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ABSENCE OF FOVEAL DEPRESSION AND ITS ASSOCIATION WITH REFRACTIVE STATUS AND STRABISMUS IN CHILDREN WITH HISTORY OF RETINOPATHY OF PREMATURITY

PREMATÜRE RETİNOPATİSİ ÖYKÜSÜ OLAN ÇOCUKLARDA FOVEAL DEPRESYON YOKLUĞUNUN REFRAKTİF KUSURLAR VE ŞAŞILIK İLE İLİŞKİSİ

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ABSTRACT

Objective: To evaluate the foveal depression (FD) status on optical coherence tomography (OCT) and its relationship with strabismus, amblyopia and refractive errors in children with a history of retinopathy of prematurity (ROP).

Material and Method: Medical records were reviewed for demographic data, ocular and medical history, systemic disorders, ophthalmologic and OCT findings. Patients were categorized into two groups according to foveal depression status on OCT: absence of FD (Non-FD Group) and presence of FD (FD Group). Demographic data, refractive errors (RE), strabismus, amblyopia and anisometropia were compared between the groups.

Result: Mean age of the patients was 11.1±2.7 years in the Non-FD group and 10.1±2.9 years in the FD group (p=0.136). Mean gestational age (GA) at birth and birth weight (BW) of the Non-FD group (28.8±2.7 weeks, 1269.1±455.5 grams) were significantly lower than those of the FD group (30.8±2.1weeks, 1530.8±415.2 grams) (p=0.002 and p=0.02, respectively). Although there was no significant difference between the groups in the mean spherical equivalent (SE) RE (-1.19± 4.86D in the Non-FD group and 0.77±4.08D in the FD group, p=0.09), the distribution of SE refractive errors was significantly different (p=0.001). 54.5% of patients in the Non-FD group had myopia and 72% of the patients in the FD group had hypermetropia. Mild myopia was significantly more in the Non-FD group and mild hypermetropia was significantly more in the FD group (p<0.05 for both). Astigmatism equal or greater than 1.50D was detected in

ÖZET

Amaç: Prematüre retinopatisi (ROP) öyküsü olan çocuklarda optik koherens tomografide (OKT) foveal depresyon (FD) durumunu ve şaşılık, ambliyopi ve refraktif kusurlar ile ilişkisini değerlendirmek.

Gereç ve Yöntem: ROP öyküsü olan hastaların klinik kayıtlarından; demografik veriler, oküler ve medikal öykü, sistemik hastalıklar, oftalmolojik ve OKT bulguları incelendi. Hastalar OKT'de FD durumuna göre iki gruba ayrıldı: FD yokluğu (Non-FD Grup) ve FD varlığı (FD Grup). Demografik veriler, refraktif kusurlar, şaşılık, ambliyopi ve anizometropi iki grup arasında kaşılaştırıldı.

Bulgular: Hastaların ortalama yaşı; Non-FD grupta 11,1±2,7 yıl, FD grupta 10,1±2,9 yıl idi (p=0,136). Ortalama doğum haftası (DH) ve doğum ağırlığı (DA) Non-FD grupta (28,8±2,7 hafta, 1269,1±455,5 gram) FD gruba göre (30,8±2,1 hafta,1530,8±415,2 gram) anlamlı olarak daha düşüktü (p=0,002, p=0,02). Ortalama sferik ekivalan (SE) refraktif kusurlar gruplar arasında anlamlı farklılık göstermemekle birlikte (Non-FD grupta -1,19±4,86D, FD grupta 0,77±4,08D, p=0,09), SE refraktif kusurların dağılımı anlamlı olarak farklıydı (p=0,001). Non-FD grubun %54,5'inde miyopi, FD grubun %72'sinde hipermetropi mevcuttu. Hafif miyopi Non-FD grupta, hafif hipermetropi FD grup'ta daha fazla saptandı (p<0,05). Non-FD grubun %56,5'inde, FD grubun %36'sında 1,50D ve üzeri astigmatizma mevcuttu (p>0,05). Şaşılık, ambliyopi ve anizometropi insidasında gruplar arasında anlamlı fark saptanmadı (p>0,05).

