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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From the VMR Institute, Huntington Beach, California (C.D.R., J.S.); the Doheny Eye Institute, Keck/University of Southern California School of Medicine, Los Angeles, California (C.D.R., A.A.S., J.S.); the Ludwig Boltzmann Institute for Retinology and Biomicroscopic Lasersurgery, Department of Ophthalmology, Rudolf Foundation Clinic, Vienna, Austria (I.K., S.B.); 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...
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-mHz 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 Status 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.

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 detected by OCT.

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

<table>
<thead>
<tr>
<th>TABLE 1. Incidence of Posterior Vitreous Detachment in Age-Related Macular Degeneration via Ultrasonography</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PVD</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Active AMD (n = 29)</td>
</tr>
<tr>
<td>Wet AMD</td>
</tr>
<tr>
<td>Dry AMD</td>
</tr>
<tr>
<td>End-stage AMD (n = 10)</td>
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<tr>
<td>Disciform scar</td>
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<tr>
<td>Geographic atrophy</td>
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</tbody>
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AMD = age-related macular degeneration; PVD = posterior vitreous detachment.

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

<table>
<thead>
<tr>
<th>No VMA</th>
<th>VMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Active stage (n = 29)</td>
<td>.008</td>
</tr>
<tr>
<td>Wet AMD</td>
<td>18</td>
</tr>
<tr>
<td>Dry AMD</td>
<td>26</td>
</tr>
<tr>
<td>End stage (n = 10)</td>
<td>.48</td>
</tr>
<tr>
<td>Disciform scar</td>
<td>8</td>
</tr>
<tr>
<td>Geographic atrophy</td>
<td>10</td>
</tr>
</tbody>
</table>

AMD = age-related macular degeneration; VMA = vitreomacular adhesion.
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 exudative14–16 and advanced17,18 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 nonequidistant AMD in the fellow eye to mitigate the influence of environmental and genetic factors. Additionally, active AMD (exudative or nonequidistanttract) 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 nonequidistant AMD, whereas VMA is related strongly to exudative AMD. In active AMD, complete PVD was found in 69% of patients with nonequidistant AMD, as opposed to only 21% of patients with exudative AMD (P = .002). This compares favorably with the results of a study19 of 551 subjects that determined that complete PVD was found in 69% of patients with nonexudative AMD, whereas 7 (70%) of 10 eyes with geographic atrophy were pseudophakic (P = .25). The 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 studies3 are confirmed and the observations regarding the potential role of vitreous in AMD3,4 are not influenced by genetic and environmental factors. The possible mechanisms by which VMA may promote exudative AMD are as follows.

Anomalous PVD 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 factor25 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 nonequidistant AMD, and thus anomalous PVD may be an important risk factor for progression of nonequidistant AMD to exudative AMD. If future prospective studies confirm these findings, then it may be valuable to consider vitrectomy or pharmacologic vitreolysis29–31 as prophylaxis in preventing exudative AMD.
REFERENCES


Biosketch

Jerry Sebag, MD, FACS, FRCSophth, is a Founding Director at VMR Institute, Huntington Beach, California, and a Professor of Clinical Ophthalmology at Doheny Eye Institute, University of Southern California School of Medicine, Los Angeles, California. An alumni of Columbia and Harvard, Dr Sebag was a Guggenheim Fellow and has authored 2 books, 54 articles, 32 chapters, and 14 editorials. He won prizes from the American Health Foundation, Harvard Medical School, the Ophthalmological Society of the United Kingdom, the Heed and Knapp fellowships, and honor awards from the American Academy of Ophthalmology in 1994 and the Vitreous Society. In 2006, Dr Sebag was inducted as a member of the American Ophthalmological Society.
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