Posterior Vitreomacular Adhesion and Risk of Exudative Age-related Macular Degeneration: Paired Eye Study

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Directed by Professor Hyoung Jun Koh

The Master's Thesis submitted to the Department of Medicine, the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science

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I dedicate this research to my beloved wife, Jin Sook Yoon, has helped me in innumerable ways.
LIST OF FIGURES

Figure 1. Representative images showing posterior vitreomacular adhesion as a risk factor of exudative age-related macular degeneration. (Case 1) .......................... 8

Figure 2. Representative images showing posterior vitreomacular adhesion as a risk factor of exudative age-related macular degeneration. (Case 2) ......................... 9

Figure 3. Incidence of posterior vitreomacular adhesion in patients with unilateral exudative AMD. ......................................................... 10

LIST OF TABLES

Table 1. Characteristics of patients with and without vitreomacular adhesion in their unilateral exudative AMD eyes. ................................................................. 12
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Purpose: To evaluate posterior vitreomacular adhesion as a risk factor for choroidal neovascularization (CNV) in age-related macular degeneration (AMD).

Methods: We retrospectively reviewed optical coherence tomography (OCT) and fluorescein angiography (FA) of 251 consecutive patients with unilateral exudative AMD. Fellow eyes had no sign of exudative AMD. Vitreomacular adhesion was defined when posterior hyaloid line attached to inner retinal surface was seen in OCT. We compared the incidence of posterior vitreomacular adhesion between the two eyes and the association between CNV location and vitreomacular adhesion.

Results: We found posterior vitreomacular adhesion in 56 patients (22.3%), and 3 cases in which it was present in both eyes. CNV was mostly present in eyes with vitreomacular adhesion (44/53, 83%), and rarely found in eyes without vitreomacular adhesion (6/53, 11.3%; P=0.0007). The location of vitreomacular adhesion was always observed over the area of the CNV in exudative eyes (50/50).

Conclusion: Posterior vitreomacular adhesion is associated with CNV in AMD. Chronic vitreomacular traction may be a risk factor for the development of exudative AMD.

Key words: posterior vitreomacular adhesion, age-related macular degeneration, choroidal neovascularization, optical coherence tomography
I. INTRODUCTION

Age-related macular degeneration (AMD) is one of the most common irreversible causes of severe loss of vision and legal blindness in developed countries.\textsuperscript{1} Despite intensive basic and clinical research, the pathogenesis and risk factors for AMD are incompletely characterized.\textsuperscript{2}

Recent studies have demonstrated that the posterior vitreoretinal relationship may play an important role in development of AMD.\textsuperscript{3} In particular, the prevalence of posterior vitreous detachment (PVD) was significantly lower in eyes with macular degeneration \textsuperscript{4} and the incidence of persistent central vitreoretinal adhesion was significantly higher in eyes with exudative (wet) AMD compared with eyes with non-exudative (dry) AMD and normal controls.\textsuperscript{5}

Previous studies have compared vitreomacular adhesions of the eyes of patients with wet AMD and the normal eyes of other patients, but have not compared the normal eye and the eye with wet AMD in individual patients with unilateral AMD. Thus, the results of these previous studies may be confounded by demographic differences and other factors such as age, sex, myopia, lens status, diabetes mellitus, genetic, and environmental factors.\textsuperscript{6-8} In the present
study, we controlled for confounding variables by selecting patients with unilateral exudative AMD and compared the incidence of vitreomacular adhesion, as documented by optical coherence tomography (OCT), in both eyes. The purpose of this study was to evaluate the association between posterior vitreomacular adhesion and choroidal neovascularization (CNV) in exudative AMD.
II. MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of the Yonsei University College of Medicine and adhered to the tenets of the Declaration of Helsinki. We retrospectively reviewed data for consecutive patients who were diagnosed with unilateral exudative AMD at the vitreoretinal service clinic of the Yonsei University Eye, and Ear, Nose, and Throat Hospital (Seoul, Korea) from October 2005 to December 2007. We used the hospital clinical database (CDR software, Yonsei University Severance Hospital, Seoul, Korea) to identify patients with AMD who had bilateral OCT examination. Data were abstracted from the consecutive charts of 503 patients. A total of 251 patients (502 eyes) who met the eligibility criteria were included in the analysis.

Eligibility criteria were: (a) age >50 years; (b) unilateral exudative AMD proven by fundus photo and fluorescein angiography (FA), with the other eye having dry AMD or no sign of AMD; and (c) availability of results from a bilateral OCT examination. Exclusion criteria were: (a) intraocular surgery, including cataract extraction; (b) history of previous treatment for AMD, such as verteporfin photodynamic therapy and intravitreal anti-vascular endothelial growth factor (VEGF) therapy; (c) myopia of more than 3 diopters; (d) evidence of diabetic retinopathy; and (e) presence of inflammatory ocular disease.