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56.5% of the Non-FD group and 36% of the FD group (p>0.05). There was no significant difference between the groups in the incidence of strabismus, amblyopia and anisometropia (p>0.05).

Conclusion: We detected lower GA and BW in the Non-FD group than those of the FD group. Myopia is more prevalent in patients with a history of ROP and absence of FD than in those with a normal foveal structure.

Keywords: Retinopathy of prematurity, optical coherence tomography, myopia, astigmatism, strabismus, refractive errors

Sonuç: FD yokluğu olan hastalarda daha düşük doğum haftası ve doğum ağırlığı saptanmıştır. ROP öyküsü olan hastalarda FD yokluğu eşlik etmesi durumunda, normal foveal yapı gösterenlere göre daha sık miyopi izlenmiştir.

Anahtar Kelimeler: Prematüre retinopatisi, optik koherens tomografi, şaşılık, refraktif bozukluk

INTRODUCTION

Long-term ophthalmologic pathologies associated with retinopathy of prematurity (ROP) have been more prevalent with improvement in neonatal care. The ROP associated ocular pathologies are strabismus, amblyopia, refractive errors, retinal detachment, cataracts and glaucoma (1-3). In recent years, the development of imaging technology has allowed the foveal structure to be evaluated in detail, and structural abnormalities such as foveal dysplasia and absence of foveal depression (FD) can be detected in patients with a history of ROP (4-7). Absence of FD has also been reported in healthy children and children without a history of ROP (6).

In previous studies, optical coherence tomography (OCT) findings were evaluated according to ROP status and/or ROP treatment. The aim of this study is to evaluate the FD status on OCT and its relationship with strabismus, amblyopia and refractive errors in children with a history of ROP.

MATERIAL and METHODS

The study was carried out retrospectively in the Department of Ophthalmology, Istanbul University, Istanbul Faculty of Medicine. Clinical records of 90 children with a history of ROP were reviewed for demographic data, medical history, systemic disorders, ocular and OCT findings. Ophthalmologic examination including best corrected Snellen visual acuity (BCVA), biomicroscopic and fundus evaluation, cycloplegic autorefraction and strabismus testing (Hirschberg, prism cover and/or Krimsky testing) was performed. Gestational age (GA) at birth, birth weight (BW), presence of ROP and treatment for ROP, BCVA, cycloplegic autorefraction and presence of strabismus, amblyopia and anisometropia were recorded.

For pupil dilation, 1% cyclopentolate was applied 3 times at 5-minute intervals. Cycloplegic autorefraction by an automatic keratorefractometer (ARK-530A, Nidek, Gamagori Aichi, Japan) was performed 30 minutes after the last drop was instilled. Visual acuity values obtained using the Snellen chart were converted to the logarithm of the minimum angle of resolution (logMAR).

Central macular thickness (CMT) and FD status were analyzed from OCT scans obtained with spectral-domain optical coherence tomography (SD-OCT) (Heidelberg Engineering, Heidelberg, Germany). Automated retinal thickness map was used in OCT analysis. The retinal thickness map consists of inner, middle, and outer rings with radii of 1 mm, 3 mm, and 6 mm, respectively, corresponding to the foveal, parafoveal, and perifoveal areas. CMT was defined as the mean thickness within the inner circle. FD was determined by subtracting CMT from mean parafoveal thickness. Values less than 56.4 µm were defined as an absence of FD as reported before (6).

