ORIGINAL ARTICLE

The Increased Epiretinal Membrane Frequency in Patients with Glaucomatous Optic Atrophy

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ABSTRACT

Purpose: To investigate the epiretinal membrane (ERM) frequency in patients with glaucomatous optic atrophy (GOA).

Materials and Methods: Medical records of patients with GOA were investigated. The macular ERM was assessed using high definition images obtained from enhanced depth optical coherence tomography (OCT) and evaluated according to Hwang's classification. Outer macular thickness, inward projection of outer layers and cystic changes were assessed. Age, gender, and findings of OCT were assessed and logistic regression analysis was performed to evaluate possible factors which can cause ERM. Comparison between eyes with and without ERM in terms of OCT findings was also investigated.

Results: Eighty-eight eyes of 68 patients were included in the sample. The mean age for patients was 70.13±9.43 years. Types of glaucoma were primary open angle glaucoma in 61 eyes, primary closed angle glaucoma in 7 eyes and pseudoexfoliative glaucoma in 20 eyes. The history of ocular surgery was present in 55 eyes. Out of 88 eyes, 45 (51.1%) was diagnosed as ERM, and 15 eyes (17.04%) were type 1A, 17 eyes (19.31%) type 1B, 8 eyes (9.09%) type 1C and 5 eyes (5.68%) type 2B according to Hwang's classification. Age and presence of previous surgeries were not found as statistically significant (p:0.054, p:0.277, respectively). Vertical cup to disc ratio (c/d) was larger in eyes with ERM (p:0.049).

Conclusion: The frequency of ERM in patients with GOA was found to be 51.1 % and vertical c/d ratio was higher in these patients. This unique result was independent of potential influential factors such as age and history of previous surgeries.

Keywords: Glaucoma, Optic Atrophy, Epiretinal Membrane

INTRODUCTION

An epiretinal membrane (ERM) is defined as a transparent, avascular, fibrocellular membrane on the inner retinal surface adherent to internal limiting membrane of the retina. This membrane formation is the result of proliferation of glia, retina pigment epithelium (RPE) or hyalocytes at the vitreoretinal interface, especially at the posterior pole.[1]

The main risk factors of idiopathic ERM are aging and the presence of posterior vitreous detachment. Additional risk factors are inflammation, trauma and posterior segment tumours.[2] Besides, the prevalence of ERM has revealed to increase after cataract surgery and trabeculectomy procedure.[2,3]

Optical coherence tomography (OCT) is a non-invasive, noncontact, transpupillary imaging technology that provides high resolution images of the optic disc and the retina. It has been widely used in retinal diseases and glaucoma. Recently, structural changes in the inner retina in glaucoma that were revealed by OCT have been reported. Peripapillary retinoschisis, microcystic macular edema seen in optic neuropathies are thought to be the result of nerve fiber damage and retrograde loss of ganglion cells. As well as retinal traction might cause microcystic macular edema in glaucomatous or non-glaucomatous optic neuropathies.[4]

The association between idiopathic ERM and glaucoma was reported by Asrani et al. They found that more than 10% of glaucomatous eyes had ERM that caused artifacts seen in OCT macular scans.[5] Sakimoto et al. suggested that unilateral severity in eyes with primary open angle glaucoma might be affected by the concomitance of ERM

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in these eyes.[4] Although, the effect of ERM on severity of glaucoma or on OCT image distortions was studied previously, the frequency of ERM in eyes with glaucoma was not studied widely. In literature, Mavrommatis et. al. found that eyes with early glaucoma had a higher frequency of ERMs than glaucoma suspects and controls.[6]

In this current study, we aimed to investigate the frequency of ERM in eyes with severe glaucomatous optic neuropathy. In our knowledge, this is the first study that examined this concommitance.

MATERIALS AND METHODS

This study was conducted at the Department of Ophthalmology. Prior approval from the Institutional Review Board was taken (71522473/050.01.04/180) and written informed consent was obtained from each subject. The study was performed in adherence to the Declaration of Helsinki.