Demographic, medical, and ocular data were obtained through retrospective chart review and included age, gender, medical history (diabetes mellitus, hypertension), and history of ocular disease.

Fluorescein angiograms and indocyanine green angiograms, using the Heidelberg Retina Angiograph (Heidelberg Engineering, Heidelberg, Germany), were reviewed to verify diagnoses. The location of the neovascular complex was classified as subfoveal, juxtafoveal, or extrafoveal. The lesion composition
was classified into two categories: predominant classic and occult (occult with minimally classic, pure occult).

A commercially available OCT instrument (Stratus OCT3, Zeiss Humphrey, San Leandro, CA, USA) was used for analysis. The macula was scanned in the horizontal and vertical meridians using the crosshair pattern, or six radial lines at internals of 30 degrees with a scan length of 4–6 mm centered through the fovea and at any sites of suspected macular lesion, as determined by simultaneous evaluation of the red-free image on the OCT computer monitor. The presence of vitreomacular adhesion was assessed on the OCT computer monitor.

Statistical analysis was performed using SPSS software version 13.0 (SPSS, Chicago, IL, USA). Both paired eyes were compared with respect to the presence of vitreomacular adhesion using McNemar’s non-parametric test. Categorical data were assessed using the Chi-square test and continuous variables were compared with the Student’s $t$-test. P values < 0.05 were considered statistically significant.
We included 502 eyes from 251 consecutive patients with unilateral exudative AMD. The fellow eyes had dry AMD in 182 patients and no sign of AMD in 69 patients. A total of 143 patients were men and 108 were women. Patient age ranged from 50 to 93 years (mean ± standard deviation, 68.4 ± 8.11). Forty-three patients had diabetes mellitus and 82 had hypertension.

OCT analysis indicated posterior vitreomacular adhesion in at least one eye of 56 patients (22.3%). Representative fundus photographs, FAs, and OCT images of both eyes are shown for two patients (Figure 1 and 2). We detected posterior vitreomacular adhesion in the exudative AMD eyes of 47 patients (18.7%), in the fellow eyes of 6 patients (2.4%), and in both eyes of 3 patients (1.2%; Figure 3). All fellow eyes with posterior vitreomacular adhesion had no sign of AMD. This means that CNV was present almost exclusively in eyes with vitreomacular adhesion (44/53, 83%), but was rarely present in eyes without vitreomacular adhesion (6/53, 11.3%).

Eyes with exudative AMD had a significantly higher incidence of posterior vitreomacular adhesion than fellow eyes (P = 0.0007, McNemar’s test). Vitreomacular adhesion in exudative AMD was always found above the CNV area, regardless of CNV location (subfoveal, juxtafoveal, extrafoveal) in 50 of 50 eyes. In contrast, we noted vitreomacular adhesion in all nine eyes with non-exudative AMD in the foveal area.

