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Topographic and refractive findings in osteogenesis imperfecta

Osteogenezis imperfektada topografik ve refraktif bulgular

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ABSTRACT

Aim: *To research ocular findings in patients with osteogenesis imperfecta (OI).*

Methods: *Patients were grouped according to the type of OI. Age and gender data were noted. Refraction, intraocular pressure (IOP), and central corneal thickness (CCT) values were measured. Corneal topography images were obtained. Fundus examinations were made in all patients. Best corrected visual acuity (BCVA) and spherical equivalent (SE) values were recorded. Data about patients' scleral color changes were noted.*

Results: *In this study, 30 eyes from 15 patients were examined. Of the 15 patients, 8 had OI Type 1, 5 had OI Type 4, and 2 couldn't be classified by Sillence's classification. One of these patients had a FKBP10 and the other a WNT1 mutation. The minimum CCT was 397 µm and maximum was 588 µm. Average CCT was 492±67.49 µm. Corneal apex keratometry (K) and corneal astigmatism values were higher for the OI Type 4 group than Type 1 ($p<0.01$, $p<0.05$, respectively). BCVA values were significantly higher in the OI Type 1 group than the OI Type 4 ($p=0.002$) Out of 30 eyes, 8 had blue sclera (26.7%). All of the patients with blue sclera had OI Type 1. There was no significant difference in terms of CCT, posterior elevation values, or corneal astigmatism values between patients with and without blue sclera ($p>0.05$). Corneal apex K value was statistically lower in the patients with blue sclera ($p<0.05$).*

Conclusion: *Our findings in patients with OI included thinner CCT, blue sclera, steep K values especially in Type 4 group. So patients should be followed regularly for keratoconus. Because of corneal thinning, physicians must be aware of underestimation of IOP. Patients and their relatives should be advised to use protective glasses for probable trauma.*

Keywords: *Osteogenesis imperfecta, keratoconus, blue sclera, topography, refraction*

ÖZ

Amaç: *Osteogenezis imperfekta hastalarında oküler bulguları incelemek amaçlanmıştır.*

Yöntemler: *Hastalar Osteogenezis imperfekta (OI) tiplerine göre gruplandırıldı. Yaş ve cinsiyetleri not edildi. Refraksiyon, göz içi basıncı (GİB) santral korneal kalınlık (SKK) değerleri ölçüldü. Korneal topografi görüntüleri alındı. Tüm hastaların fundus muayeneleri yapıldı. Sferik eşdeğerleri ve en iyi düzeltilmiş görme keskinlikleri (EDGK) kaydedildi. Hastalarda skleral renk değişikliği olup olmadığı not edildi.*

Bulgular: *Bu çalışmada, 15 hastanın 30 gözü incelenmiştir. On beş hastanın 8'i Tip 1 OI, 5'i Tip 4 OI ve 2'si de Sillence sınıflandırma sistemine göre sınıflandırılamadı. Sınıflandırılamayan hastaların birinde FKBP10 mutasyonu ve diğerinde WNT1 mutasyonu vardı. Santral korneal kalınlık minimum 397 µm iken, maksimum 588 µm'di. Ortalama santral korneal kalınlık 492±67,49 µm'di. Korneal apeks keratometri (K) ve korneal astigmatizma değerleri Tip 4 OI grubunda Tip 1 OI grubuna göre daha yüksek bulunmuştur (sırasıyla $p<0,01$, $p<0,05$). EDGK Tip 1 OI grubunda Tip 4 OI grubuna göre anlamlı olarak daha yüksek bulunmuştur ($p<0,01$). Çalışmaya alınan 30 gözden 8'inde mavi sklera saptanmıştır (%26,7). Mavi sklerası olan hastaların tamamı Tip 1 OI hastasıdır. Mavi sklerası olan ve olmayan hastalar arasında SKK, posterior elevasyon veya korneal astigmatizma değerleri açısından anlamlı fark saptanmamıştır ($p>0,05$). Korneal apex K değerleri mavi sklerası olan hastalarda istatistiksel anlamlı derecede düşüktü ($p<0,05$).*

Sonuç: *OI hastalarında bulgularımız daha ince SKK, mavi sklera ve özellikle Tip 4 OI hastalarında dik K değerleridir. Bu nedenle hastalar keratokonus açısından düzenli takip edilmelidir. İnce SKK nedeniyle yalancı göz içi basıncı düşüklüğüne karşı dikkatli olunmalıdır. Olası bir travmaya karşı hasta ve hasta yakınlarına koruyucu gözlük kullanımı önerilmelidir.*

