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Research Article

The Role of Posterior Vitreous Detachment in the Development of Exudative Age-Related Macular Degeneration

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Abstract

Purpose: To compare the state of the posterior vitreous in eyes with exudative age-related macular degeneration (AMD) with eyes with non-exudative AMD and controls.

Design: Prospective, Comparative Study

Methods: B-scan ultrasonography and Optical Coherence Tomography (OCT) were performed in 330 eyes of 165 subjects older than 65 years. Of these 330 eyes, 171 eyes had exudative AMD, 138 had non-exudative AMD and 21 eyes had no evident clinical presentation of AMD. At the same time a control group of 44 normal eyes of 22 patients was under regular follow up. B-scan ultrasonography and Optical Coherence Tomography (OCT) revealed the eyes with total posterior vitreous detachment (PVD), the eyes with persistent central vitreoretinal adhesion and the eyes that developed exudative (AMD) from non-exudative (AMD). Follow up time was 48 months (all the eyes were examined at the 1st, 3rd, 6th, 12th, 24th, 36th and 48th month).

Results: By ultrasonography and OCT, 16/171 eyes with exudative AMD (9.36%) of 165 patients (mean age 73,7) had complete PVD, while the rest 155/171 (90.64%) of 165 patients (mean age 80,05) had attached posterior vitreous. Eleven of 138 eyes with non-exudative AMD (7.97%) of 165 patients (mean age 82,93) had total (PVD), whereas the remaining 127 eyes (92.03%) of 165 patients (mean age 77,02) had attached posterior vitreous. Finally, from the 21 eyes with no clinical evidence of AMD with fellow eye of any type AMD, 10 eyes (47.62%) of 165 patients (mean age 71,92) had total PVD, while the rest 11 eyes (52.38%) of 165 patients (mean age 70,97) had attached posterior vitreous. Moreover, in the control group of 44 eyes of 22 patients (mean age 72,45), 20 eyes (45,45%) of 22 patients (mean age 71,80) had PVD while the rest 24 eyes (54,54%) of 22 patients (mean age 66,70) had attached posterior hyaloid. During the 48 months of the study, none of the 21 eyes with detached vitreous of 165 patients with AMD (mean age 77,43, stage of AMD-drusen) progressed to exudative AMD whereas 28 of 159 eyes with attached vitreous of 165 patients with AMD (mean age 73,96, stage of AMD- drusen) progressed to exudative AMD (Fisher exact 0.027).

Conclusions: Compared to normal healthy controls, vitreomacular adhesions appear to be associated with both dry and exudative AMD. Progression to exudative AMD seems to be lower in eyes with the presence of total vitreous detachment. Larger studies and longer studies need to replicate these findings and explore the potential therapeutic option of induced PVD.

Keywords: *Posterior Vitreous Detachment; Exudative Age-Related; Macular Degeneration*

Introduction

The cause of exudative AMD is not yet fully understood. Genetic factors and environmental factors, ischemia, inflammation, oxidative stress and the normal aging process have already been proposed [1]. Previous studies have found higher incidence of attached posterior vitreous in AMD [2,3] with no discrimination between exudative and non exudative form, the latter is noted in the most recent observations [4]. The role of the vitreoretinal interface has to be examined sufficiently in the context of AMD as it has been studied extensively for other macular diseases [5,6]. In the present study we used both B ultrasound and optical coherence tomography (OCT) to detect the status of the posterior vitreous in subjects with both forms of AMD as well as controls.

Methods

This prospective, comparative study included both eyes of 165 patients 65 years of age or older and both eyes of 22 patients older than 65 years with normal macula. All the evidence was gathered from the outpatient clinic of the Ophthalmology Department in the University Hospital of Patras during the period 2015-2019.The patients were frequently examined at the 1st, 3rd, 6th, 12th, 24th, 36th and 48th month. All the eyes sustained full ophthalmologic examination (sufficient visualization of the retina by physical examination was required) and a fluoroangiographic confirmation of the exudative type of AMD was an absolute requirement in order to design the study.

In all eyes under examination, B Ultrasonography and Optical Coherence Tomography, not only posterior segment biomicroscopy was performed to confirm the complete posterior vitreous detachment. In addition, Optical Coherence Tomography detected the partial posterior vitreous detachment (PVD) with the remaining vitreomacular adhesion and/or traction. The study excluded patients who had undergone intravitreal injections with anti-VEGF agents in either eye or any kind of ophthalmic surgery. Additional exclusion criteria included diabetic retinopathy, epiretinal gliosis and refractory myopia more than 2 dioptres. It was of great interest to identify the normal and dry AMD eyes that switched to exudative AMD during the study. In the following table we can see the patients' demographics.

	N (%)
Age (Years), Mean (SD)	79.7 (7.6)
Sex	
Men	75 (45.5)
Women	90 (54.5)

Table 1: *Patients' demographics.*

The eyes under examination were divided in four groups (Diagram A)

- 1st group: 138 eyes with non- exudative AMD (drusen or pigment changes)
- 2nd group: 171 eyes with active exudative AMD
- 3rd group: 21 eyes with no clinical evidence of AMD with any AMD in the fellow eye [7]
- 4th group: control group of extra 22 patients with 44 normal eyes and mean age 72,45 years. 20 eyes out of 44 had PVD while the rest 24 eyes appeared with attached posterior hyaloid via simple adhesion only without traction.