The medical records of patients with glaucoma were investigated retrospectively and the records of patients with severe glaucomatous optic neuropathy were recruited. Glaucoma severity classification was made according to the modified Hodapp-Anderson-Parrish grading scale based on the mean deviation (MD) of VF.[7] Severe glaucoma was defined as MD worse than −12 dB, and at least one of the following criteria: A ratio of ≥50 but < 75% of the pattern deviation plot depressed below the 5% level and a ratio of ≥25 but < 50% of the pattern deviation plot depressed below the 1% level, or a ratio of ≥1 in the central 5˚ with a sensitivity of 0 dB, or ratio with the central 5˚ with a sensitivity of <15 dB in both hemifields.

The exclusion criteria were additional macular or retinal diseases, presence of corneal and lenticular pathologies, history of vitreoretinal surgeries, high refractive errors (more than 3 diopter myopia and hypermetropia) and presence of diabetes mellitus.

The mean age, gender, best corrected visual acuity (BCVA) measured by Snellen chart, the intraocular pressure (IOP) measured by Goldmann applanation tonometer, the mean central corneal thickness (CCT) measured by ultrasonic pachymetry were noted. Type of glaucoma and previous surgeries were reported.

Spectral domain optical coherence tomography was performed using the Cirrus HD-OCT (Model 4000, software version 6.0, Carl Zeiss Meditec, Dublin, CA) for peripapillary RNFL and GC-IPL thickness measurements. Mean RNFL thickness has been measured according to "Optic Disc Cube 200*200" method. In addition to that, ganglion cell analysis has been conducted in accordance with "Macular Cube 512*128" program. Mean and fragmented RNFL thickness, mean and six fragmented GC-IPL thicknesses have been evaluated. Besides, rim and disc area, mean and vertical cup-to-disc (c/d) ratio, the mean cup volume were also noted. The images with signal quality which were worse than 7/10 have been excluded. Scans with misalignment, segmentation failure, decentration of the measurement circle, poor illumination and the ones which were out of focus have also been excluded.

The macular ERM was assessed by using high definition images obtained from Macular Cube 512*128 scan protocol and classified according to Hwang's classification.[8] This classification was based on foveal morphology. Table 1 revealed the whole classification (Figure 1-5).

Standard Automated Perimetry, the 10-2 SITA FAST program (Humphrey Field analyzer, Carl Zeiss Meditec, Dublin, CA, USA) was used for visual field (VF) testing. Fixation losses more than 20%, false-positive and false-negative errors more than 20% were not acceptable. The perimeter software was used to calculate mean deviation (MD) and pattern standard deviation (PSD). The comparison of mean MD and PSD between eyes with and without ERM was performed.

Table 1: *Hwang's OCT-based morphologic classification of idiopathic epiretinal membranes*

Group 1: Fovea-involving ERM	
IA	Outer retinal thickening. minimal inner retinal change
IB	Outer retinal inward projection. inner retinal thickening
IC	Prominent thickening of the inner retinal layer
Group 2: Fovea-sparing ERM	
2A	Formation of a macular pseudohole
2B	Schisis-like intraretinal splitting
ERM: Epiretinal Membrane. OCT: Optical Coherence Tomography	