We classified eyes with exudative AMD according to the presence of posterior vitreomacular adhesion to evaluate the effect of other variables on this condition (Table 1). In the vitreomacular adhesion (+) group, 60% (30/50) were subfoveal, 28% (14/50) were juxtafoveal, and 12% (6/50) were extrafoveal. In the vitreomacular adhesion (-) group, 47.8% (96/201) were subfoveal, 37.8% (76/201) were juxtafoveal, and 14.4% (29/201) were extrafoveal. There was no
significant difference between these groups ($P = 0.295$). In the vitreomacular adhesion (+) group, classic type CNV and occult type CNV occurred in 38\% (19/50) and 62\% (31/50) of patients, respectively. The corresponding numbers for the vitreomacular adhesion (-) group were 38.3\% (77/201) and 61.7\% (124/201), respectively. Again, there was no significant difference between the two groups. ($P = 0.968$). There were also no significant differences between the two groups with regard to age, sex, medical history (diabetes mellitus, hypertension), and diagnosis of control eye (Table 1).
Figure 1. Representative images showing posterior vitreomacular adhesion as a risk factor of exudative age-related macular degeneration. Fundus photograph (Top row), fluorescein angiogram (Second row – early phase, third row – late phase) and optical coherence tomography (OCT, Bottom row) of a 69-year-old man (case 1) with subfoveal choroidal neovascularization (CNV) in the right eye. OCT image of the eye with CNV shows thin posterior vitreal adhesion and cystoids macular edema in CNV area (Bottom left), while fellow eye without CNV shows focal thickening of the hyperreflective retinal pigment epithelium/choriocapillaris band, but no sign of vitreal adhesion (Bottom right).
Figure 2. Representative images showing posterior vitreomacular adhesion as a risk factor of exudative age-related macular degeneration. Fundus photograph (Top row), fluorescein angiogram (Second row – early phase, third row – late phase) and optical coherence tomography (OCT, Bottom row) of a 69-year-old man (case 2) with subfoveal choroidal neovascularization (CNV) in the right eye. OCT image of the eye with CNV shows traction of the posterior hyaloids (Bottom left), while fellow eye without CNV showed no posterior vitreal adhesion, but the presence of fine undulation of the retinal pigment epithelium (Bottom right).
Figure 3. Incidence of posterior vitreomacular adhesion in patients with unilateral exudative AMD. Eyes with exudative AMD have a significantly higher incidence of posterior vitreomacular adhesion than fellow eyes (p = 0.0007).
Table 1. Characteristics of patients with and without vitreomacular adhesion in their unilateral exudative AMD eyes.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Vitreomacular adhesion (+) group (n =50)</th>
<th>Vitreomacular adhesion (-) group (n =201)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, years (range)</td>
<td>68.36 ± 9.35 (51-82)</td>
<td>68.37 ± 8.14 (50-93)</td>
<td>0.758&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sex, no. of patients (%)</td>
<td></td>
<td></td>
<td>0.152&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Male</td>
<td>24 (48)</td>
<td>119 (59)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26 (52)</td>
<td>82 (41)</td>
<td></td>
</tr>
<tr>
<td>Medical history, no. of patients (%)</td>
<td></td>
<td></td>
<td>0.191&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (12)</td>
<td>37 (18.4)</td>
<td>0.282&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (30)</td>
<td>67 (33.3)</td>
<td>0.653&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diagnosis of fellow eye, no. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No sign of AMD</td>
<td>10 (20)</td>
<td>59 (29)</td>
<td></td>
</tr>
<tr>
<td>Non-exudative AMD</td>
<td>40 (80)</td>
<td>142 (71)</td>
<td></td>
</tr>
<tr>
<td>Location of CNV, no. of patients (%)</td>
<td></td>
<td></td>
<td>0.295&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Subfoveal</td>
<td>30 (60)</td>
<td>96 (47.8)</td>
<td></td>
</tr>
<tr>
<td>Juxtafoveal</td>
<td>14 (28)</td>
<td>76 (37.8)</td>
<td></td>
</tr>
<tr>
<td>Extrafoveal</td>
<td>6 (12)</td>
<td>29 (14.4)</td>
<td></td>
</tr>
<tr>
<td>Type of CNV, no. of patients (%)</td>
<td></td>
<td></td>
<td>0.968&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Classic</td>
<td>19 (38)</td>
<td>77 (38.3)</td>
<td></td>
</tr>
<tr>
<td>Occult</td>
<td>31 (62)</td>
<td>124 (61.7)</td>
<td></td>
</tr>
</tbody>
</table>

CNV = choroidal neovascularization; AMD = age-related macular degeneration.

<sup>a</sup>Student’s t-test.

<sup>b</sup>Chi-square test.
IV. DISCUSSION

We are unaware of previous paired eye study to examine the association between vitreomacular adhesion and CNV. Our results indicate that exudative AMD eyes had a significantly higher incidence of posterior vitreomacular adhesion than fellow eyes that did not have exudative AMD. These results are consistent with previously published research. However, due to non-paired eye design of the previous studies, confounding variables (e.g., genetic factors, environmental factors, diabetes mellitus, intraocular surgeries) may have influenced the results. The paired eye design of our study obviates these limitations. We excluded patients with previous intraocular surgery (including cataract surgery) and those who had previously been treated for exudative AMD. This allowed us to study patients who were newly diagnosed with AMD and to decrease the time delay between vitreomacular traction (VMT) and the development of CNV so as to better examine their association. We also assessed the relationship between the location and type of CNV and vitreomacular adhesion. In 50 of 50 eyes, we found vitreomacular adhesion in exudative AMD above the CNV area, regardless of CNV location (subfoveal, juxtafoveal, extrafoveal). This suggests a strong correlation between CNV location and adhesion site. However, we found no significant differences in vitreomacular adhesion with respect to CNV location (subfoveal, juxtafoveal, extrafoveal) and CNV type.