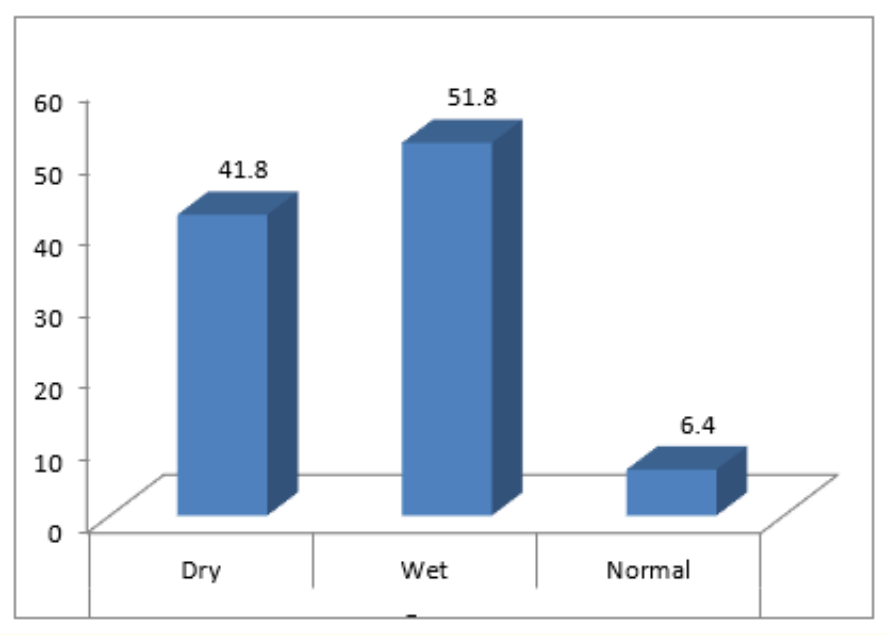


Diagram A: *Percentage of normal eyes, eyes with exudative and dry AMD.*

In the above diagram the percentage of normal and AMD eyes is given.

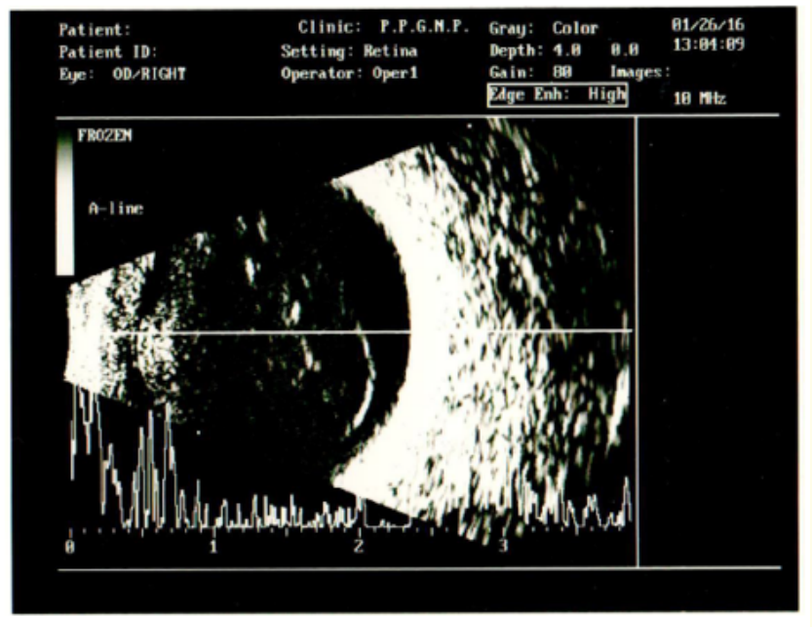
From the moment exudative AMD was diagnosed anti-VEGF treatment started and there was no additional follow up, meaning that the active exudative eyes included at the commencement had not undergone treatment yet. The reason is that intravitreal injections may alter the status of the posterior hyaloid and cause PVD.

Assignment to the subgroups (non-exudative AMD, exudative AMD, and control) was performed according to the results of posterior segment biomicroscope, Optical Coherence Tomography (OCT) and FA with the Heidelberg Retina Angiography (Heidelberg Engineering, Heidelberg, Germany).

All of the eyes were studied with B scan ultrasonography and Optical coherence tomography in order to recognize complete posterior vitreous detachment and vitreomacular adhesion and traction.

It was of great interest the number of eyes with exudative AMD in one eye and non- exudative in the fellow eye and different state of posterior vitreous detachment, while this study was mainly focused on the eyes that deteriorated to the active exudative type during the research and the appearance of the posterior vitreous [8].