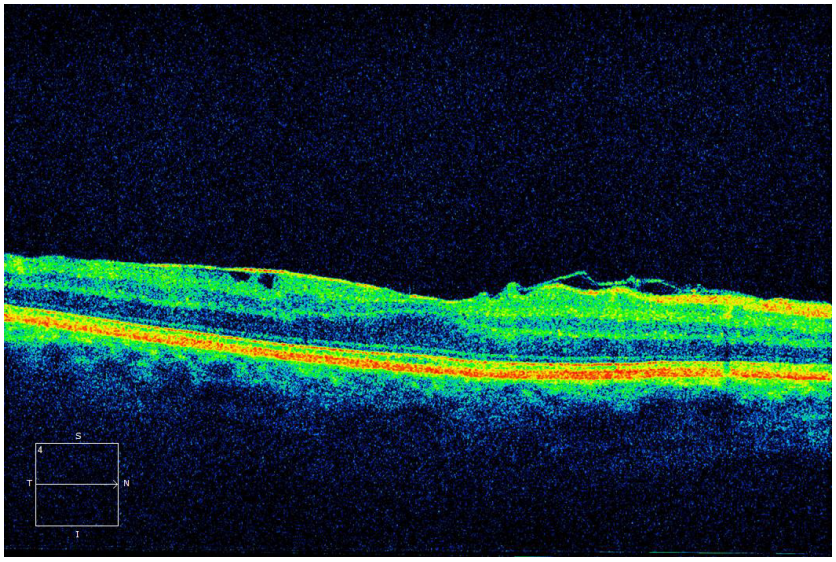

Figure 1: *1 A Outer retinal thickening, minimal inner retinal change*

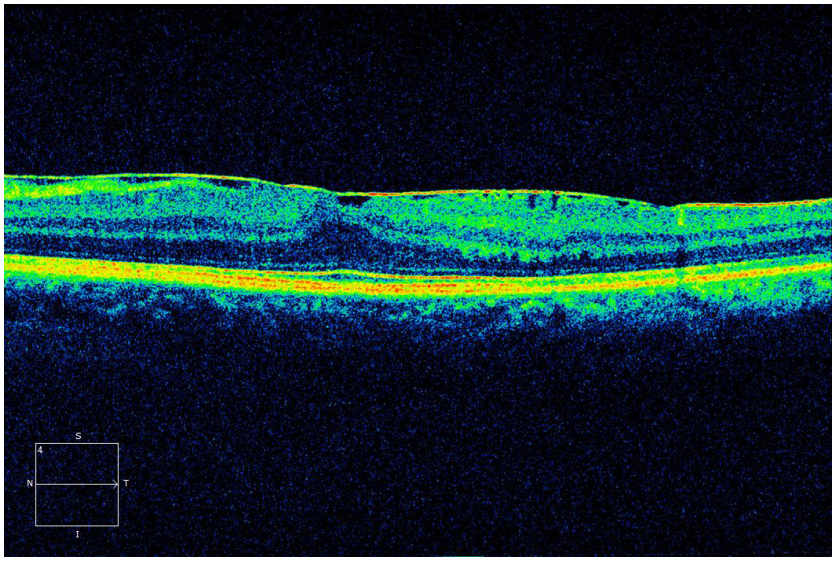

Figure 2: *1 B Outer retinal inward projection, inner retinal thickening*

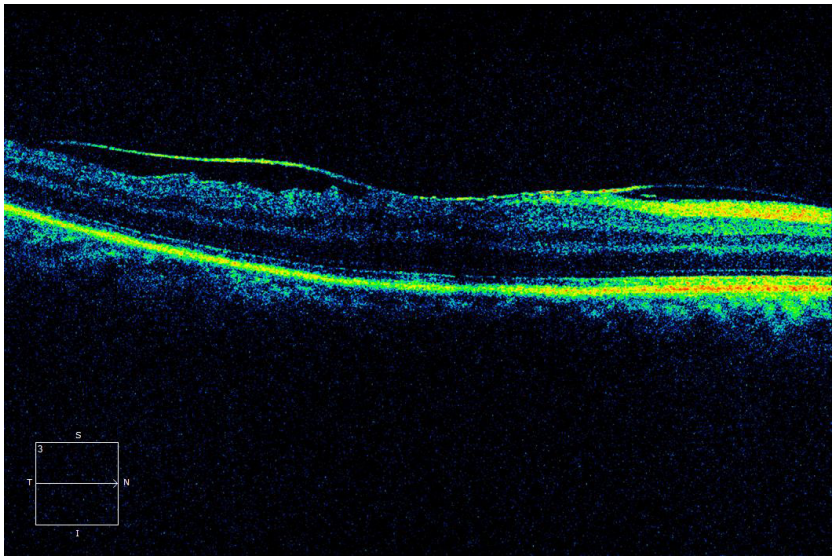

Figure 3: *1 C Prominent thickening of the inner retinal layer*

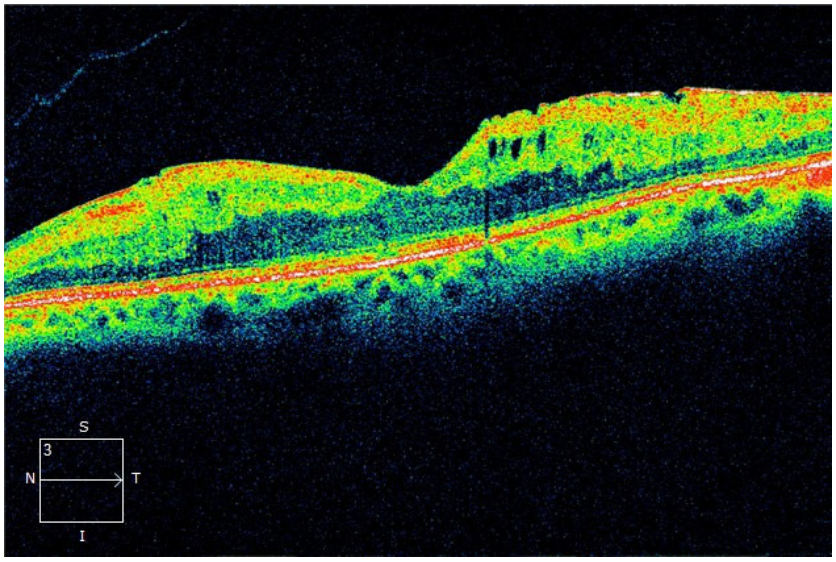

Figure 4: *2 B Schisis-like intraretinal splitting*

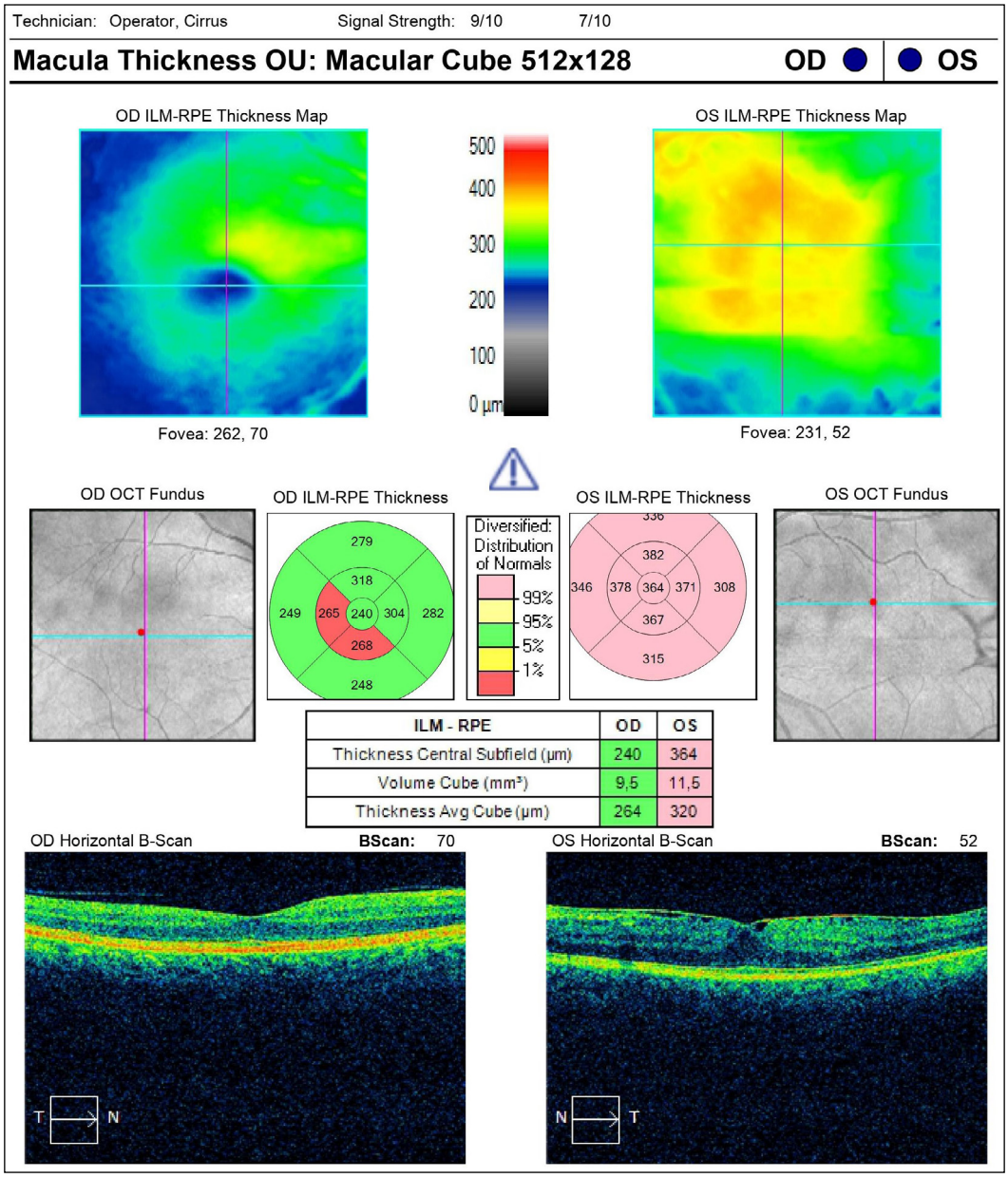

Figure 5: *Map of bilateral macular thickness*

The mean, superior, inferior, temporal, nasal RNFL and mean, six-fragmented GC-IPL thicknesses and optic disc parameters were compared between eyes with and without ERM.

Statistical analysis was performed by using SPSS 21.0 (Statistical Package for Scientific Studies for Windows, SPSS Inc., Chicago, IL). Descriptive analysis were presented using means and standard deviations for normally distributed variables. Student-t test was used to compare parameters