Anahtar kelimeler: *Osteogenesis imperfekta, keratokonus, mavi sklera, topografi, refraksiyon*

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INTRODUCTION

Osteogenesis imperfecta (OI) is a connective tissue disorder that occurs because of impaired collagen production and metabolism. It increases bone fragility and is accompanied by blue sclera and deafness[1]. It was first reported at the end of the 18th century, and in 1918, Van der Hoeve was the first to describe it as a clinical syndrome. There is no gender or racial dominance, and it has autosomal dominant inheritance. There are also rare reports of autosomal recessive and sporadic cases[2]. Its incidence is between 1:15000 and 1:20000, but the real incidence may be higher because of undiagnosed, mild-type cases[3]. Sillence classified the disease into 4 subtypes by clinical and radiological findings. OI Type 1 is mild, OI Type 2 is prenatal lethal, OI Type 3 is progressive and leads to deformities, and OI Type 4 results in moderate deformities. COLA1/COLA2 gene mutations are present in 90% of the patients. However, various new mutations have been identified; therefore, classification has recently been expanded[5].

The most frequent ophthalmic finding is blue sclera. Blue sclera is seen in OI Type 1 patients but doesn't occur in OI Type 4 patients. There is a weak correlation between blue sclera and other findings of the disease[6]. Another important and common ocular finding in this disease is thinning in the central corneal thickness (CCT)[1,7,8]. Other ocular findings include decreased ocular rigidity, myopia, glaucoma, keratoconus, corneal opacities, small corneal radius, congenital Bowman's layer agenesis, and posterior embryotoxon[1,9]. Congenital glaucoma, zonular cataract, choroidal sclerosis, subhyaloid hemorrhage, ectopia lentis, optic neuropathy, or atrophy because of compression deformities and cranial fractures are other ophthalmologic disorders that rarely occur with OI[9].

In this study, our aim was to research ocular findings in children with OI at our hospital's pediatric clinic.

MATERIAL and METHODS

Thirty eyes of 15 patients were included in this study. Local ethics committee approval was obtained for the study. The ethical principles of Helsinki declaration were followed during the study. All patients were examined by the same physician in the same room and at the same time of the day. Patients with history of dry eye and corneal injury, patients who used topical eye drops or contact lenses, and patients who were examined with gonioscopy were excluded from the study. Patients were divided into groups by Sillence classification. Ages and genders of the patients were noted. Firstly, 1% tropicamide and 1% cyclopentolate hydrochloride were both instilled once at 5 minute-intervals aparts, and after 30 minutes, refractive values were measured with a Canon RK-F1 autorefractometer (Canon, Tokyo, Japan). The best corrected visual acuity (BCVA) was obtained with a Snellen chart according to refractive values. Corneal apex, posterior elevation, corneal astigmatism values, and CCT were measured 3 times with Sirius topography (Costruzione Strumenti Oftalmici, Florence, Italy), and mean values were recorded. Intraocular pressure (IOP) was measured with a Topcon CT 80 non-contact tonometer (Topcon, Tokyo, Japan), and the corrected IOP levels were calculated by the CCT. Fundus examinations were made with a 90D lens at biomicroscopy.

Descriptive statistics such as mean along with standard deviation, minimum, maximum values and median were reported for the data. Kolmogorov-Smirnov test was used to test normality of the distributions. Mann-Whitney test was used to compare groups for quantitative variables, and for nominal variables we used chi-square test. Hypothesis test results with $p<0.05$ was considered to be statistically significant. SPSS 22.0 (SPSS, Inc., Chicago, Illinois) was used for statistical analysis.

RESULTS

A total of 30 eyes from 15 patients were included in the study. Of these 15 patients, 8 had OI Type 1, 5 had OI Type 4, and 2 couldn't be classified by Sillence's classification. One of that patients had an FKBP10 mutation, and another one a WNT1 mutation. Mean age of the patients was 15.3±5.4 years. Mean val-

Table 1. Characteristics of patients.