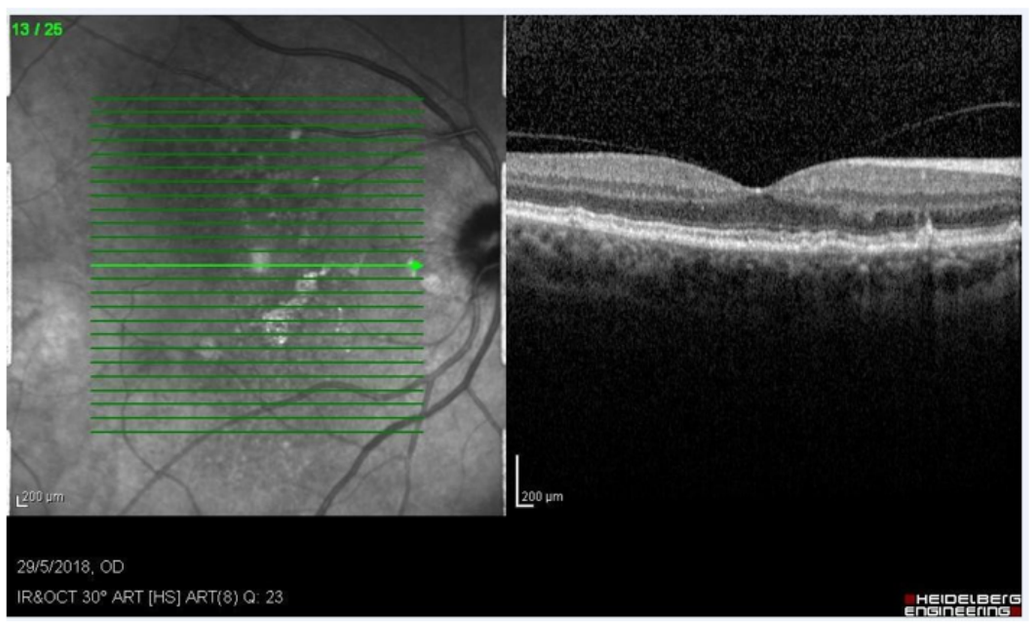
B scan Ultrasonography through-the-lid contact technique was used with a high-gain, real-time ultrasound device (Alcon Ultra Scan) in order to verify the complete PVD. The mobility of the posterior vitreous was examined during ocular saccades. (Picture 1) A- scan ultrasound complemented the B-scan ultrasound examination.



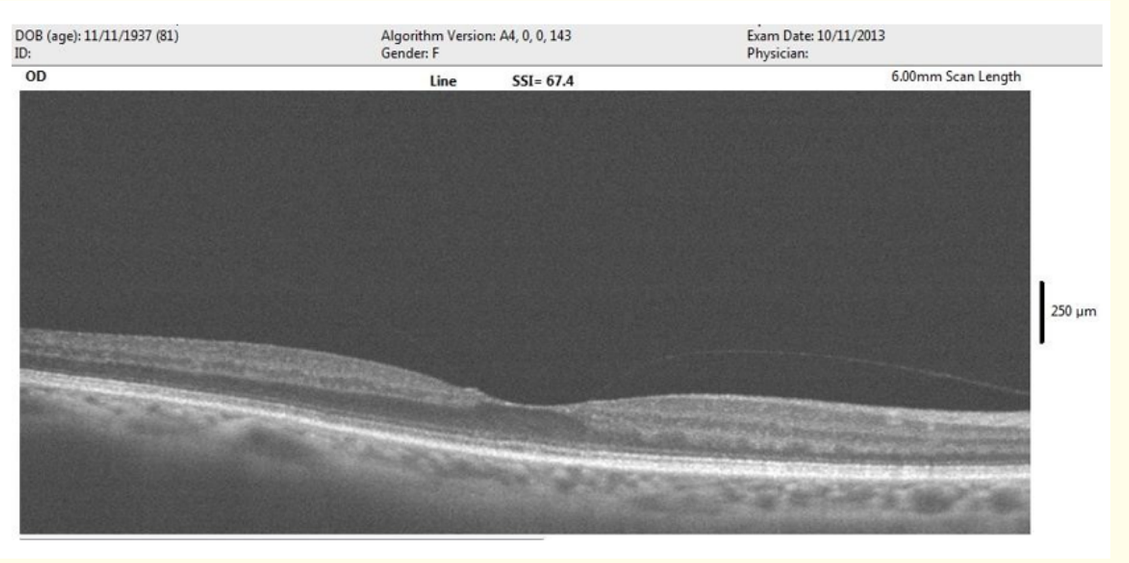
Picture 1: *Complete posterior vitreous detachment.*

Optical coherence tomography

After dilation of the pupil, multiple scans were performed with the Heidelberg Spectralis OCT-FA (Heidelberg Engineering, Heidelberg, Germany) in order to detect persistent vitreomacular adhesion (always in the fovea) (Picture2 and 3) [9].



Picture 2: *Partial posterior vitreous detachment-remaining vitremacular adhesion with no traction.*



Picture 3: *Partial posterior vitreous detachment with traction and disturbance of the foveal anatomy.*

Statistical analysis

The eyes included in the above groups were compared with respect to the presence of a complete PVD or partial PVD with the presence of central vitreomacular adhesion surrounded by localized vitreoretinal separation, determined by OCT. P values of 0.05 or less were considered statistically significant.