between eyes with and without ERM. For the multivariate analysis, the possible factors indentified with univariate analysis were further entered into the logistic regression analysis to determine independent predictors of patient outcome. Hosmer-Lemeshow goodness of fit statistics were used to asses model fit. A p value of less than 0.05 was considered to show statistically significant result.

RESULTS

The records of 889 patients with the diagnosis of glaucoma were evaluated and out of 112 patients, 88 eyes of 68 patients with severe glaucoma were recruited in this current study. Twenty four of 112 patients were not included according to exclusion criteria. The mean age of 29 (42.65%) female, 39 (57.35%) male patients with severe glaucomatous optic neuropathy (OA) were 70.1±9.4 years.

Types of glaucoma were primary open angle glaucoma (PAAG) in 61 (69.31%) eyes, primary angle closure glaucoma (PACG) in 7 (7.96%) eyes and pseudoexfoliative glaucoma (PSEX) in 20 (22.73%) eyes. Table 2 revealed the frequency of ERM in each type of glaucoma. The mean BCVA, IOP and CCT were 0.56±0.76 and 13.1±3.2 mmHg, 549.4±31.3µm, respectively.

The history of ocular surgery was present in 55 eyes. Table 3 revealed the number of eyes underwent intraocular surgery and ratios of eyes with epiretinal membrane.

Forty five eyes (51.13 **%**) was diagnosed as ERM in 88 eyes. 15 eyes (17.04 %)were type 1A, 17 eyes (19,31 %) were type 1B, 8 eyes (9,09 %) were type 1C and 5 eyes (5,68 %) were type 2B (Table 4).

The mean, superior, inferior, nasal, temporal RNFL thicknesses were 56±7 µm, 62.29±10.38 µm, 60±10.47 µm, 55.11±9.27 µm, 46.41±11.89 µm, respectivey. The mean, superior, inferior GC-IPL thicknesses were 56.4±9 µm, 57.14±12.09 µm, 55.79±11.56 µm, respectively. The mean MD and PSD were -22.56±5.9 dB and 10.5±2.36 dB, respectively. The mean cup volume, rim, disc area, vertical c/d ratio were 0.59±0.27 mm^3, 0.6±0.2 mm^2, 2.03±0.38 mm^2 and 0.81±0.08, respectively.

