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The association of outer retinal tubulation with vitreomacular adhesion and epiretinal membrane in eyes with age-related macular degeneration

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Abstract

Aim of this study to investigate the relationship between outer retinal tubulation (ORT) and vitreomacular adhesion (VMA) or epiretinal membrane (ERM) in eyes with age-related macular degeneration (ARMD). 251 eyes of 138 (46 female, 92 male) patients were included in the study. Of those, 84 eyes were with dry type ARMD, 167 eyes were with wet type ARMD. Medical records of the cases were evaluated retrospectively. Evaluation of the vitreomacular interface (including VMA and ERM), and ORT was checked by using optical coherence tomography. VMA was observed in 26 eyes of 251 eyes and ERM in 46 of 251 eyes. In eyes with VMA, while ORT was not found in dry type ARMD, ORT was found in 5 (29.4%) of 17 eyes with wet type ARMD. In eyes with ERM, while ORT was found in one of 13 eyes (7.7%) with dry type ARMD, ORT was found in 6 (18.2%) of 33 eyes with wet type ARMD. No statistically significant difference was found between ORT presence and ERM or VMA presence in dry or wet type ARMD patients ($p \geq 0.05$). Our study results suggest that, although there is no correlation between VMA and ERM with development of ORT in ARMD, further large-scale studies are required to confirm these findings and to establish a definite conclusion.

Keywords: Age-related macular degeneration, vitreomacular interface, epiretinal membrane, outer retinal tubulation, vitreomacular adhesion

Introduction

The microstructure of the retina is currently imaged *in vivo* almost at the histopathology level with the developments in retinal imaging and especially spectral domain optical coherence tomography (SD-OCT) [1]. These developments enable more detailed evaluation of posterior segment pathologies. Outer retinal tubulation (ORT) has first been defined by Zweifel et al. in 2009 as branching tubular structures at the outer nuclear layer of the retina observed as round or ovoid hyporeflexive areas surrounded by a hyperreflective border [1]. Histological analysis of the lesions has shown interconnecting tubes composed of surviving cone photoreceptors that interleave Muller glia processes and are also enclosed by them, overlying disciform scars of age-related macular degeneration (ARMD) [2,3]. ORT has been identified in ARMD as well as other conditions such as retinal and choroidal dystrophies, multifocal choroiditis, central serous chorioretinopathy, acute zonal occult

outer retinopathy and dry type ARMD with geographic atrophy. The presence of ORT in eyes with choroidal neovascularization (CNV) has been found to be associated with worse final visual acuity [4]. Another clinical significance of ORT is the necessity of differentiating it from intraretinal cysts that are indicators of exudative activity in disorders such as ARMD, diabetic macular edema and vascular occlusions [1,4-7].

The vitreous is in gel form at birth but becomes liquefied with age, creating a tendency to posterior vitreous detachment. Retina and lens oxygenation are higher with the liquefied vitreous compared to the gel form. There is a barrier against cellular migration from the retina to the vitreous and the diffusion of large molecules. Posterior vitreous detachment (PVD) develops with the liquefaction of the vitreous and normally results in a complete and clean separation between the internal limiting membrane of the retina and the cortical vitreous. When abnormal PVD is present, various vitreomacular interface disorders can develop [8-10]. Abnormal adhesions between the retina and the posterior vitreous surface are the cause of several vitreoretinal complications and, also form the framework for intact posterior hyaloid vascular growth and anterior-posterior tractions [11]. Vitreomacular adhesion (VMA)

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is defined as an incomplete separation with persistent adhesion of the posterior vitreous to the macula. VMA can disturb the supply of oxygen from the vitreous to the retina and can also influence the progress of wet type ARMD by causing tractional macular detachment, retinoschisis and macular edema [12].

An epiretinal membrane (ERM) is a non-vascular cellular membrane proliferation on the inner retinal surface at the macula and can cause visual impairment and metamorphopsia [13]. Retinal glial cells originating from astrocytes or Muller cells are the most important cellular component of ERMs [14]. ERMs can cause macular structural changes such as retinal folds, pseudohole formation, vascular leakage, macular thickening and foveal detachment by tractional forces on the retinal surface. Idiopathic ERMs are observed in the same age group as ARMD [13-15].

Our aim in this study was to evaluate whether there is a relationship between outer retinal tubulation and the vitreomacular interface disorders such as VMA and ERM in eyes with ARMD.