Results

Of the 171 eyes with exudative AMD, 16 (9.36%) had a complete PVD and in the rest 155 (90.64%) a partial PVD was observed.

Of the 138 eyes with non-exudative AMD, 11 (7.97%) had a complete PVD and in the rest 127 (92.03%) a partial PVD was observed.

Finally, in the 21 eyes with no clinical evidence of AMD in the 3rd group, 10 (47.62%) had complete PVD and the rest 11 (52.38%) maintained the posterior vitreous attached with only one eye with vitreomacular traction. It is important to note that 16 from the above 21 eyes had no complete PVD and the fellow eye had exudative AMD with no PVD as well.

The eyes in the 4th group remained stable during the study. No development of AMD, no evolution of partial PVD to complete, no evolution of adhesion to traction was noted. Table 2 contains the clinical characteristics of the eyes under investigation, exudative, dry or normal, the number of the eyes that had undergone complete PVD and the number of the eyes that deteriorated.

	N	**%**
Eye		
Dry	138	41.8
Wet	171	51.8
Normal	21	6.4
Deterioration to nvAMD		
No	131	82.4
Yes	28	17.6
PVD		
No	293	88.8
Yes	37	11.2

Table 2: *Clinical characteristics of the eyes.*

During the study 28 eyes (from the 138 dry and the 21 with no clinical evidence of AMD) in total of the 159, meaning (17.61%) turned into the exudative form of AMD. To be more specific, 18.8% of the dry eyes and 9.52% of the eyes with no clinical evidence of AMD. 26 eyes of the above 28 belonged to the non- exudative AMD group with partial PVD and the other 2 were eyes with partial PVD as well. In conclusion 100% of the eyes that deteriorated to the exudative type of AMD appeared with a persistent adhesion in the central macula surrounded by a detached vitreous cortex.

In more detail, the following diagram B demonstrates that 100% of the eyes that deteriorated into the exudative AMD had the posterior vitreous attached, meaning that 100% was no-PVD. From the 131 eyes that remained stable (159 - 28 = 131), 21 had PVD (11 from the dry group and 10 eyes with no clinical evidence of AMD) which is 16%.

On the other hand, 127 dry no PVD plus 11 eyes with no clinical evidence of AMD and no PVD, equals 138 eyes, minus 28 eyes that deteriorated leaves 110 stable eyes (84%) out of the 131 eyes.

As a result, 84% of the eyes that did not deteriorate had attached the posterior vitreous and the remaining 16% had complete PVD which applies to the observation period only as these eyes continued with the potential to deteriorate.

The eyes with dry AMD with drusen in the posterior pole that developed exudative AMD had mean age 79,6 years while the eyes with no clinical evidence of AMD that developed exudative AMD had mean age 81,5 years.

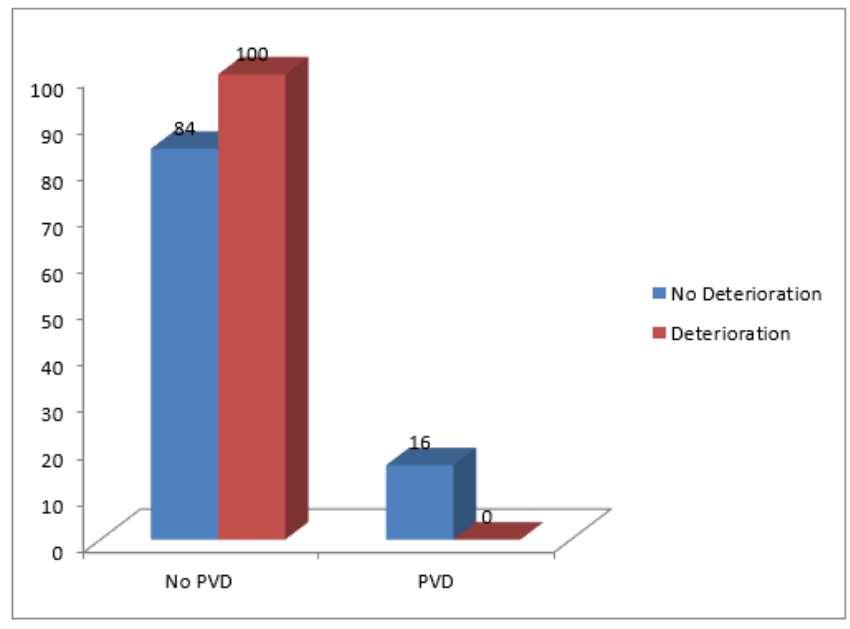


Diagram B: *Percentage of the eyes that were PVD or non-PVD regarding to deterioration.*

The correlation of the data that is of interest can be seen in the following table. The state of the posterior vitreous (complete or partial detachment) and the deterioration or not of the disease (from non-exudative or normal to exudative AMD). Statistical significance has been set to 0.05 and the analyses has been conducted with SPSS (version 22.0).