	Min-Max	Median	Mean±S.D/n-%	
Age	8.0-29.0	16.0	15.3±5.4	
SE (D)	-4.5-0.6	-0,1	-0.5±1.2	
BCVA (Snellen)	0.3-1.0	1.0	0.8±0.2	
CCT (µm)	397-588	481	492±67	
IOP (mmHG)	9.0-22.0	16.0	16.1±2.6	
Blue Sclera				
(-)			22	73.3%
(+)			8	26.7%
Gender				
Female			8	26.7%
Male			22	73.3%

ues for spherical equivalent (SE) (-0.5±1.2 D), BCVA (0.8±0.2), IOP (16.1±2.6 mmHg) were as indicated. The lowest CCT value was 397 µm, and the highest value was 588 µm. Mean CCT was 492±67.49 µm. For 16 eyes of 8 patients, the CCT values were under 500 µm. Of these patients, 6 had CCT values under 450 µm and 1 had a CCT value under 400 µm. Blue sclera was discovered in 8 eyes of 4 patients (26.7%). All of these patients were classified as OI Type 1. Also, 50% of all of the OI Type 1 patients had blue sclera. Characteristics of the patients are shown in Table 1.

When OI Type 1 and Type 4 patients were compared, there were no statistically significant differences in terms of age, gender, SE, IOP, or CCT values . BCVA was significantly higher in the OI Type 1 group than the OI Type 4 group (p<0.01; Table 2). In our topography measurements, there was no significant difference between groups in terms of posterior elevation (p=0.417) but there was a statistically significant difference in terms of corneal apex keratometry (K) and corneal astigmatism values (p<0.01, p<0.05, respec-

Table 3. Topographic values of OI Type 1 and Type 4 patients.

	N	Mean	Median	Std. Deviation	Min.	Max.
Type 1						
Corneal Apex K (D)	16	44.34	44.21	2.06	42	50
Posterior Elevation (µm)	16	9.44	9	2.4	7	15
Corneal Astigmatism (D)	16	0.72	0.63	0.33	0.24	1.3
Type 4						
Corneal Apex K (D)	10	47.99	47.64	1.76	46	51
Posterior Elevation (µm)	10	10	9.5	2.26	6	14
Corneal Astigmatism (D)	10	2.03	2.73	1.20	0.1	3.15

K: keratometry, D: dioptry

Table 2. Comparison of OI Type 1 and Type 4 patients.

	Type 1			Type 4			
	Mean±S.D./n-%	Med	(Min-Max)	Mean±S.D./n-%	Med	(Min-Max)	p
Age	14.4±3.5	15.5	8.0- 19.0	12.6±3.6	12	8- 17	0.337
SE (D)	-0.1±0.5	-0.1	-1.4- 0.6	-0.3±0.8	0,0	-1.8- 0.6	0.874
BCVA(Snellen)	0.96±0.12	1.00	0.66- 1.00	0.70±0.21	0.63	0.50- 1.00	0.002
CCT (µm)	461±44	441	406- 534	508±79	549	397- 588	0.108
IOP (mmHG)	16.2±3.1	16.5	9.0- 22.0	16.0±1.9	16.0	13.0- 18.0	0.810
Gender							
Female	4	25%		4	40%		0.420
Male	12	75%		6	60%		
Blue Sclera							
(-)	8	50%		10	100%		0.007
(+)	8	50%		0	0%		

SE: spherical equivalent, BCVA: best corrected visual acuity, CCT: central corneal thickness IOP: intraocular pressure, D:dioptry

tively; Table 3). Corneal apex K and corneal astigmatism values were higher in the OI Type 4 group than the Type 1 group.

There was no significant difference in terms of posterior elevation values and corneal astigmatism values between patients with and without blue sclera (p=0.141, p=0.674, respectively). Contrary to expectations, this meant that CCT was higher in the patients with blue sclera than the patients without blue sclera (508.2±71.9 µm vs. 449.3±21.1 µm), but the difference was not significant (p=0.318). However, the corneal apex K value was significantly different between these two groups (p<0.05; Table 4).

Table 3. Topographic values of OI Type 1 and Type 4 patients.

	N	Mean	Median	Std. Deviation	Min.	Max.
Blue sclera (+) Pachymetry (µm)	8	449.3	441.0	21.1	428	482
Corneal Apex K (D)	8	44.07	44.28	21.1	42	46
Posterior Elevation (µm)	8	8.5	9	1.30	7	10
Corneal Astigmatism (D)	8	0.849	0.83	0.37	0.38	1.3
Blue sclera (+) Pachymetry (µm)	18	508.2	532.5	71.9	397	588
Corneal Apex K (D)	18	46.49	46.64	2.68	42	51
Posterior Elevation (µm)	18	10.17	9.5	2.57	6	15
Corneal Astigmatism (D)	18	1.39	0.89	1.15	0.1	3.15

K: keratometry, D: dioptry

Funduscopic examination revealed bone spicules in both eyes of a patient. Also, FKBP mutation was present, and altered electroretinogram values were compatible with retinitis pigmentosa. There was no significant retinal pathology in the fundoscopies of other patients.