All patients with systemic or neurologic disorders (hydrocephalus, epilepsy, cerebral palsy, mental-motor retardation), history of intraocular surgery and all eyes with abnormal retinal findings (retinal detachment, retinal traction, macular folds and dragging) and poor OCT image quality were excluded from the study. Patients were categorized into 2 groups: presence of FD (FD group) (Figure 1A), absence of FD (non-FD group) (Figure 1B). Spherical, cylindrical and spherical equivalent (SE) refractive errors were recorded for each eye. SE refractive errors were categorized into 3 groups: emmetropia (-0.74

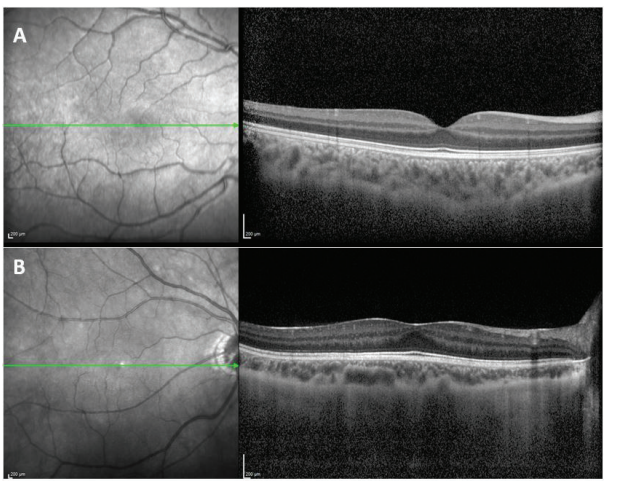

Figure 1: Optical coherence tomography images of the patients in foveal depression (FD) group (A) and non-foveal depression (non-FD) group (B)

diopters [D] to +0.74D), myopia (mild:-0.75D to -2.99D, moderate: -3.00D to -5.99D, high: -6D or more extreme), hypermetropia (mild: +0.75D to +2.99D, moderate: +3.00 D to +4.99D, high: +5.00D or more extreme). Astigmatism was categorized into 3 groups: mild (0.25 to 1.49D), moderate (1.5 to 2.99D) and high (3D or more extreme).

Ophthalmologic findings and OCT scans were recorded for both eyes of all patients.

One eye of each patient was randomly selected and included in the analysis.

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 27.05.2022, No: 10). Prior to treatment for ROP, patients' families or caregivers gave written informed consent.

A statistical software package (SPSS for Windows, v. 21.0, IBM Corp, ARMONK, NY: USA) was used for statistical analysis. Fischer's Exact test, Student's T-test, Mann-Whitney U test and Pearson Chi-Square test were performed to compare the numerical variables among 2 groups. Post-hoc analysis was used to evaluate the distribution of spherical refractive errors. Results of $p < 0.05$ were considered significant.

RESULTS

Seventy one patients (71 eyes) were included in the study. There were 46 patients in the Non-FD group and 25 patients in the FD group. Mean age of the patients at the last examination was 11.1±2.7 years in the Non-FD group and 10.1±2.9 years in the FD group (p=0.136). Mean GA and mean BW of the Non-FD group were significantly lower than those of the FD group (p=0.002 and p=0.02, respectively). There was no significant difference between the two groups in terms of gender distribution (p=0.08). Thirty-two patients (69.6%) in the Non-FD group and 12 patients (48%) in the FD had history of laser treatment for ROP (p=0.074). Of the patients who underwent laser treatment in the Non-FD group; 6 had zone 1 aggressive ROP, 4 had zone 2 stage 2 ROP with plus disease, 22 had zone 2 stage 3 ROP with plus disease.

All patients who underwent laser treatment in the FD group had zone 2 stage 3 ROP with plus disease. The demographic data of the patients in the groups are shown in Table 1.

At last examination, the mean logMAR BCVA of the patients was 0.14±0.17 LogMAR in the Non-FD group and 0.18±0.32 LogMAR in the FD group (p=0.467). Mean spherical equivalent (SE) refractive error of the patients was -1.19±4.86D in the Non-FD group and 0.77±4.08D in the FD group (p=0.09). 54.5% of the patients in the Non-FD group had myopia and 72% of the patients in the FD group had hypermetropia. Distribution of SE refractive errors was significantly different between two groups (p=0.001). Mild myopia was significantly more in the Non-FD group and mild hypermetropia was significantly more in the FD group ($p<0.05$ for both in post-hoc analysis). Strabismus was detected in 45.6% of patients in the Non-FD group and 44% of patients in the FD group (p=0.894). Esotropia was the most detected type of strabismus in both groups. There was no significant difference between the groups in terms of amblyopia and anisometropia (p=0.565 and p=0.562, respectively). Refractive errors, strabismus and amblyopia distributions of the groups are shown in Table 2.