		PVD				
		No		Yes		
		N	%	N	%	P
Deterioration	No	110	84.0	21	16.0	0.027
	Yes	28	100.0	0	0.0	
Fisher's exact test						

Table 3: *Percentage of the eyes that were PVD or non-PVD regarding to deterioration.*

During the study, 28 eyes deteriorated and 100% of them belong to the category of non-PVD and the above correlation is statistically significant ($p < 0.05$). In conclusion, the development of exudative AMD is not independent of the status of the posterior vitreous, on the contrary, in the total of the eyes that deteriorated the posterior vitreous had been partially detached with remaining vitreomacular adhesion or traction. In table 4 and diagram C, the deterioration of the eyes during time is presented. 53,6% of the eyes that deteriorated to the exudative type of AMD developed neovascularization during the first 12 months.

Eyes that Deteriorated	In 12 mont hs	In 24 mont hs	In 36 mont hs	In 48 mont hs
Eyes with no clinical evidence of any AMD that developed exudative AMD	1	-	-	1
Dry eyes that developed exudative AMD	14	7	5	-
Total	15	7	5	1

Table 4: *Deterioration in time.*

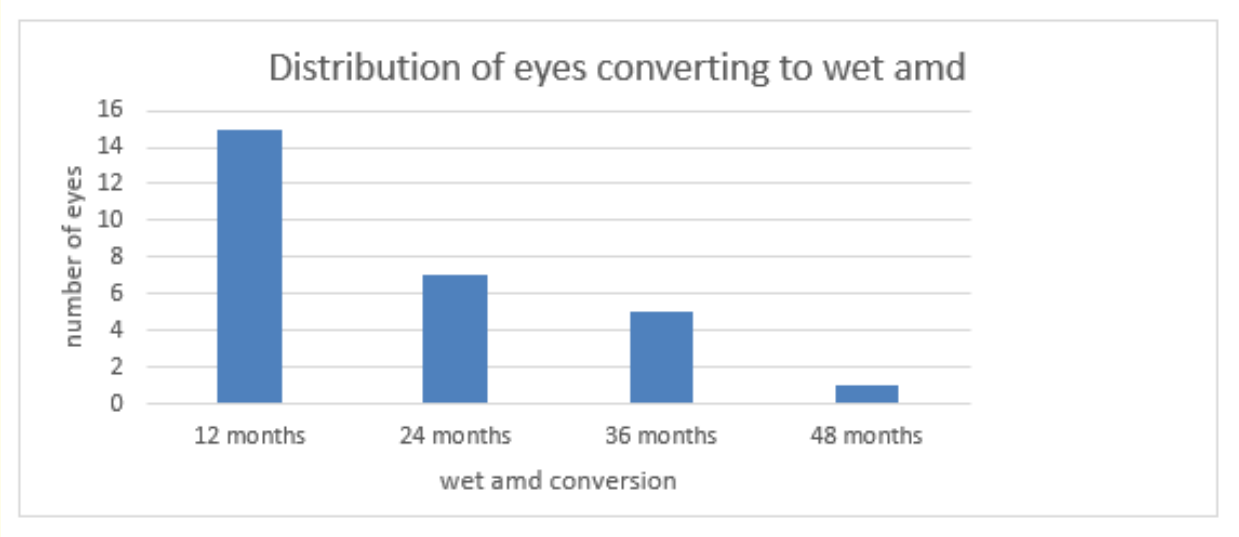


Diagram C: *Distribution of eyes converting to wet AMD*

Discussion

The dominating theory regarding the pathogenesis of AMD supports that the disease is multifactorial under the effect of genetics and environment. Large studies have already verified cigarette smoking, dietary elements, drusen and pigment changes [10-13] as known risk factors while hereditary factors have been identified to be responsible for the development of active only exudative AMD [14-17]. However differences in grading of AMD in both eyes cannot be explained by environmental and genetic factors only. Taking into account the important role of the posterior vitreous cortex (already verified in large clinical trials) in other retinal disorders with main representative the diabetic retinopathy, it would be sensible to raise the assumption that in the case of AMD as well, the vitreoretinal interface has to be considered of great value in the deterioration of dry AMD to exudative AMD with the dramatic reduction in visual acuity and quality of daily life of patients.

Which is the role of the vitreoretinal interface? Through which mechanism the posterior vitreous can evolve (not trigger because the disease has already started) dry to neovascular AMD? Krebs., *et al*. in 2007 presented clear indications that partial PVD could be a potential risk factor for exudative AMD.

Persistent vitreomacular adhesion holds a positive relation to the appearance of early signs of AMD [18] while it has been already proved that there is correlation between attached posterior vitreous and typical AMD [19]. Additionally double prevalence of vitreomacular adhesion is observed in patients with typical exudative AMD [20].

During the normal aging process of PVD, incomplete detachment of the posterior vitreous can lead to vitreomacular adhesion surrounded by a shallow detachment of the vitreous cortex and promote exudative AMD via the following possible routes.

Anomalous PVD with vitreomacular adhesion can cause low grade inflammation in the macula [21-23]. The effect of inflammation in AMD has already been verified.

