerek Cobb metodu ile skolyoz açıları hesaplandı.

Bulgular: Ondokuz hasta (6 kız, 13 erkek) değerlendirmeye alındı. Çalışmaya dahil edilen hastaların 7'sinde (2 kız, 5 erkek) skolyoz tespit edildi, 12'si (4 kız, 8 erkek) normal olarak değerlendirildi. Hastaların %36.84'ünün skolyoz açısı 5°'nin üzerinde , %15.79'unun 10°- 19° arasında bulundu. Skolyoz tespit edilen grubun, normal gruba oranla hematokrit (p= 0.009), kalsiyum (p= 0.044) ve lomber KMY değerleri daha düşük (p= 0.001), ferritin (p= 0.043) ve alkalen fosfataz değerleri (p= 0.033) daha yüksek bulundu. Diğer laboratuvar ve DXA değerleri arasında gruplar arasında anlamlı fark tespit edilmedi (p >0.05).

Sonuçlar: TM'li çocuk hastalarımızda skolyoz oranı normal popülasyona oranla yüksek bulundu. Skolyoz gelişiminde hematokrit, kalsiyum ve KMY düşüklüğünün, ferritin ve alkalen fosfataz yüksekliğinin rolü olabileceği sonucuna varıldı.

Anahtar sözcükler: Talasemi majör, skolyoz, hematokrit, kemik mineral yoğunluğu, rehabilitasyon

Introduction

Thalassemia Major (TM) is a multisystemic disease, which is characterized with absent or severely reduced synthesis of beta-globin from the globin chains of hemoglobin (1). According to the World Health Organization (WHO), there are at least 70 million thalassemia carriers in the world and in each year 42,000 homozygote children are born. Turkey is one of the countries where the disease is common and even though the carrier ratio is 2-2.5% in the country, this ratio can raise up to 10% in some areas (2). Recent therapeutic advancements increased the life expectancy of these patients; thus, the secondary complications are beginning to be seen (3, 4, 5, 6). The bone abnormalities such as rickets, spinal deformities, severe osteoporosis, and pathological fractures are important morbidity causes (7). Among the spinal deformities, scoliosis prevalence was reported as 70% in various studies in the patients with TM (3). The early diagnosis and treatment of scoliosis is important since without treatment scoliosis can cause cosmetic, psychosocial, cardiopulmonary problems and severe disability (8).

The aim of this study is to investigate whether children with TM have increased risk for scoliosis and to evaluate the association between the development of scoliosis and the parameters such as anthropometric features, hematological levels and bone mineral density.

Materials and Method

The approval was obtained from the local ethical committee of our hospital. The health records of the children under 18 years old, who presented to the pediatric hematology and the physical therapy and rehabilitation clinic, between July 2010 and December 2012, due to secondary musculoskeletal problems, were reviewed. Following parameters were recorded: age, gender, weight, height, transfusion frequency, the use of chelating agent and other medications, the levels of hematocrite (Hct), ferritin, fasting blood glucose (FBG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), calcium (Ca), phosphorous (P), alkaline phosphatase (ALP), thyroid stimulating hormone (TSH), free thyroxin (sT4), intact parathyroid hormone (i-PTH). Bone-specific alkaline phosphatase, 25 OH vitamin D, gonadal hormone levels and pubertal development data are not included in this retrospective study because file data could not be obtained. The lack of such data is limitation of the the study. Lumbar spine and femoral bone mineral density measured by dual energy X-ray absorptiometry (Hologic QDR-4500 W model) (DXA) values were recorded, in accordance with international values. Osteoporosis was defined as DXA Z-score < -2 (9). Standard anterior-posterior X-rays were evaluated to detect spinal deformity and two different physicians measured scoliosis angles using Cobb method. Cobb method, recommended by Scoliosis Research Society, was performed as follows: the upper and lower margins of the vertebrae were determined. Parallel lines were drawn to the upper plate of these vertebras and the deflection angle (the upper angle) between the perpendicular lines, which was drawn to the parallel lines were measured to determine the scoliosis angle (10).

Statistical Analysis

Analysis was performed using Statistical Package for Social Sciences version 15.0 (SPSS, inc., Chicago, USA). Complementary statistical methods, independent-t test Mann-Whitney U and Chi-square tests were used. All of the results were demonstrated as mean ± standard deviation. A p value less than 0.05 was considered as statistically significant.

