Vitreomacular Adhesion in Active and End-Stage Age-related Macular Degeneration

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• PURPOSE: To evaluate vitreomacular relations in different stages of age-related macular degeneration (AMD) without the influence of genetics and environmental factors.

• DESIGN: Retrospective, observational case series.

• METHODS: This was a multicenter study consisting of 29 previously untreated subjects with active exudative (wet) AMD in one eye and active nonexudative (dry) AMD in the fellow eye who were compared with 10 previously untreated subjects with end-stage geographic atrophy in one eye and an end-stage fibrotic (disciform) scar in the fellow eye. All subjects were studied with ultrasonography to identify the presence of posterior vitreous detachment (PVD) and by optical coherence tomography to detect vitreomacular adhesion (VMA).

• RESULTS: The incidence of PVD in eyes with nonexudative AMD was 20 (69%) of 29, compared with 6 (21%) of 29 with active exudative AMD ($P = .002$). VMA was present in 11 (38%) of 29 of eyes with exudative AMD and in only 3 (10%) of 29 eyes with nonexudative AMD ($P = .008$). The incidence of PVD in geographic atrophy was 7 (70%) of 10, compared with 4 (40%) of 10 with disciform scar ($P = .44$). VMA was present in 2 (20%) of 10 eyes with disciform scars and in 0 (0%) of 10 eyes with geographic atrophy ($P = .48$).

• CONCLUSIONS: PVD may protect against exudative AMD, whereas VMA may promote exudative AMD. This phenomenon is not evident in end-stage disease because of an increased incidence of PVD and a decreased incidence of VMA in eyes with disciform scars. Genetic and environmental factors do not seem to influence these observations. (Am J Ophthalmol 2009;148:79–82. © 2009 by Elsevier Inc. All rights reserved.)

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THE CAUSE OF CHOROIDAL NEOVASCULARIZATION (CNV) in exudative age-related macular degeneration (AMD) is not fully understood, especially regarding the role of vitreous. Etiologic research has proposed the actions and interactions of multiple genes and environmental factors as causative,[1] whereas other proposed etiologic factors include oxidative stress, ischemia, aging of the retinal pigment epithelium (RPE), and inflammation.[2] Previous studies[3–5] have described the relationship between the posterior vitreous and the macula in AMD and have suggested that vitreomacular adhesion (VMA) is important in the development of exudative changes. Whether genetic and environmental factors specifically affect this relationship is yet to be described. Furthermore, previous studies examined only patients with active disease and not those with end-stages of AMD (ie, disciform scar or geographic atrophy). This study aims to mitigate any influence of genetics and environmental factors by studying patients with exudative (wet) AMD in one eye and nonexudative (dry) AMD in the fellow eye. The study also compares patients with active disease with those with end-stage AMD.

METHODS

THIS OBSERVATIONAL CASE SERIES INCLUDED 39 PATIENTS enrolled from the Ludwig Boltzman Institute for Retinology in Vienna, Austria; the Vitreous-Retina-Macula Consultants of New York, New York, New York; and the VMR Institute, Huntington Beach, California. Medical records at each center were reviewed retrospectively to identify patients diagnosed with exudative AMD in one eye and nonexudative AMD in the fellow eye for inclusion in the active disease group, or disciform scar in one eye and geographic atrophy in the fellow eye for inclusion in the end-stage group. Subjects were excluded from the study if there had been prior AMD treatment of any kind (laser, photodynamic therapy, or injections). Other exclusion criteria were a history of vitreoretinal surgery; retinal detachment; or the presence of diabetic retinopathy, macular pucker, macular holes, uveitis, myopia of more than −2 diopters, asteroid hyalosis, or synchysis scintillans.