Moreover, the presence of attached posterior cortex could prevent the normal diffusion of oxygen and nutrients causing relative ischemia, VEGF production and choroidal neovascularization (CNV).

In addition, the presence of attached posterior cortex exposes macula to cytokines or free radicals in the vitreous resulting in the development of CNV [24]. The above mentioned ischemia results in the production of VEGF-A and the promotion of Ang-2 which is normally in low levels. The complex of Ang-2 with the receptor Tie2 causes destabilization of the retinal vessels' wall and potential neovascularization [25-27].

In the present study of 330 eyes there is high prevalence of exudative AMD eyes (90,64%) with persistent vitreomacular adhesion and it is quite remarkable that the total of the eyes that evolved to neovascular AMD had sustained partial PVD. At the same time, the total amount of the dry eyes that remained stable had sustained complete PVD. Could complete separation of the posterior vitreous play a protective role?

Compared with large epidemiologic studies examining the known risk factors for AMD, the sample of the participants is small in the current study and it would be inappropriate to jump into final conclusions. Large scale clinical trials have to be conducted regarding the relationship of incomplete PVD and the development of neovascular AMD. There are more known risk factors that need to be co-examined such as genetics, smoking and antioxidants. However, a significant correlation has risen from our research between VMA and active exudative AMD.

In conclusion, ultrasonography and optical coherence tomography were used to determine the status of the posterior vitreous in eyes with dry AMD, neovascular AMD and controls. The total number of eyes that fell into the neovascular form appeared with partial PVD and

the total number of dry and control eyes that remained stable during the study appeared with complete PVD. Although, VMA is not the cause of neovascular AMD, the traction forces deteriorate the situation. As a result, in everyday clinical practice it is currently necessary to register and follow up the state of the posterior vitreous for the treatment and the prognosis of the patient. High prevalence of VMA and neovascular AMD in combination with the successive role of vitrectomy in vitreoretinal disorders prove the significant role of the posterior cortex. Furthermore, the presence of VMA can affect not only the development of neovascular AMD but the following response to treatment with anti-VEGF agents as well.

Moreover, as far as the treatment of exudative AMD is concerned, it seems that the vitreous has no role in the distribution and diffusion of the anti- VEGF as there is no need for dosology adjustment for vitrectomized eyes [28]. Perhaps the complete PVD alters the initial drug penetration in the retina, however, three days later it is similar regardless the state of the posterior vitreous [29].

In addition, intravitreal injections seem to be causing complete PVD which can affect the final outcome of the disease [30], but this detachment is rather uncommon. It is quite remarkable that the number of the injections increases the reflectivity in the vitreous B scan [31]. Eyes with focal vitreomacular adhesion are more likely to develop complete PVD compared to eyes with broad adhesion [32,33]. Lately, there are more treatment options with new anti-VEGFs such as brolucizumab or abicipar and substances against the receptor of angiopoietin-2 like faricimab [34-38].

Considering the role of posterior vitreous in the final outcome of the anti-VEGF treatment, it seems that eyes with complete PVD need in total fewer injections [39], while eyes with VMA require more intensive treatment with more injections and worse visual outcome [40-42]. In the case of aflibercept and bevacizumab the anatomical and functional outcome in typical AMD depend on the initial visual acuity, age and retinal thickness [43-45]. This could be the trigger for personalized therapeutic approach in exudative AMD with anti-VEGF since vitreomacular adhesion or traction can compete the effectiveness of the of the regimen [46,47]. Moreover, it is essential that eyes with vitreomacular traction should be followed up closely for relapse after discontinuation of therapy [48].

Finally, it could be supported that since vitreomacular adhesion is indicated as a potential risk factor for the development of exudative active AMD, complete PVD could act as a protective factor reasonably raising the concept of protective pharmaceutic vitreolysis or even vitrectomy in high risk patients for exudative AMD [49-51]. There are already clear indications for the effectiveness of intravitreal ocriplasmin in focal vitreomacular adhesion in neovascular AMD [52]. The role of statins could be also examined in future studies as it seems that there are lower levels of Ang-2 and VEGF in diabetic patients under simvastatin treatment that have undergone vitrectomy [53-56].

Bibliography

1. Spaide RF., *et al*. "Choroidal neovascularization inage- related macular degeneration - what is the cause?" *Retina* 23 (2003): 595-614.

2. Ondes F., *et al.* "Role of the vitreous in age-related macular degenera-tion". *The Japanese Journal of Ophthalmology* 44 (2000): 91-93.

3. Weber-Krause B and Eckardt C. "[Incidence of posterior vitreous detachment in the elderly]". *Ophthalmologe* 94 (1997): 619-623."

4. Krebs I., *et al.* "Posteriormacular adhesion: a potential risk factorfor exudative age-related macular degenera-tion?" *American Journal of Ophthalmology* 144 (2007): 741-746.

5. Ito Y., *et al*. "Mapping posterior vitreous detachment by optical coherence tomography in eyes with idiopathic macular hole". *American Journal of Ophthalmology* 135 (2003): 351-355.