Results

Records of 26 patients (8 females, 18 males) with TM were reviewed. Seven patients who had incomplete health records and did not come to follow-ups were excluded from the study; thus only 19 (6 females, 13 males) patients were included. Of these patients, scoliosis was detected in 7 (2 females, 5 males). Twelve patients (4 females, 8 males) were considered as normal. Scoliosis ratio was 36.84% in the study group, 38.4% in the males

and 33.3% in the females. There was no significant difference between the genders (p=0.829).

Anthropometrical features, and laboratory results of the patients were shown in Table 1 and 2; the comparison of the groups based on the anthropometric features, laboratory and BMD results were demonstrated in Table 3. The group with scoliosis had lower Htc (p=0.009) and Ca (p=0.044) but higher ferritin (p=0.043) and ALP (0.033) levels compared to the patients without scoliosis. No significant differences were noted among the following parameters: age, height, weight, BMI, annual transfusion frequency, FBG, ALT, AST, P, TSH, sT4 and i-PTH.

Lumbar BMD values of the scoliosis group were found lower than the patients without scoliosis (p=0.001); however, no significant differences were noted between total femoral BMD values. Osteoporosis was determined in the lumbar vertebras of all patients with scoliosis; in one patient, it was found in both lumbar and femoral region (Z-score <-2.0). Only 4 patients without scoliosis had osteoporosis in lumbar vertebras (Table 4).

All of the patients were receiving oral deferasirox (20-40 mg/kg daily) for chelating therapy. None of our patients were radiologically diagnosed with congenital spinal defects and spinal fractures.

Discussion

In a healthy vertebral column, vertebras are lined up in a neutral position on frontal and transverse planes. In an anterior-posterior X-ray, all of the vertebras are noted as arranged in the same direction from C1 to L5. Disordered configuration of vertebral column in the frontal plane and the presence of an abnormal curvature is called scoliosis. It is the most common vertebral deformity (11,12). Scoliosis can be idiopathic (80%), or it can be seen as secondary (20%) to a number of diseases (10,11,12).

An increase in scoliosis incidents associated with thalassemia was reported approximately twenty years ago (3, 13). In Greece, the ratio of the patients who had at least 5° frontal curve was reported as 67% by Korovessis et al. (4), 67.7% by Papageorgiou et al. (14) and 79% by Dimitris et al. (3). In Turkey, this ratio was reported as 40% by Onur et al. (15). The ratio of the patients who had at least 10° frontal curve was reported 20.8% by Korovessis et al. (4), 29.5% by Papageorgiou et al. (14), 28% by Dimitris et al. (3) and 5% in the study from Turkey (15). In the present study, this ratio was 15.8%. Likewise, in a study from United States regarding children between the age of 5 and 14, the ratio of the patients who had frontal curve > 5^0 was reported as 4-5% and >10^0 frontal curve rate was 2% (16). Similarly, in a study conducted in our country regarding 6-13 years old children, the scoliosis ratio >5^0 was found as 1.07% (17). Our results demonstrated that the scoliosis rate in thalassemic children was significantly higher compared to the healthy children in the same age group. This finding supports the fact that scoliosis was significantly more common in the patients with thalassemia (3, 13). In the present study, the ratio of the patients with frontal curve was parallel to the similar studies conducted in Turkey; however, the ratio was higher in the Greek population. These differences between two countries can be attributed to genetic differences, narrow age range and small sample size of our study.

There are different findings from the studies regarding the association of scoliosis and the age of the patients with thalassemia (3, 4, 5, 14). Papageorgiou et al. reported that scoliosis in thalassemic children was first detected between the ages 3 and 7; and after 7 years, no increase in prevalence was seen (14). Likewise, in the study of Dimitris et al. it was demonstrated that the scoliosis ratio was not related to the age of the patients (3). On the other hand, Korovessis et al. observed that the age of thalassemic patients with scoliosis was significantly higher than those of the patients without scoliosis (5). In our study no significant differences between these two groups were noted and the spinal curve was diagnosed in very early years. Our findings were concordant with the previous studies, which demonstrated that the scoliosis rate was not associated to the age of the patient (3, 14).