Fundus photography and fluorescein angiography were performed with the Heidelberg Retina Angiograph (Heidelberg Engineering, Heidelberg, Germany) or the Topcon

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TABLE 1. Incidence of Posterior Vitreous Detachment in Age-Related Macular Degeneration via Ultrasonography

	No PVD		Partial PVD		Complete PVD		
	No.	%	No.	%	No.	%	*P* value
Active AMD (n = 29)							.002
Wet AMD	14	(48)	9	(31)	6	(21)	
Dry AMD	3	(10)	6	(21)	20	(69)	
End-stage AMD (n = 10)							.44
Disciform scar	4	(40)	2	(20)	4	(40)	
Geographic atrophy	3	(30)			7	(70)	

AMD = age-related macular degeneration; PVD = posterior vitreous detachment.

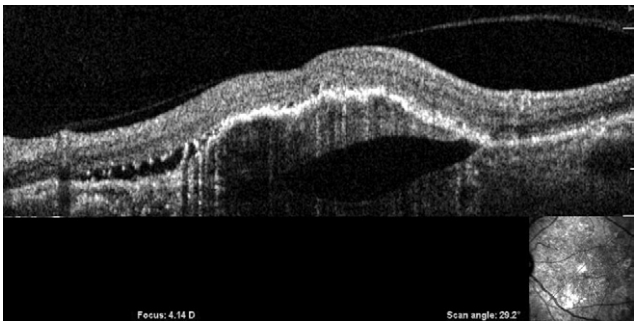

FIGURE. Combined optical coherence tomography and scanning laser ophthalmoscopy image showing the posterior vitreous cortex attached to the macula in the area of choroidal neovascularization.

Imagenet 2000 (Topcon, Tokyo, Japan) to diagnose and classify AMD as either active nonexudative (drusen and pigment clumping), active exudative (choroidal neovascularization, RPE detachment, etc.), end-stage nonexudative (geographic atrophy), or end-stage exudative (fibrotic disciform scar) AMD.

High-gain, real-time ultrasonography was performed using a 10-mgHz probe (Quantel Inc, Clermont Ferrand, France) using a through-the-lid contact technique. Without knowledge of the AMD status, the mobility of the posterior vitreous was determined during ocular saccades to detect the presence of a posterior vitreous detachment (PVD), partial PVD, or no PVD.

Optical coherence tomography (OCT) was performed with either the spectral-domain OCT-SLO (OTI Inc, Toronto, Canada), the OCT-1000 (Topcon), or the Stratus III OCT Scanner (Carl Zeiss, San Leandro, California, USA) to detect vitreomacular adhesion. Six radial scans through center of the fovea were performed with additional lines through the upper and lower arcades, as well as radial lines through the optic disc.

Statistical analysis was performed using the McNemar test for correlated proportions to obtain Chi-square distributions for evaluations of the OCT scans and lens status. Each subject was analyzed for discordant pairs (VMA in one eye, no VMA in fellow eye; phakic lens status in one eye, pseudophakic in fellow eye). The incidence of posterior PVD by ultrasound was evaluated using the Wilcoxon signed-rank test to accommodate 3 variables. *P* values of .05 or less were considered to be statistically significant.

RESULTS

IN THE ENTIRE STUDY POPULATION, 14 (36%) OF 39 PATIENTS were men and 25 (64%) of 39 patients were women. In subjects with active AMD, the mean age ± standard deviation (SD) was 79.4 ± 6.1 years, whereas in the group with end-stage AMD, the mean age ± SD was 85.1 ± 9.1 years. The age and gender distributions in the subgroups were similar. There were no subjects with polypoidal choroidal vasculopathy and only 2 subjects (5% of the study population) with retinal angiomatous proliferation.

TABLE 2. Incidence of Vitreomacular Adhesion in Age-Related Macular Degeneration via Optical Coherence Tomography

	No VMA		VMA		
	No.	%	No.	%	*P* value
Active stage (n = 29)					.008
Wet AMD	18	62	11	38	
Dry AMD	26	90	3	10	
End stage (n = 10)					.48
Disciform scar	8	80	2	20	
Geographic atrophy	10	100			

AMD = age-related macular degeneration; VMA = vitreomacular adhesion.