6. Johnson MW. "Perifoveal vitreous detachment and its macular complications". *Transactions of the American Ophthalmological Society* 103 (2005): 537-567.

7. Category 1 (No AMD): a few (5-15), small (<63µm) or no drusen without pigment changes. Age-related macular degeneration (Retina / Vitreous ,Contributors: Brittni A. Scruggs, MD, PhD, Armin Avdic, MS, and Karen M. Gehrs, MD Posted (2019).

8. Retina "Prediction of Individual Disease Conversion in Early AMD Using Artificial Intelligence Ursula Schmidt-Erfurth; Sebastian M. Waldstein; Sophie Klimscha; Amir Sadeghipour; Xiaofeng Hu; Bianca S. Gerendas; Aaron Osborne; Hrvoje Bogunović) (2018).

9. Kim YC., *et al.* "Enhanced high-density line spectral-domain optical coherence tomography imaging of the vitreoretinal interface: Description of selected cases". *Seminars in Ophthalmology* 31 (2016): 559-566.

10. Clemons TE., *et al.* "Age-Related Eye Disease Study Research Group. Risk factors for the incidence of advanced age-related macular degeneration in the Age-Related Eye Disease Study (AREDS): AREDS Report No. 19". *Ophthalmology* 112 (2005): 533-539.

11. Chakravarthy U., *et al*. "Cigarette smoking and age-related macular degeneration in the EUREYE Study". *Ophthalmology* 114 (2007): 1157-1163.

12. Francis PJ., *et al.* "The LOC387715 gene, smoking, body mass index, environmental association with advanced age-related macular degeneration". *Human Heredity* 63 (2007): 212-218.

13. Age-Related Eye Disease Study Research Group. "Risk factors associated with age- related macular degeneration. A case-control study in the age-related eye disease study: Age- Related Eye Disease Study (AREDS) Report No. 3". *Ophthalmology* (2000).

14. Edwards AO., *et al.* "Complement factor H polymorphism and age- related macular degeneration". *Science* 308 (2005): 421-424.

15. Scott WK., *et al*. "Independent effects of complement factor H Y402H polymorphism and cigarette smoking on risk of age-related macular degeneration". *Ophthalmology* 114 (2007): 1151-1156.

16. Souied EH., *et al.* "The epsilon4 allele of the apolipoprotein E gene as a potential protective factor for exudative age-related macular degeneration". *American Journal of Ophthalmology* 125 (1998): 353-359.

17. Churchill AJ., *et al*. "VEGF polymorphisms are associated with neovascular age-related macular degeneration". *Human Molecular Genetics* 15 (2006): 2955-2961.

18. Schulze S., *et al.* "Appearance of age-related macular degeneration in vitrectomized and nonvitrectomized eyes: An intraindividual case study". *Acta Ophthalmologica* 90 (2012): 244-247.

19. Nomura Y., *et al.* "Vitreomacular interface in typical exudative age-related macular degeneration and polypoidal choroidal vasculopathy". *Ophthalmology* 118 (2011): 853-859.

20. Jackson TL., *et al.* "Vitreous attachment in age-related macular degeneration, diabetic macular edema, and retinal vein occlusion: A systematic review and metaanalysis". *Retina* 33 (2013): 1099- 1108.

21. Anderson DH., *et al.* "A role for local inflammation in the formation of drusen in the aging eye". *American Journal of Ophthalmology* 134 (2002): 411-431.

22. Donoso LA., *et al*. "The role of inflammation in the pathogenesis of age-related macular degeneration". *Survey of Ophthalmology* 51 (2006): 137-152.

23. Zarbin MA. "Current concepts in the pathogenesis of age-related macular degeneration". *Archives of Ophthalmology* 122 (2004): 598-614.

24. Adamis AP and Shima DT. "The role of vascular endothelial growth factor in ocular health and disease". *Retina* 25 (2005): 111-118.

25. Identification of ANGPT2 as a New Gene for Neovascular Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy in the Chinese and Japanese Populations (2017).

26. Li Ma., *et al.* "Investigative Ophthalmology and Visual Science 58 (2017): 1076-1083.

27. Danny S Ng., *et al.* "Elevated angiopoietin 2 in aqueous of patients with neovascular age related macular degeneration correlates with disease severity at presentation (2017).

28. Danny SNg., *et al.* "Expressions of Angiopoietins and Tie2 in Human Choroidal Neovascular Membranes Atsushi Otani; Hitoshi Takagi; Hideyasu Oh; Shinji Koyama; Miyo Matsumura; Yoshihito Honda". I*nvestigative Ophthalmology and Visual Science* 40 (1999): 1912-1920.

29. Ahn SJ., *et al.* "Intraocular pharmacokinetics of ranibizumab in vitrectomized versus nonvitrectomized eyes". *Investigative Ophthalmology and Visual Science* 55 (2014): 567-573.

30. Goldenberg DT., *et al.* "Posterior vitreous detachment with microplasmin alters the retinal penetration of intravitreal bevacizumab (avastin) in rabbit eyes". *Retina* 31 (2011): 393-400.