Mean CMT of the patients was 312.5±31.1 µm in the Non-FD group and 272.8±24.4µm in the FD group ($p<0.001$). Mean foveal depression of the patients was 32.6±17.1µm in the Non-FD group and 70.5±11.9µm in the FD group ($p<0.001$).

When the patients who underwent laser treatment were compared, spherical equivalent refractive error distribution, mean CMT and foveal depression were found to be significantly different between the groups (p=0.043, p=0.001 and $p<0.001$, respectively). The demographic data, refractive errors, strabismus and amblyopia distributions of the patients who underwent laser treatment in

Table 1: Demographic data analysis of the groups

	Non-FD group (n=46)	FD group (n=25)	P values
Gestational age (weeks)	28.8±2.7	30.8±2.1	0.002[a]
Birth weight (grams)	1269.1±455.5	1530.8±415.2	0.020[a]
Gender			
Female, n (%)	20 (43.5)	16 (64)	0.080[b]
Male, n (%)	26 (56.5)	9 (36)	
Laser treatment, n (%)	32 (69.6)	12 (48)	0.074[c]
Laser treatment week	36.3±2.4	36.2±1	0.840[a]

FD: Foveal depression, [a]: Student t test, [b]: Fischer's exact test, [c]: Chi square test

Table 2: Refractive errors, strabismus and amblyopia distributions of two groups

	Non-FD group (n=46)	FD group (n=25)	P values
LogMAR BCVA (Snellen BCVA) (mean ± standard deviation)	0.14±0.17 (0.77±0.23)	0.18±0.32 (0.78±0.29)	0.467[a]
Spherical equivalent (SE) (D) (mean ± standard deviation)	-1.19±4.86	0.77±4.08	0.090[a]
Spherical refractive error (D)	-0.15±4.8	1.54±3.9	0.134[a]
Cylindrical refractive error (D)	-2.07±1.27	-1.50±1.1	0.065[a]
Emmetropia - total n (%) (-0.75D> SE <0.75D)	7 (15.2)	3 (12)	**0.001[b(*)]**
Myopia - total n (%) mild -0.75D ≥SE ≥ -2.99D** moderate -3.0D≥ SE≥-5.99D high -6.0D or more extreme	25 (54.4) **9** 9 7	4 (16) **0** 2 2	
Hypermetropia - total n (%) mild +0.75D≤ SE ≤ +2.99D** moderate +3.0D≤ SE ≤ +4.99D high +5.0D or more extreme	14 (30.4) **3** 9 2	18 (72) **12** 4 2	
Astigmatism - total n (%) no astigmatism mild 0.25 to1.49D moderate 1.5 to 2.99D high ≥3D	45 (97.8) 1 19 13 13	24 (96) 1 15 5 4	0.419[b]
Strabismus - total n (%) esotropia (ET) exotropia (XT) hypertropia hypotropia	21 (45.6) 13 8 1 (with XT) 0	11 (44) 8 3 1 (with ET) 0	0.894[b]
Anisometropia, n (%)	10 (21.7)	4 (16)	0.562[b]
Amblyopia, n (%)	14 (30.4)	6 (24)	0.565[b]

FD: Foveal depression, BCVA: Best corrected visual acuity, logMAR: Logarithm of the minimum angle of resolution, D: Diopter, a: Student t test , b: Chi Square test, *:The distribution of spherical refractive errors is significantly different among the groups. **: Group 1 vs group 2, p <0.05 in post-hoc analysis.