Materials and Methods

The retrospective study has received Institutional Review Board/Ethics Committee approval and adhered to the tenets of the Declaration of Helsinki. We included patients who have ARMD and were followed-up at Inonu University Medical Faculty's Department of Ophthalmology Retina Unit in this study. Eyes with diabetic retinopathy, retinal vascular diseases, inflammatory diseases, vitreomacular traction or vitrectomized were excluded. The pupils were dilated with 2.5% Mydrin (phenylephrine hydrochloride) and 1% Tropicamide Fort (tropicamide) in all cases. The age, gender, presence of ORT and vitreomacular interface characteristics were recorded in all cases. Colour fundus photography were taken and fluorescein angiography was performed if necessary. SD-OCT scans were evaluated at the final follow-up in all cases. The images were obtained with Nidek RS-3000 OCT Retina Scan Advance (Nidek Inc Ca. USA) device. The 5 Line Raster protocol and, also the macular cube 512x128 protocol, when good images of the vitreomacular interface could not be obtained, were used in all patients. Besides, a 30-degree long scan was horizontally performed up to the optic disc to cut through the macula all the way to help in the differentiation of complete posterior vitreous detachment (PVD) from partial PVD.

SD-OCT images and clinical ophthalmoscopic examination findings were evaluated regarding the vitreomacular interface characteristics. ORT has been defined by Zweifel et al. as round or oval structures with hyperreflective borders, localized in the outer nuclear layer of the retina [1]. They are thus differentiated from intraretinal cysts that have hyporeflective borders and are located in the inner retina. The cases were excluded from the study if there was no consensus among the investigators.

Statistical analyses were performed with SPSS for Windows version 22.0 program. Continuous data are reported as mean \pm standard deviation (SD). Categorical data were expressed by count and percentage. Comparisons between groups were made by Fisher's exact test or continuity corrected chi-square test. In all analysis significance level was considered as 0.05.

Results

We included 251 eyes of 138 patients in this study. There were 46 (33.3%) females and 92 (66.7%) males. The mean age was 72.6 ± 3.5 (58-93) years. Of 251 eyes, 84 eyes were with dry type ARMD, 167 eyes were with wet type ARMD.

VMA was observed in a total of 26 of 251 eyes, 9 (10.7%) with dry type and 17 (10.2%) with wet type ARMD ($p \geq 0.05$). ERM was observed in a total of 46 of 251 eyes, 13 (15.5%) eyes with dry type ARMD and 33 (19.8%) eyes with wet type ARMD ($p \geq 0.05$). ORT was found in 5 (5.9%) of 84 eyes with dry type ARMD and in 33 (19.8%) of 167 eyes with wet type ARMD in our study ($p \leq 0.05$) (Table 1).

In eyes with dry type ARMD, while ORT was not found in eyes with VMA, ORT was found in one of 13 eyes (7.7%) with ERM. In eyes with wet type ARMD, ORT was found in 5 (29.4%) of 17 eyes with VMA and ORT was found in 6 (18.2%) of 33 eyes with ERM. No statistically significant difference was found between ORT and ERM or VMA in dry or wet ARMD patients ($p \geq 0.05$) (Table 2,3). Figure 1 shows the OCT images of two eyes that detected ORTs in patients with wet type ARMD.

Table 1. Prevalence of VMA, ERM and ORT in eyes with dry and wet type age-related macular degeneration

Diagnosis	Dry type ARMD n:84 eyes (%)	Wet type ARMD n:167 eyes (%)	p value
VMA	9 (10.7)	17 (10.2)	>0.05
ERM	13 (15.5)	33 (19.8)	>0.05
ORT	5 (6.0)	37 (22.2)	≤ 0.05

ARMD: Age-related macular degeneration, ERM: Epiretinal membrane, ORT: Outer retinal tubulation, VMA: Vitreomacular adhesion

Table 2. Comparison between eyes with and without VMA/ERM according to the presence of ORT in eyes with dry type ARMD

Diagnosis	ORT (n)	%	p value
VMA or no VMA			
VMA (n:9)	0	0	>0.05
No VMA (n:75)	5	6.7	
ERM or no ERM			
ERM (n:13)	1	7.7	>0.05
No ERM (n:71)	4	5.6	

ARMD: Age-related macular degeneration, ERM: Epiretinal membrane, ORT: Outer retinal tubulation, VMA: Vitreomacular adhesion

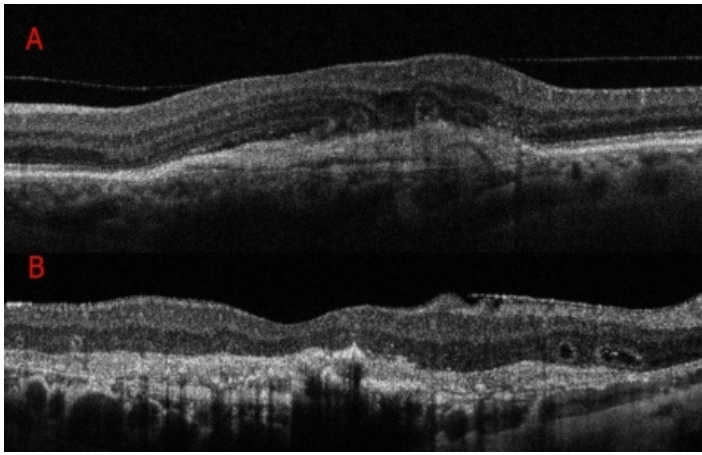


Figure 1: A. ORTs and VMA are noted on scan of the left eye of a patient with wet type ARMD. B. ORTs and ERM are noted on scan of the right eye of a patient with wet type ARMD.