In normal population, it is known that idiopathic scoliosis and the gender are associated and more the curvature is increased, more significant the association (18,19). In a study, the female/male ratio was reported as 1/1 in the angles 6^0 to 10^0, 1.4/1 in 11^0-20^0 and 5.4/1 in the angles over 21^0 (19). However, it was reported that there were no significant differences between two genders based on the development of scoliosis in thalassemic patients (3, 5, 15). There was also no significant difference between the genders in the present study; this can be attributed to the small spinal curve degree.

It was reported that hematological dysfunction might be responsible from the pathogenesis of scoliosis associated with thalassemia (3, 13). Korovessis et al. who investigated the association of scoliosis with the hematological levels demonstrated that Htc of thalassemic patients with scoliosis was significantly lower compared to the patients without scoliosis and the most of the skeletal abnormalities might be prevented by obtaining hemoglobin level of more than 10g/dL in the thalassemic patients (5). In the present study, Htc levels of scoliotic patients were found significantly lower

Table 1. Anthropometric features, treatment frequency and laboratory values of the patients with scoliosis.

Patient	Gender	Age (year)	Weight (cm)	Height (kg)	Vki kg/m²	Tx frequency (Tx/year)	Hct (37.7-53.7) %	Ferritin (13-300) ng/ml	FBG (74-102) mg/dL	ALT (10-49) U/L	AST (15-37) U/L	Ca (8.5-10.1) mg/ dL	P (2.4-5.1) mg/ dL	ALP (90-300) IU/L	TSH (0.7-6.4) uIU/ mL	sT4 (0.8-2.0) uIU/ mL	iPTH (9-52) qg/mL
1	Male	4	105	15.5	13.6	12	25.0 ↓	1308 ↑	98	40	37	8.8	5.3 ↑	208	2.20	1.02	41.8
2	Male	7	119	23	16.2	17	22.5 ↓	1276 ↑	102	25	32	8.5	3.9	227	3.40	0.80	28.9
3	Male	6	110	16	13.2	12	23.1 ↓	3805 ↑	73	29	35	8.9	3.5	258	2.70	1.20	80.0 ↑
4	Male	10	129	24	14.4	17	22.7 ↓	2492 ↑	85	25	43 ↑	8.5	4.2	212	3.20	0.90	34.7
5	Male	8	123	24	15.9	12	23.8 ↓	3195 ↑	76	27	25	9.6	4.9	244	2.07	1.08	13.2
6	Female	5	95	11	12.2	17	22.5 ↓	1743 ↑	82	20	43 ↑	8.0 ↓	5.1	240	2.10	1.10	86.0 ↑
7	Female	8	118	20	14.4	17	25.2 ↓	3710 ↑	94	25	23	8.7	5.6 ↑	307 ↑	5.02	1.17	51.0

Table 2. Anthropometric features, treatment frequency and laboratory values of the patients without scoliosis.

Patient	Gender	Age (year)	Weight (cm)	Heigt (kg)	Vki kg/m²	Tx frequency (Tx/year)	Hct (37.7-53.7) %	Ferritin (13-300) ng/ml	FBG (74-102) mg/dL	ALT (10-49) U/L	AST (15-37) U/L	Ca (8.5-10.1) mg/ dL	P (2.4-5.1) mg/ dL	ALP (90-300) IU/L	TSH (0.7-6.4) uIU/ mL	sT4 (0.8-2.0) uIU/ mL	iPTH (9-52) qg/mL
1	Male	5	105	12	10.9	12	25.70 ↓	717 ↑	98	40	37	8.7	4.9	152	2.10	0.80	47.0
2	Male	4	102	18	17.3	12	25.30 ↓	1432 ↑	91	22	20	9.3	4.1	132	2.57	0.80	43.8
3	Male	9	123	23	15.2	12	25.80 ↓	2623 ↑	106 ↑	38	31	9.0	4.7	203	2.30	1.40	35.9
4	Male	6	126	22	13.9	17	25.20 ↓	571 ↑	99	34	42 ↑	9.0	5.4 ↑	280	3.10	1.08	88.3 ↑
5	Male	7	121	21	14.3	12	29.70 ↓	4853 ↑	92	31	22	8.8	5.2 ↑	199	3.87	1.02	35.3
6	Male	7	114	19	14.6	12	24.90 ↓	217	86	18	31	9.2	4.7	176	4.50	1.01	46.0
7	Male	6	114	18	13.9	12	24.39 ↓	681 ↑	73	17	19	9.4	6.3 ↑	138	0.50 ↓	1.68	45.0
8	Male	6	109	17	14.3	12	24.25 ↓	501 ↑	90	15	22	8.7	3.3	62 ↓	3.60	1.50	42.0
9	Female	8	124	23	10.9	17	25.90 ↓	1201 ↑	82	20	43 ↑	9.3	4.5	156	4.70	1.60	53.4 ↑
10	Female	11	153	38	16.2	17	24.70 ↓	499 ↑	84	14	26	9.2	4.3	227	2.60	1.40	33.7
11	Female	14	150	40	17.8	17	24.39 ↓	681 ↑	78	23	25	9.4	6.3 ↑	138	0.50 ↓	1.68	45.0
12	Female	6	120	20	13.9	17	24.25 ↓	501 ↑	84	33	19	8.7	3.3	62 ↓	3.60	1.50	42.0