The results of comparison between eyes with and without ERM in terms of OCT findings were summarized in Table 5. Vertical c/d ratio was higher in eyes with ERM (p:0.049).

There was no correlation between mean MD and the presence of ERM and between mean PSD and the

Table 2: *Demographic characteristics and types of glaucoma*

	Total eye number (%) n=88	Eyes with ERM n=45
Age	70.1±9.4 years	72.1±8.4 years
Male/Female (n)	39/29 (57,35% / 42,65%)	21/17 (46,66% / 37.77%)
POAG	61 (69.31 %)	30 (66.66%)
PACG	7 (7,96 %)	4 (8.89%)
PSEX	20 (22.73 %)	11 (24.45%)

POAG: Primary Open Angle Glaucoma. PACG: Primary Angle Closure Glaucoma. PSEX: Pseudoexfoliative Glaucoma. ERM: Epiretinal Membrane

Table 3: *Characteristics of patients who underwent intraocular surgery*

	Number of eyes	Eyes with ERM n (%)
Cataract Surgery	31	18 (40%)
Trabeculectomy	13	6 (13.33%)
Combined cataract surgery and trabeculectomy	11	5 (11.11%)

ERM: Epiretinal Membrane

Table 4: *Distribution of eyes in different types of ERM (45 eyes in totally 88 eyes)*	
Number of eyes in Group 1 (Fovea-involving ERM)	
IA	15 eyes (17,04%)
IB	17 eyes (19.31%)
IC	8 eyes (9.09 %)
Number of eyes in Group 2 (Fovea-sparing ERM)	
2A	0
2B	5 eyes (5.68 %)
Total	45 eyes (51.13%)
ERM: Epiretinal Membrane	

Table 5: *Comparison between eyes with and without ERM in terms of OCT parameters*			
	Eyes without ERM	**Eyes with ERM**	**p**
The mean RNFL thickness	56.2 ± 6.5 µm	55.8 ± 7.6 µm	0.828
Superior RNFL thickness	61.3 ± 9 µm	63.2 ± 11.6 µm	0.431
Inferior RNFL thickness	60.6 ± 11.2 µm	59.3 ± 9.7 µm	0.582
Nasal RNFL thickness	55.4 ± 9.9 µm	54.7 ± 8.6 µm	0.749
Temporal RNFL thickness	46.9 ± 11.5 µm	45.8 ± 12.7 µm	0.709
The mean GC-IPL thickness	55.4 ± 10.6 µm	57.4 ± 8.9 µm	0.411
Supero- temporal GC-IPL thickness	54.7 ± 12.2 µm	57.3 ± 11.5 µm	0.390
Supero GC-IPL thickness	55.6 ± 12.3 µm	58.5 ± 11.8 µm	0.338
Supero- nasal GC-IPL thickness	57 ± 10.7 µm	60.2 ± 13.9 µm	0.314
Infero- temporal GC-IPL thickness	54.1 ± 13.3 µm	55.3 ± 12.6 µm	0.719
Inferior GC-IPL thickness	55 ± 12.3 µm	56.4 ± 10.9 µm	0.642
Infero- nasal GC-IPL thickness	55.7 ± 11.8 µm	56.8 ± 8.9 µm	0.686
Rim area	0.6 ± 0.2 µm	06.6 ± 0.2 µm	0.328
Disc area	2 ± 0.3 µm	2 ± 0.3 µm	0.961
Vertical c/d ratio	0.79 ± 0.08 µm	0.83 ± 0.8 µm	**0.049**
RNFL: retinal nerve fiber layer. GC-IPL: ganglion cell- internal plexiform layer. c/d: cup to disc			

presence of ERM (p=0.874 r=0.022, p=0.054 r= -0.297, respectively).

According to logistic regression analysis, age and previous surgeries were not found as determinant factors (p:0.054, p:0.277).