Complete PVD was present by ultrasound in 6 (21%) of 29 eyes with active exudative AMD, as compared with 20 (69%) of 29 eyes with nonexudative AMD (*P* = .002; Table 1). In end-stage AMD, PVD was detected in 7 (70%) of 10 eyes with nonexudative AMD (geographic atrophy), whereas 4 (40%) of 10 eyes with end-stage exudative AMD (disciform scar) had a PVD (*P* = .44) by ultrasound.

Optical coherence tomography revealed VMA (Figure) in 11 (38%) of 29 eyes with exudative AMD and in only 3 (10%) of 29 eyes with nonexudative AMD (*P* = .008; Table 2). OCT revealed VMA in 2 (20%) of 10 eyes with disciform scar and in 0 (0%) of 10 eyes with geographic atrophy (*P* = .48). There were no instances of vitreoschisis[6] detected by OCT.

Pseudophakia was present in 15 (52%) of 29 eyes with active exudative AMD, whereas 12 (41%) of 29 eyes with

nonexudative AMD were pseudophakic ($P = .25$). The findings were similar in end-stage disease, where 5 (50%) of 10 eyes with disciform scarring were pseudophakic, whereas 7 (70%) of 10 eyes with geographic atrophy were pseudophakic ($P = .25$).

DISCUSSION

THE KNOWN RISK FACTORS FOR AMD FALL INTO TWO CATEgories. Environmental factors include smoking,[7,8] body mass index,[9] and diet,[10] with smoking in particular representing a risk factor for progression to advanced AMD.[11] Genetic factors also have been identified,[12,13] with many specifically contributing to exudative[14–16] and advanced[17,18] AMD. Recently, Krebs and associates proposed that total PVD is protective against exudative AMD, whereas VMA is a risk factor for exudative AMD.[3] To explore this hypothesis further, this study evaluated patients with exudative AMD in one eye and nonexudative AMD in the fellow eye to mitigate the influence of environmental and genetic factors. Additionally, active AMD (exudative or nonexudative) was compared with end-stage AMD (disciform scar or geographic atrophy) with respect to the status of vitreous.

The results demonstrate that in active AMD, PVD is highly associated with nonexudative AMD, whereas VMA is related strongly to exudative AMD. In active AMD, complete PVD was found in 69% of patients with nonexudative AMD, as opposed to only 21% of patients with exudative AMD ($P = .002$). This compares favorably with the results of a study[19] of 551 subjects that determined that for a group of individuals with a mean age of 80 years (79.4 years was the mean age of the active AMD subjects reported herein), the incidence of PVD was 73%, very close to the 69% incidence observed in the present study for the eyes with dry AMD and very different from the 21% incidence of PVD detected in the eyes with wet AMD.

Vitreomacular adhesion was found in 38% of patients with active exudative AMD, as compared with 10% of patients with nonexudative AMD ($P = .008$). In end-stage disease, however, there is a greater incidence of PVD and a lower incidence of VMA in eyes with disciform scars. Because of the small sample size (n = 10), it is inappropriate to draw any definitive conclusions from these results, and thus larger studies are needed to test more adequately the hypothesis that disciform scarring in the macula can promote PVD. Because a fibrotic scar in the macula has devastating effects on all the cells in the central neural retina, it is plausible that the effects on Mueller cells in particular would alter the integrity of the internal limiting lamina and promote vitreoretinal dehiscence, facilitating PVD.[20] Although this may explain the decreased incidence of VMA from 38% in active exudative AMD to 20% in eyes with disciform scars and the increased incidence of PVD from 21% in active exudative AMD to 40% in end-stage disciform scars, the study population reported herein is too small to draw such conclusions definitively.

Thus, it seems that for active AMD, the findings in previous studies[3] are confirmed and the observations regarding the potential role of vitreous in AMD[3,4] are not influenced by genetic and environmental factors. The possible mechanisms by which VMA may promote exudative AMD are as follows.