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Table 3. The comparison of the anthropometric features, laboratory and BMD values of two groups (*p<0.05).

	Patients with scoliosis (n=7) (Mean±SD)	Patients without scoliosis (n=12) (Mean±SD)	P
Age (year)	6.85 ± 2.03	7.41 ± 2.77	0.649
Weight (cm)	114.14 ± 11.58	121.75 ± 15.82	0.284
Heigt (kg)	19.07 ± 5.03	22.58 ± 8.25	0.325
VKİ (kg/m²)	14.27 ± 1.43	14.77 ± 1.79	0.536
Tx frequency (Tx/year)	14.85 ± 2.67	14.08 ± 2.57	0.541
Hct (%)	23.54 ± 1.15	25.46 ± 1.46	0.009*
Ferritin (ng/ml)	2504.14 ± 1091.03	1218.08 ± 1309.04	0.043*
FBG (mg/dL)	87.14 ± 11.11	88.58 ± 9.37	0.929
ALT (U/L)	27.28 ± 6.23	25.41 ± 9.26	0.884
AST (U/L)	34.00 ± 7.93	28.08 ± 8.69	0.124
Ca (mg/ dL)	8.71 ± 0.48	9.12 ± 0.33	0.044*
P (mg/ dL)	4.64 ± 0.78	4.64 ± 0.78	0.997
ALP (IU/L)	242.28 ± 33.58	183.50 ± 61.16	0.033*
TSH (uIU/ mL)	2.95 ± 1.05	3.05 ± 1.22	0.862
sT4 (uIU/ mL)	1.03 ± 0.14	1.19 ± 0.31	0.286
iPTH (qg/mL)	47.94 ± 26.67	46.52 ± 14.45	0.881
BMD g/cm2 Lumber (1-4)	0.380 ± 0.047	0.511 ± 0.076	0.001*
BMD g/cm2 Total femur	0.565 ± 0.110	0.602 ± 0.081	0.402

Table 4. Lumber (L1-4) and total femoral BMD values, Z-scores Cobb angles and vertebral rotation degree of the patients*.

Patient	BMD g/cm² Lumber(1-4)	DXA Z-skores Lumber(1-4) (> -2)	BMD g/cm² Femur total	DXA Z-skores Femur total (> -2)	Cobb angles	Vertebral rotation degree
1	0.333	-3.6 ↓	0.510	Do not calculate	5°- 9°	-
2	0.430	-2.6 ↓	0.708	1.1	5°- 9°	-
3	0.403	-2.5 ↓	0.530	-1.1	5°- 9°	-
4	0.312	-6.7 ↓	0.420	-3.5 ↓	10°- 19°	5°
5	0.440	-2.6 ↓	0.710	1.1	10°- 19°	-
6	0.381	-2.9 ↓	0.491	-0.7	10°- 19°	3°
7	0.365	-2.9 ↓	0.586	-0.3	5°- 9°	-
8	0.390	-2.8 ↓	0.590	-0.2	-	-
9	0.456	-1.5	0.526	Do not calculate	-	-
10	0.498	-2.1 ↓	0.604	-1.7	-	-
11	0.418	-2.5 ↓	0.544	-1.0	-	-
12	0.472	-1.9	0.564	-1.2	-	-
13	0.510	-1.7	0.550	-0.7	-	-
14	0.532	-0.7	0.531	-0.4	-	-
15	0.480	-1.2	0.630	-0.9	-	-
16	0.627	-0.1	0.642	-0.5	-	-
17	0.585	-2.0	0.677	-1.3	-	-
18	0.634	-2.5 ↓	0.813	-0.8	-	-
19	0.540	-0.5	0.562	-0.2	-	-