Discussion

ORT related structural changes were started to be described systematically when SD-OCT entered common use and ORT was described by Zweifel et al. for the first time [1]. Although ORT was initially characterized as tubules providing a connection between degenerated photoreceptors and Muller cells, clinicopathologic findings obtained on later showed the reflective border of ORT to represent mitochondria inside a degenerated inner segment, internally translocated to the external limiting membrane without outer segments [2]. Recent studies have stated that the presence of ORT reflects the photoreceptor degeneration process and the final stage of various disorders such as ARMD, polypoidal choroidal vasculopathy, retinal or choroidal dystrophies, central serous chorioretinopathy, and acute zonal occult chorioretinopathy [1,4-7]. Changes such as collapse, recurrence and enlargement can develop in ORTs in time. These changes may be spontaneous or can occur due to anti-VEGF treatment. Certain ORTs are thought to have a vascular component or to be vascular in nature. Some ORTs are formed only by degenerative photoreceptor cells and can collapse spontaneously, independent of anti-VEGF treatment [16]. In previous studies, ORT incidence has been reported in a wide range in eyes with dry and wet ARMD, although it is more common in eyes with wet type ARMD [1,4,17]. ORT was found in 5 (6.0%) of 84 eyes with dry type ARMD, 37 (22.2%) of 167 eyes with ARMD in our study.

Vitreomacular adhesion has been noticed by clinicians to be more common than its clinical detection rate once OCT entered clinical practice, indicating that PVD could be a part of normal development [8]. The presence of VMA has been found to be significantly more common in cases with wet type ARMD than in those with the dry type and the control groups [12,18-20]. The response to anti-vascular endothelial growth factor (anti-VEGF) in cases with wet type ARMD has been found to be decreased in the presence of VMA. The release of VMA might therefore improve the response to anti-VEGF treatment [18-20]. VMA is thought to show its effect in wet type ARMD through various mechanisms. VMA can induce a chronic, low-grade inflammation with a mechanical effect. It can also increase VEGF secretion with mechanical tension and cause the retention of VEGF and proangiogenic cytokines between the ILM and posterior vitreous cortex in front of the macula [12].

Since ORT is considered a sign of advanced disease in macular pathologies, it can be expected to be seen at higher rates in eyes with VMA. In eyes with VMA, while ORT was not found in dry type ARMD, ORT was found in 5 (29.4%) of 17 eyes with wet type ARMD. No statistically significant difference was found between the eyes with and without VMA in terms of ORT in eyes with dry type ARMD ($p \geq 0.05$). Although the ORT incidence was higher in eyes with VMA than eyes without VMA in eyes wet type ARMD, the difference was not statistically significant ($p \geq 0.05$).

Epiretinal membrane is defined as fibro cellular proliferation in the inner retinal surface at the macula. Leuschen et al. reported that ARMD cases had an ERM rate of 38.2% and VMA rate of 20.6% [21]. It is not clear whether the relationship between ERM and ARMD is coincidental or causal. Lee et al. propose that the migration and proliferation of RPE cells and activation of glial cells as a response to retinal damage could result in the production of cytokines and growth factors that cause ERM formation [22]. We wondered whether these two pathologies are related due to the presence of Müller glia cells in the pathogenesis of both ORT and ERM. In eyes with ERM, while ORT was found in one of 13 eyes (7.7%) with dry type ARMD, ORT was found in 6 (18.2%) of 33 eyes with wet type ARMD. No statistically significant difference was found between the eyes with and without ERM in terms of ORT in eyes with wet type ARMD in our study ($p \geq 0.05$). Although the ORT incidence was higher in eyes with ERM than eyes without ERM in eyes dry type ARMD, the difference was not statistically significant ($p \geq 0.05$).

Studies on the role of vitreomacular interface on the natural history of various ocular diseases are continuing. Increasing present knowledge about the effects of vitreomacular interface disorders on the retina may be important in developing new therapeutic approaches. So, we conducted this study to investigate whether a relationship is present between the presence of VMA or ERM and ORT development in eyes with ARMD. However, we could not find any relationship between ORT development and the presence of VMA or ERM. The limitations of our study include the inclusion of eyes that had undergone cataract surgery and the fact that the eyes with CNV had received multiple intravitreal injections. We believe that our results need to be confirmed by further studies, and we therefore hope that our study will guide such studies.