Anomalous PVD[21] with VMA can cause chronic traction on the macula and can induce low-grade inflammation. The effects of inflammation on AMD have previously been established.[22–24] The presence of the posterior vitreous cortex attached to the macula may prevent oxygen and perhaps nutrients from diffusing from the ciliary body into the macula. The resulting state of relative ischemia may promote CNV via the action of vascular endothelial growth factor. An adherent posterior vitreous cortex may trap proangiogenic cytokines such as vascular endothelial growth factor [25] within the macula, contributing to neovascularization. Bishop and associates have argued that vascular endothelial growth factor may be bound to vitreous collagen fibers altered by aging, and therefore, persistent VMA may contribute to the development of exudative AMD.[26] Vitreomacular traction may impact the chorioretinal interface and may disrupt the normal interactions between the RPE and its junctional proteins. Indeed, disruption of junctional RPE proteins has been shown to increase CNV.[27]

It is also possible that as soon as the CNV begins in exudative AMD, an attached posterior vitreous promotes further vessel proliferation, similar to how it contributes to retinal and optic disc neovascularization in diabetic retinopathy,[28] that is, via traction.

In conclusion, ultrasonography and OCT were used to determine the incidence of PVD and VMA in previously untreated patients with active AMD, as well as in patients with end-stage AMD. Vitreous is more likely to be attached in exudative AMD than in nonexudative AMD, and thus anomalous PVD may be an important risk factor for progression of nonexudative AMD to exudative AMD. If future prospective studies confirm these findings, then it may be valuable to consider vitrectomy or pharmacologic vitreolysis[29–31] as prophylaxis in preventing exudative AMD.

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S.B., L.A.Y., J.S.); data collection (C.D.R., I.K., I.A.B., A.I.K., J.S.); provision of materials, patients, or resources (I.K., S.B., I.A.B., A.I.K., L.A.Y., J.S.); obtaining funding (S.B., L.A.Y., A.A.S., J.S.); literature search (C.D.R., J.S.); and administrative, technical, or logistic support (S.B., L.A.Y., A.A.S., J.S.). Institutional review board (IRB) approval was obtained from the University of Southern California Health Sciences Center IRB, Los Angeles, California; the "Ethikkomission der Stadt Wien nach Wr. KAG, AMG und MPG," Vienna, Austria; and the Lenox Hill Hospital IRB, New York, New York.