* Total femoral DXA Z-scores of the patients under 5-years were not shown in the Table since the machine do not calculate.

than those of the patients without scoliosis. Our results support the theory which anemia might also play a role in the etiology of scoliosis of thalassemic patients (4, 5, 6, 14, 20).

It was noted that iron deposition in the bone and the connective tissues in the thalassemic patients might encourage the scoliosis development (3, 5). Iron storage in the bones causes impairment of mineralization (21,22). Furthermore, iron overload decreases the unit stretching resistance of the bone. This impairment of mineralization and decrease in the resistance might facilitate of deformity development (13, 23, 24). Korovessis et al. reported that ferritin levels of the thalassemia patients with scoliosis were significantly higher than those of the patients without scoliosis (5). In concordant with these findings, our results also showed that ferritin levels of the patients with scoliosis were significantly higher compared to the other group. It is thought that the excessive iron deposition in the structural elements that consist the vertebral column facilitates the development of scoliosis by impairing the stability and strength of the vertebrae (3, 4, 25).

Increased bone catabolism and diminished bone mineralization occur as a result of various genetic and acquired factors in thalassemic patients (20, 26). DXA of the spine/hip is considered a gold standard for BMD assesment, but the vertebral axial rotations accompanying the sagittal and frontal plane changes in spine contour might influence the truth of BMD assessed by DXA (27). The degree of spinal rotation influences apparent bone mineral density by increasing the apparent vertebral segment area (28). Larnach et al. found that vertebral rotation of more than 8° would lead to errors in BMD assessment (29). Snyder et al. showed that axial rotations up to 25° had little effect (10%) on the vertebral body BMD (30). In our series, the maximum axial rotation of scoliosis patients was 5°. It was concluded that the vertebral rotation did not significantly affect the BMD values of our patients, based on the results of the published articles.In the present study, lumbar BMD values of the patients with scoliosis were found significantly lower, whereas there was no significant difference between the femoral BMD . It has been reported that children with beta-thalassemia major have low z- score value at lumbar spine compared to femur (31). This may be explained in terms of the nature of beta-thalassaemia major where trabecular bones such as lumbar vertebrae are mainly affected by bone marrow expansion because of ineffective haematopoiesis (32). In the light of recent findings, it was thought that the significant decrease in the BMD values of lumber vertebrae in our patients was secondary to the disease, instead of the technical difficulties. Decrease in BMD increases the incidence of scoliosis and skeletal deformities (23). Various studies investigating the association of idiopathic adolescent scoliosis and BMD demonstrated that diminished BMD of the individuals with idiopathic adolescent scoliosis was general and persistent and reported as an important risk factor in the increase of scoliotic curvature angle (33,34). In the light of our results, it can be concluded that decreased BMD is a risk factor in development of scoliosis.

Calcium levels of the scoliotic group were lower than the group without scoliosis; on the other hand, ALP levels were higher and the differences were statistically significant. The cause of these differences might be the decreased BMD values of the scoliotic group. Furthermore, it was reported that rickets can develop in thalassemic children due to impaired bone mineralization (7, 25) and the risk of spinal deformities in children with rickets is higher (23). However, none of our patients was diagnosed with rickets. Prospective studies with larger sample sizes investigating the association of scoliosis and rickets in thalassemic children will be helpful to enlighten the connection.

In conclusion, the scoliosis ratio was found higher than the normal population in our patients with thalassemia. Lower hematocrit, calcium and BMD and higher ferritin and alkaline phosphatase levels might play a role in the development of scoliosis. In the follow-up of thalassemic children, not only close monitoring the BMD values, but also adequate transfusion, effective chelating treatment can help the prevention of scoliosis. This theory needs supportive data from new studies. Our data should be supported by prospective studies with larger sample sizes, with the focus of investigation in the association of scoliosis and rickets, vitamin D level and postural exercises.

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