2 groups are shown in Table 3. Of six patients with zone 1 aggressive ROP in the Non-FD group; high myopia in 2, moderate myopia in 1, high hypermetropia in 1 and low hypermetropia in 2 were detected. High astigmatism was found in 2 patients, moderate in 1 patient, and low in 3 patients. Of these patients, 2 had amblyopia, 2 had anisometropia and 2 had strabismus.

DISCUSSION

In the present study, we aimed to evaluate the FD status on OCT and its relationship with strabismus, amblyopia and refractive errors in children with a history of ROP.

A previous histological study demonstrated that foveal pit formation begins at approximately at 25 weeks gestational age, it becomes wider and shallower after birth and appears mature by 15 months (8). Absence of FD, a type of abnormal foveal morphology, has been reported in aniridia, albinism, nanophthalmos, regressed ROP and also in preterm and healthy children (4-6, 9-14). Wu et al. suggested that normal development of fovea is affected in preterm infants and laser treatment/cryotherapy may have an additional effect on these changes by destroying avascular retina (6). In their study, patients treated for ROP had not only thicker maculas, but also lower GA and BW than untreated patients. A previous study evaluating preterm children suggested that the degree of prematurity is more important for foveal development than ROP (15). In our study, the mean GA and BW was significantly lower in the Non-FD group than in the FD group. On the other hand, when only the patients who underwent laser treatment were compared, the mean GA and BW were slightly lower in the Non-FD group, but the difference between the two groups was not statistically significant. In our study, consistent with the study by Akerblom

Table 3: Demographic data, refractive errors, strabismus and amblyopia distribution of patients with laser treatment in two groups

	Only laser treatment in Non-FD group (n=32)	Only laser treatment in FD group (n=12)	P values
Birth weight (grams)	1184.4±436	1409.2±435	0.097[a]
Gestational age (weeks)	28.5±2.7	29.7±1.5	0.117[a]
Mean central macular thickness	322.4±30.4	285.7±26.4	**0.001**[a]
Mean foveal depression	28.8±17.2	64.2±7.1	**<0.001**[a]
Anisometropia, n (%)	9 (28.1)	3 (25)	0.579[b]
Amblyopia, n (%)	13 (40.6)	3 (25)	0.276[b]
Strabismus - total n (%) esotropia (ET) exotropia (XT)	9 (28.1) 6 3	3 (25) 1 2	0.579[b]
LogMAR BCVA (mean ± standard deviation)	0.17±0.17	0.25±0.36	0.979[a]
Spherical equivalent (SE) (D) (mean ± standard deviation)	-2.38±4.82	-0.80±5.14	0.225[a]
Spherical refractive error (D)	-1.27±4.72	0.25±4.89	0.225[a]
Cylindrical refractive error (D)	-2.20±1.32	-2.02±1.14	0.721[a]
Astigmatism - total n (%)	32 (100)	12 (100)	0.942[c]
mild 0.25 to1.49D moderate 1.5 to 2.99D high ≥3D	14 9 9	5 4 3	
Emmetropia - total n (%) (-0.75D> SE <0.75D)	3 (9.3)	2 (16.7)	**0.043**[c]
Myopia - total n (%) mild -0.75D ≥SE ≥ -2.99D[a] moderate -3.0D≥ SE≥-5.99D high -6.0D or more extreme	22 (68.8) 7 9 6	3 (25) 0 1 2	
Hypermetropia - total n (%) mild +0.75D≥ SE ≥ +2.99D[b] moderate +3.0D≥ SE ≥ +4.99D high +5.0D or more extreme	7 (21.9) 2 5 0	7 (58.3) 5 2 0	

FD:foveal depression, BCVA: best corrected visual acuity, logMAR: logarithm of the minimum angle of resolution, D:diopter
[a]: Mann-Whitney U Test [b]: Fisher exact test, [c]: Chi Square test

et al, the degree of prematurity seems to have a greater effect on foveal development, but additional factors other than ROP and/or laser treatment may play a role in abnormal foveal development (15).

Previous studies demonstrated that absence of FD is not correlated with visual acuity in patients with a history of ROP (4,5). It has been suggested that photoreceptor maturation may have more impact than inner retinal layer migration on visual acuity (16). In our study, visual acuity did not differ significantly between the presence and absence of FD in the groups, which was consistent with previous studies.