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REFERENCES

1. Haddad S, Chen CA, Santangelo SL, Seddon JM. The genetics of age-related macular degeneration: a review of progress to date. Surv Ophthalmol 2006;51:316–363.
2. Zarbin MA. Current concepts in the pathogenesis of age-related macular degeneration. Arch Ophthalmol 2004;122: 598–614.
3. Krebs I, Brannath W, Glittenberg C, et al. Posterior vitreomacular adhesion: a potential risk factor for exudative age-related macular degeneration? Am J Ophthalmol 2007; 144:741–746.
4. Ondes F, Yilmaz G, Acar MA, Unlü, Kocaoğlan H, Arsan AK. Role of the vitreous in age-related macular degeneration. Jpn J Ophthalmol 2000;44:91–93.
5. Weber-Krause B, Eckardt C. Incidence of posterior vitreous detachment in the elderly. Ophthalmologe 1997;94:619–623.
6. Sebag J. Vitreoschisis. Graefes Arch Clin Exp Ophthalmol 2008;246:329–332.
7. Chakravarthy U, Augood C, Bentham GC, et al. Cigarette smoking and age-related macular degeneration in the EUREYE Study. Ophthalmology 2007;114:1157–1163.
8. Seddon JM, George S, Rosner B. Cigarette smoking, fish consumption, omega-3 fatty acid intake, and associations with age-related macular degeneration: the US Twin Study of Age-Related Macular Degeneration. Arch of Ophthalmol 2006;124:995–1001.
9. 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 Report No. 3. Ophthalmology 2000;107:2224–2232.
10. O'Connell ED, Nolan JM, Stack J, et al. Diet and risk factors for age-related maculopathy. Am J Clin Nutr 2008;87:712–722.
11. Tan JS, Mitchell P, Kifley A, Flood V, Smith W, Wang JJ. Smoking and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. Arch Ophthalmol 2007;125:1089–1095.
12. Edwards AO, Ritter R III, Abel KJ, et al. Complement factor H polymorphism and age-related macular degeneration. Science 2005;308:421–424.
13. Scott WK, Schmidt S, Hauser MA, et al. Independent effects of complement factor H Y402H polymorphism and cigarette smoking on risk of age-related macular degeneration. Ophthalmology 2007;114:1151–1156.
14. Souied EH, Benlian P, Amouyel P, et al. The epsilon4 allele of the apolipoprotein E gene as a potential protective factor for exudative age-related macular degeneration. Am J Ophthalmol 1998;125:353–359.
15. Churchill AJ, Carter JG, Lovell HC, et al. VEGF polymorphisms are associated with neovascular age-related macular degeneration. Hum Mol Genet 2006;15:2955–2961.
16. Hughes AE, Orr N, Patterson C, et al. Neovascular age-related macular degeneration risk based on CFH, LOC387715/HTRA1, and smoking. PLoS Med 2007;4:e355.
17. Seddon JM, George S, Rosner B, Klein ML. *CFH* gene variant, Y402H, and smoking, body mass index, environmental associations with advanced age-related macular degeneration. Hum Hered 2006;61:157–165.
18. Francis PJ, George S, Schultz DW, et al. The *LOC387715* gene, smoking, body mass index, environmental associations with advanced age-related macular degeneration. Hum Hered 2007;63:212–218.
19. Hikichi T, Hirokawa H, Kado M, et al. Comparison of the prevalence of posterior vitreous detachment in whites and Japanese. Ophthalmic Surg 1995;26:39–43.
20. Bringmann A, Pannicke T, Grosche J, et al. Müller cells in the healthy and diseased retina. Prog Retin Eye Res 2006; 25:397–424.
21. Sebag J. Anomalous PVD—a unifying concept in vitreoretinal diseases. Graefes Arch Clin Exp Ophthalmol 2004; 242:690–698.
22. Anderson DH, Mullins RF, Hageman GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. Am J Ophthalmol 2002;134:411–431.
23. Donoso LA, Kim D, Frost A, Callahan A, Hageman G. The role of inflammation in the pathogenesis of age-related macular degeneration. Surv Ophthalmol 2006;51:137–152.
24. Zarbin MA. Current concepts in the pathogenesis of age-related macular degeneration. Arch Ophthalmol 2004;122: 598–614.
25. Adamis AP, Shima DT. The role of vascular endothelial growth factor in ocular health and disease. Retina 2005;25: 111–118.
26. Bishop PN, Holmes DF, Kadler KE, et al. Age-related changes on the surface of vitreous collagen fibrils. Invest Ophthalmol Vis Sci 2004;45:1041–1046.
27. Imamura Y, Noda S, Hashizume K, et al. Drusen, choroidal neovascularization, and retinal pigment epithelium dysfunction in SOD1-deficient mice: a model of age-related macular degeneration. Proc Natl Acad Sci U S A 2006;103:11282–11287.
28. Sebag J. Diabetic vitreopathy. Ophthalmology 1996;103: 205–206.
29. Sebag J. Pharmacologic vitreolysis. Retina 1998;18:1–3.
30. Sebag J. Is pharmacologic vitreolysis brewing? Retina 2002; 22:1–3.
31. Sebag J. Molecular biology of pharmacologic vitreolysis. Trans Am Ophthalmol Soc 2005;103:473–494.

Biosketch

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Biosketch

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