DISCUSSION

The cornea and sclera consist of collagen. Therefore, it is expected to see corneal and scleral abnormalities in OI. In their study, Heabra et al. found immature collagen structures in patients with OI (10). In research on postmortem tissues from 4 OI Type 4 patients by Chan et al. and research on OI Type 3 patients by Miatz et al., it was indicated that there was a 25% decrease in collagen fiber diameters, 50% decrease in scleral fibers, and a decrease in collagen cross linings. These authors also stated that scleral collagen alignment becomes more uniform and scleral light transmission increases, causing underlying uveal tissue to become visible, which is the reason why sclera appears to be blue in OI patients[11,12].

In the present study, there were 8 eyes with blue sclera. All of these patients were in the OI Type 1 group, and 50% of OI Type 1 patients had blue sclera. In our opinion, evaluation of blue sclera in OI patients is a subjective method, and this leads to inconsistencies in literature data. Evereklioğlu et al. compared CCT of 12 OI Type 1 patients with blue sclera and 11 OI Type 4 patients without blue sclera with a healthy control group by using ultrasonic pachymetry. They found that in 95.6% of patients, CCT thickness was under 500 µm, and in 65.2% of patients, CCT thickness was under 450 µm. Also, when they compared these findings with the control group, they found statistically significant thinning in OI patients. Mean CCT in the Type 1 patients with blue sclera (446.5±16.3 µm) was thinner than in the Type 4 patients without blue sclera (473.6±25 µm), and this difference was statistically significant[1].

In the present study, CCT was under 500 µm in 16 eyes out of 30 (53%). Mean CCT was 461±44 µm in the Type 1 group and 508±79 µm in Type 4 group. Mean CCT was thinner in the Type 1 group, but this difference wasn't statistically significant. Evereklioğlu et al. found no significant difference in the terms of IOP between Type 1 and Type 4 patients. However, mean IOP of OI patients (12.7±1.8 mmHg) was lower than mean IOP of the control group (15.6±1.9 mmHg), and this difference was statistically significant[1]. In the present study,

mean IOP was 16.1±2.6 mmHg in all of the patients: 16.2±3.1 mmHg in Type 1 patients and 16.1±1.9 mmHg in Type 4 patients. There was no control group in the present study, so we did not have the opportunity to compare our findings with a healthy population.

Evereklioğlu et al. compared the SE of eyes in Type 1, Type 4, and control groups and found no significant differences between them. Also, the mean refractive error was -0.32±0.5 D, and visual acuity was between the 20/40 and 20/20 range in 91.3% of the patients. In our study, mean spherical equivalence was -0.5±1.2 D, and mean BCVA was 0.8±0.2. There was no statistically significant difference between Type 1 and Type 4 patients in term of mean spherical equivalence but BCVA was significantly higher in the OI Type 1 group than the OI Type 4 group.

In Type 4 patients, the corneal apex K value was 47.99 D and corneal astigmatism was 2.0 D. These were statistically significantly higher than in OI Type 1 patients. Lower BCVA values in the Type 4 patients could be related to this difference. However, there was no statistically significant difference in terms of CCT and posterior elevation.

In this study, CCT, corneal apex K value, corneal astigmatism, and posterior elevation values were lower in the patients with blue sclera than the patients without blue sclera, but only the difference in the corneal apex K value was statistically significant. When we evaluated all of the topographical findings, we could not reach a clear conclusion about the difference between groups regarding the risk of development up keratoconus. The low number of patients in our study was a limiting factor, so studies with higher sample sizes are needed to evaluate the relationship between corneal ectasia and blue sclera.

CONCLUSION

In addition to blue sclera, plenty of ophthalmological findings can be seen in OI patients. One of the most important finding in OI is thinning in the CCT. Therefore, ophthalmologists should be cautious about underestimation of the IOP. CCT must be considered in OI patients who are candidates for refractive surgery. Patients should be warned about the use of protective glasses to prevent ocular traumas because eye rupture can occur more easily than in healthy patients and cause serious morbidities. Our findings in patients with OI were steep K values especially in Type 4 group.So patients should be followed up regularly for keratoconus.

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