Refractive status of patients with history of prematurity and/or ROP were evaluated in previous studies and the results were variable. It has been shown that there is no relationship between myopia and GA or BW in preterm children without ROP (17,18). It has been suggested that myopic refractive errors were frequently detected in children with history of ROP and/or ablative treatment (laser/cryotherapy) (6,19,20). Mild myopia has also been reported in patients with spontaneously regressed ROP and in patients born prematurely and without ROP (6). On the other hand, Darlow et al. reported no significant difference in myopia between preterms with or without ROP and the control group (21). Moreover,

Wang et al.detected hyperopia in patients with history of spontaneously regressed ROP (20). Previous studies evaluated refractive errors and foveal structure according to the status of ROP. In our study, we compared refractive status of patients with history of ROP according to presence or absence of FD and we did not find a significant difference between the groups in the mean SE. When the refractive errors were evaluated categorically, we found that most of the patients with absence of FD were myopic (54.4%), and those with normal foveal structure were mostly hyperopic (72%). In addition, we found that statistical difference was maintained when only the patients who had laser treatment were compared. The most significant difference between the groups was detected in the mild myopia and mild hypermetropia categories. Therefore, myopia may be more prevalent in patients with ROP and absence of FD than in those with a normal foveal structure.

The incidence of astigmatism which was defined as equal or greater than 1.0D was reported as 42-52% in ROP children (23,24). Villegas et al reported that astigmatism ≥1.50D was detected in 45% of normal children with fovea plana (24). In our study, astigmatism ≥1.50D (moderate or high astigmatism) was detected in 56.5% of patients with absence of FD and 36% of patients with presence of FD. The incidence of astigmatism ≥1.50D in patients with ROP and absence of FD was slightly higher than previously reported in the literature, despite the lower limit of astigmatism was 1D in the literature. However, there was no significant difference between the groups.

The incidence of strabismus in premature infants has been reported as 22-46% in previous studies and strabismus rate was higher in preterms with severe ROP (25-27). In accordance with the literature, we found the incidence of strabismus to be 45% in the Non-FD group and 44% in the FD group, and esotropia was the most frequent type of strabismus in both groups.

The incidence of anisometropia in patients with regressed ROP varies from 14% to 48% according to severity of ROP (27). In accordance with the literature, we detected anisometropia in 21.7% of the patients in the Non-FD group and in 16% of the patients in the FD group.

The incidence of amblyopia was reported as 14.3% in patients with spontaneously regressed ROP and 20.8% in patients with treatment for ROP (28). In another study grouping the prematurely born children according to GA, the incidence of amblyopia reported as 32% in patients with GA lower than 28 weeks and 22% in patients with GA between 28-32 weeks (25). Consistent with the literature, we found the incidence of amblyopia to be 30% in the Non-FD group with a mean GA of 28 weeks and 24% in the FD group with a mean GA of 30 weeks. When only the patients who underwent laser treatment were evaluated, we found a slightly higher incidence of amblyopia (40%) in the Non-FD group compared to the literature, although there was no significant difference between the two groups. In the FD group, the incidence of amblyopia was found to be similar in those with and without laser treatment.

The limitations of this study are its relatively small sample size for both groups and its cross sectional and retrospective nature. This study only demonstrates the association between the absence of FD and refractive errors in patients with a history of ROP. Further studies are needed with a larger patient population and in different patient groups with the absence of FD.

CONCLUSION

We detected lower GA and BW in the Non-FD group than those of the FD group. The degree of prematurity seems to have an impact on foveal development in patients with a history of ROP.

Although the absence of foveal depression does not affect visual acuity, foveal morphology appears to be associated with refractive errors in children with a history of ROP. Similarly, normal foveal morphology is associated with hyperopia and abnormal foveal morphology is more frequently associated with myopia in patients undergoing laser treatment.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 27.05.2022, No: 10).

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