31. Geck U., *et al.* "Posterior vitreous detachment following intravitreal drug injection". *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie* 251 (2013): 1691-1695.

32. Mato-Gondelle T., *et al.* "Ultrasonographic findings in the vitreous of patients with age-related macular degeneration treated with intravitreal anti-vascular endothelial growth factor injections". *Retina* 38 (2018): 1962-1967.

33. Veloso CE., *et al.* "Vitreomacular interface after anti- vascular endothelial growth factor injections in neovascular age-related macular degeneration". *Ophthalmology* 122 (2015): 1569-1572.

34. Üney G., *et al.* "Role of posterior vitreous detachment on outcome of anti-vascular endothelial growth factor treatment in age-related macular degeneration". *Retina* (Philadelphia, Pa.) 2014 Review". Archivos de la Sociedad Española de Oftalmología 95.2 (2020): 75-83.

35. New therapeutic targets in the treatment of age-related macular degeneration [Article in En, Spanish].

36. P V Muñoz-Ramón., *et al.* "Safety and Efficacy of Different Doses and Regimens of Faricimab vs Ranibizumab in Neovascular Age-Related Macular Degeneration The AVENUE (2020).

37. Jayashree Sahni., *et al*. "Affiliations expand Review Expert Opin Investig Drugs 28.10 (2019): 861-869.

38. Tie-2/Angiopoietin pathway modulation as a therapeutic strategy for retinal disease.

39. Rehan M Hussain., *et al.* "Systemic counterregulatory response of angiopoietin-2 after aflibercept therapy for nAMD: a potential escape mechanism (2021).

40. Reinhard Angermann Teresa Rauchegger Yvonne Nowosielski Christof Seifarth Stefan Egger First published: 16 December 2020". *EMBO Molecular Medicine* 11.5 (2019): e10362.

41. Anne Wolf and Thomas Langmann. "Anti-VEGF-A/ANG2 combotherapy limits pathological angiogenesis in the eye: a replication study (2019).

42. Waldstein SM., *et al.* "Effect of posterior vitreous detachment on treat-and-extend versus monthly ranibizumab for neovascular age-related macular degeneration". *The British Journal of Ophthalmology* 104 (2020): 899-903.

43. Mayr-Sponer U., *et al.* "Influence of the vitreomacular interface on outcomes of ranibizumab therapy in neovascular age-related macular degeneration". *Ophthalmology* 120 (2013): 2620-2629.

44. Ashraf M., *et al.* "Age-related macular degeneration: Using morphological predictors to modify current treatment protocols". *Acta Ophthalmologica* 96 (2018): 120-133.

45. Toyama T., *et al.* "Posterior vitreous detachment and macular microvasculature in the elderly". *PloS one* 15 (2020): e0231351.

46. McKibbin MA., *et al.* "The influence of vitreomacular adhesion on outcomes after aflibercept therapy for neovascular age-related macular degeneration". *Retina* 35 (2015): 1951-1956.

47. Neudorfer M., *et al.* "The role of posterior vitreous detachment on the efficacy of anti-vascular endothelial growth factor intravitreal injection for treatment of neovascular age-related macular degeneration". *Indian Journal of Ophthalmology* 66 (2018): 1802-1807.

48. Neudorfer M., *et al.* "Reply: The role of posterior vitreous detachment on the efficacy of anti-vascular endothelial growth factor intravitreal injection for treatment of neovascular age-related macular degeneration". *Indian Journal of Ophthalmology* 67 (2019): 1784.

49. Waldstein SM., *et al*. "Predictive value of retinal morphology for visual acuity outcomes of different ranibizumab treatment regimens for neovascular amd". *Ophthalmology* 123 (2016): 60-69.

50. Awasthi U., *et al.* "Comment on: The role of posterior vitreous detachment on the efficacy of anti-vascular endothelial growth factor intravitreal injection for treatment of neovascular age-related macular degeneration". *Indian Journal of Ophthalmology* 67 (2019): 1783.

51. Munk MR., *et al.* "The impact of the vitreomacular interface in neovascular age-related macular degeneration in a treat-and- extend regimen with exit strategy". *Ophthalmology Retina* 2 (2018): 288-294.

52. Sebag J. "Pharmacologic vitreolysis". *Retina* 18 (1998): 1-3.

53. Sebag J. "Is pharmacologic vitreolysis brewing?" *Retina* 22 (2002): 1-3.

54. Sebag J. "Molecular biology of pharmacologic vitreolysis". *Transactions of the American Ophthalmological Society* 103 (2005): 473-494.

55. Novack RL., *et al.* "Safety of intravitreal ocriplasmin for focal vitreomacular adhesion in patients with exudative age-related macular degeneration". *Ophthalmology* 122 (2015): 796-802.

56. Raimo Tuuminen., *et al.* "Low intravitreal angiopoietin-2 and VEGF levels in vitrectomized diabetic patients with simvastatin treatment Sari Sahanne, Sirpa Loukovaara". *Observational Study Acta Ophthalmologica* 92.7 (2014): 675-681.

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