DISCUSSION

In this current study, the frequency of ERM was found to be 51.13% in eyes with severe glaucomatous optic neuropathy and age and previous surgeries were not found as determinant factors. In advanced optic neuropathies, a specific subtype of macular edema called retrograde maculopathy might occur. Multiple small cystoid spaces in inner nuclear layer of retina might develop in both retrograde maculopathy and ERM.[9] Therefore, these entities might be overlap and make the diagnosis difficult. But in this current study, in eyes with ERM, schisis-like intraretinal splitting was found in only 5.7% proportion out of all eyes. The thickening of inner or outer layer of retina, outer retinal inward projection and minimal inner retinal changes were seen more often. And also, contracted ERMs may distort the RNFL and contribute the degeneration of the optic nerve.[10-12] They also warned clinicians to be aware of that ERM progression may cause changes in optic nerve head and RNFL parameters in glaucomatous eyes that have been associated with ERM without retinal distortion.

It is already known that advanced age was strongly correlated with prevalence of ERM. A recent meta-analysis revealed that greater age and female gender significantly conferred a higher risk of ERMs.[13] When we performed

logistic regression analysis, age was not found as a determinant factor in our study group (p:0.054). Besides, male/female ratio was 39/29. There was no female gender dominance.

The presence of ERM was found to be associated with cataract surgery in a recent study. Database of the Korea National Health and Nutrition Examination Survey was used and 14.772 participants were enrolled in this study.[14] Vieira et al. found that trabeculectomy might predispose one to the appearance and progression of ERM.[3] In our study, 64.4% percent of eyes with ERM had cataract surgery, trabeculectomy or combined surgery, previously. This might have altered our results. When we performed logistic regression analysis, previous surgeries were not found as determinant factor in our study group (p:0.277).

In this current study, eyes with severe glaucomatous optic neuropathy were enrolled. Thus, these patients have used various topical antiglaucomatous agents. Giambruni et al. investigated association between topical prostaglandin analogues (PA) and development of ERM.[15] They did not find an association between the use of PA and ERM development.[15] There was no other finding or study about association between topical antiglaucomatous agents and development of ERM.

The presence of an ERM was found to be a possible risk factor for unilateral severity in eyes with POAG. In recent study, superior and inferior RNFL was found to be thinner in eyes with ERM. Besides disc cupping and cup-to-disc ratio was found to be larger in eyes with ERM. They assumed that the pathogenesis of glaucomatous severity in eyes with an ERM may attribute to development of ERM traction on the inner retina and centripedal traction induced by ERM may cause mechanical stress on the neural fibers in a vertical direction to the optic disc cup. In addition, ERMs may develop simultaneously or even subsequently with glaucomatous retinal ganglion cell death. Another important possible hypothesis is that both ERM and progressed glaucoma are associated with loss of microcirculation of blood flow. Patients in this study was not in their advanced stage.[4] In our study, eyes with severe glaucomatous optic neuropathy were enrolled. There was no difference between eyes with and without ERM in terms of the mean, superior, inferior, temporal, nasal RNFL thicknesses and mean and six-fragmented GC-IPL thicknesses. The mean vertical cup-to-disc ratio was found to be statistically larger in eyes with ERM. In severe glaucomatous optic neuropathy, RNFL and GC-IPL thicknesses tended to be extremely low. Statistically, this situation might cause floor effect and alter the results.

In a recent study, Mavrommatis et al. aimed to use en-face slab analysis of OCT scans to examine the frequency of paravascular defects and macular ERMs and they found that glaucomatous eyes have a higher frequency of ERMs than suspects or controls.[6] They also assumed that ERMs increased in frequency with age, however, even after accounting for age by multivariable regression, glaucomatous eyes had a significantly greater frequency of ERMs, similarly with our study. This study was the only study published study about the frequency of ERM in glaucomatous eyes. Studies which will evaluate and compare frequencies of ERM in eyes with different stages of glaucoma should be performed to understand this item more precisely.

This study has some limitations. The sample size was relatively small. Type of glaucoma in patients was not homogeneous. With a much larger more homogeneous group of patients, it may be possible to create more accurate and precise results.

In conclusion; the frequency of ERM in patients with GOA was found as 51,1% in this current study. This result might have altered by the presence of previous surgeries but less than 10% frequency were reported in patients who underwent cataract surgery. So this frequency is a unique and remarkable result.

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