Conflict of interest

The authors declare that they have no competing interest.

Financial Disclosure

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Ethical approval

Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee 2017/25-6 and the number of decisions was approved.

References

1. Zweifel SA, Engelbert M, Laud K, et al. Outer Retinal Tubulation. A Novel Optical Coherence Tomography Finding. Arch Ophthalmol. 2009;127:1596-602.
2. Schaaf KB, Freund KB, Litts KM, et al. Outer Retinal Tubulation in Advanced Age-related Macular Degeneration: Optical Coherence Tomographic Findings Correspond to Histology. Retina. 2015;35:1339-50.
3. Marco RD, Litts KM, Tan ACS, et al. The evolution of outer retinal

- tubulation, a neurodegeneration and gliosis prominent in macular diseases. *Ophthalmology*. 2017;124:1-15.
4. Filho RGG, Zacharias LC, Monteiro TV, et al. Prevalence of outer retinal tubulation in eyes with choroidal neovascularization. *Int J Retina Vitreous*. 2016;2:6.
 5. Iriyama A, Aihara Y, Yanagi Y. Outer retinal tubulation in inherited retinal degenerative disease. *Retina*. 2013;33:1462-5.
 6. Goldeberg NR, Greenberg JP, Laud K, et al. Outer retinal tubulation in degenerative retinal disorders. *Retina*. 2013;33:1871-6.
 7. Kojima H, Otani A, Ogino K, et al. Outer retinal circular structures in patients with Bietti crystalline retinopathy. *Br J Ophthalmol*. 2012;96:390-3.
 8. Levison AL, Kaiser PK. Vitreomacular interface diseases: Diagnosis and management. Review article. *Taiwan J Ophthalmol*. 2014;4:63-8.
 9. Le Goff MM, Bishop PN. Adult vitreous structure and postnatal change. *Eye*. 2008;22:1214-22.
 10. Gao QY, Fu Y, H YN. Vitreous substitutes: challenges and directions. *Int J Ophthalmol*. 2015;8:437-40.
 11. De Smet MD, Gad Elkareem AM, Zwinderman AH. The Vitreous, the Retinal Interface in Ocular Health and Disease. *Ophthalmologica* 2013;230:165-78.
 12. Kang EC, Koh HJ. Effects of Vitreomacular Adhesion on Age-Related Macular Degeneration. *J Ophthalmol*. 2015;865083.
 13. Kang KT, Kim KS, Kim YC. Surgical Results of Idiopathic and Secondary Epiretinal Membrane. *Int Ophthalmol*. 2014;34:1227-32.
 14. Bu SC, Kuijer R, Li XR, et al. Idiopathic epiretinal membrane. Review. *Retina*. 2014;34:2317-35.
 15. Alkin Z, Ozkaya O, Osmanbasoglu OA, et al. The role of epiretinal membrane on treatment of Neovascular age-related macular degeneration with intravitreal Bevacizumab. *ScientificWorldJournal*. 2013;2013:958724.
 16. Espina M, Arcinue CA, Ma F, et al. Outer retinal tubulations response to anti-VEGF treatment. *Br J Ophthalmol*. 2016;100:819-23.
 17. Dirani A, Gianniu C, Marchionno L, et al. Incidence of outer retinal tubulation in ranibizumab-treated age-related macular degeneration. *Retina*. 2015;35:1166-72.
 18. Üney GÖ, Ünlü N, Acar MA, et al. Role of posterior vitreous detachment on outcome of anti-vascular endothelial growth factor treatment in exudative age-related macular degeneration. *Retina*. 2014;34:32-7.
 19. Lee SJ, Koh HJ. Effects of vitreomacular adhesion on anti-vascular endothelial growth factor treatment for exudative age-related macular degeneration. *Ophthalmology*. 2011; 118:101-10.
 20. El-Hifnawy MAE, Ibrahim HA, Gomaa AR, Elmasry MA. The vitreomacular interface in different types of age-related macular degeneration. *Int J Ophthalmol*. 2017;10:246-53.
 21. Leuschen JN, Schuman SG, Winter KP, et al. Spectral-domain optical coherence tomography characteristics of intermediate age-related macular degeneration. *Ophthalmology*. 2013;120:140-50.
 22. Lee EK, Lee SY, Yu HG. Epiretinal membrane in nonexudative age-related macular degeneration. anatomical features, visual outcomes and prognostic factors. *Retina*. 2016;36:1-9.