Seeing no isolated vitreomacular attachment doesn't mean there is no traction. The vitreous could be completely attached and still theoretically place traction on the macula. However in agreement with Sebag’s concept of ‘Anomalous posterior vitreous detachment’, individuals who experience gel liquefaction without concurrent dehiscence at the vitreo-retinal interface may experience anomalous PVD. So, focal attachment of vitreous to retina exerts
stronger traction force than broad traction, and this may cause retinal diseases such as macular hole or vitreomacular traction syndrome.\textsuperscript{10, 11} Several studies have suggested an association between vitreous traction and AMD. The magnitude, variation of mechanical forces, and the continuous shear stress of the aged vitreous gel transmitted across vitreoretinal attachments may result in a chronic stimulus to the retina and retinal pigment epithelium (RPE). Vitreomacular traction (VMT) may contribute to the subsequent formation of tears in the RPE via mechanical or cell-mediated pathways.\textsuperscript{12} The importance of vitreous involvement in pigment epithelial detachment (PED) is supported by a report from Gross-Jendroska et al.\textsuperscript{13} This group found that serous PEDs flattened after intravitreal gas injection, suggesting that the vitreous may contribute to PED formation. Weber-Krause et al.\textsuperscript{14} reported that PVD is very rare in AMD, relative to the age of the patients. In addition, these authors reported two AMD cases in which spontaneous PVD resulted from the natural regression of CNV. In another study, patients with AMD had a significantly higher prevalence of incomplete PVD (33.3\%) compared with age-matched controls (66.6\%).\textsuperscript{4} Lambert et al.\textsuperscript{15} found an attached vitreous in 80\% of patients with CNV and speculated that VMT induces mechanical traction that contributes to its progression. Schmidt et al.\textsuperscript{16} observed that intraoperative findings during vitrectomy showed little liquefaction of the vitreous gel, an incomplete PVD, and remarkably firm attachments at the macula in all cases (10 of 10). It is unclear whether vitreomacular adhesion is a cause or a consequence of AMD. It is possible that inflammation, scarring, or the consequences of chronic exudation cause the vitreous to become more adherent in the macular region. If the patient were to start to develop a posterior vitreous detachment the vitreous could remain attached to the macula. Nevertheless, all these clinical findings suggest that posterior vitreous adhesion plays an important role in the pathophysiology of AMD and that vitreomacular attachments may trigger the progression or recurrence of CNV. At a minimum,
VMT appears to be a risk factor for the progression of exudative AMD.

In the present study, the location of vitreomacular adhesion and the site of CNV were highly correlated and there was a higher incidence of vitreomacular adhesion in exudative AMD. This suggests that posterior vitreomacular adhesion may contribute to AMD. There are several possible mechanisms involving chronic inflammation, oxidative stress, and various cytokines by which vitreomacular adhesion may be associated with AMD.\textsuperscript{2,4}

Prophylactic induction of PVD may prevent CNV development in selected cases. In a previous study,\textsuperscript{17} vitrectomy was performed in 12 eyes of 11 patients with highly active CNV in whom the posterior vitreous surface remained attached. Six months after surgery, CNV disappeared completely in two eyes and six other eyes showed CNV regression. The recent introduction of pharmacologic vitreolysis may provide a novel and safe approach to improve vitreoretinal surgery. This procedure can liquefy and detach the vitreous from the retina and thereby eliminate the contribution of the vitreous to retinopathy.\textsuperscript{18,19} A controlled prospective clinical study is required to assess the effect of PVD by pharmacologic vitreolysis for prevention of exudative AMD. Otherwise, prophylactic vitrectomy for intractable wet AMD with VMT or for dry AMD with VMT appears to be an option to prevent progression.
V. CONCLUSION

The results of our paired eye comparison study demonstrate a strong association between posterior vitreomacular adhesion and exudative AMD. For patients with AMD, we suggest that ophthalmologists carefully inspect the vitreomacular relationship using OCT. If vitreomacular adhesion is present, we suggest further examination and closely follow up. Prophylactic induction of PVD may be an effective new treatment for wet AMD. Further prospective studies with new imaging techniques, such as the spectral domain OCT system$^{20}$, and longitudinal studies will allow assessment of the relationship between vitreomacular adhesion and exudative AMD.
REFERENCES


2001; 239: 325-33.


ABSTRACT (IN KOREAN)

삼출성 연령관련 황반변성의 위험인자로서의 후유리체-황반 유착: 양안 비교 연구

<지도교수 고형준>
연세대학교 대학원 의학과

이 성 준

목적: 연령관련 황반변성에서 맥락막 신생혈관의 위험인자로서 후유리체-황반 유착을 평가하고자 하였다.

방법: 단안만 삼출성 연령관련 황반변성으로 진단받은 연속적인 251명을 대상으로 후향적으로 광간섭단층촬영과 형광안저촬영을 분석하였다. 반대편 안은 삼출성 연령관련 황반변성의 징후를 가지고 있지 않았다. 유리체-황반 유착은 광간섭단층촬영 상에서 후유리체막이 망막 내면에 유착되어 있는 것이 관찰될 때로 정의하였다. 양안 사이에 후유리체-황반 유착의 발생빈도와 맥락막 신생혈관의 위치와 유착과의 연관성을 비교하였다.

결과: 후유리체-황반 유착은 총 56명의 환자(22.3%)에서 발견되었고 양안 모두에서 발견된 경우는 3례였다. 맥락막 신생혈관은 대부분 유리체-황반 유착이 있는 눈에서 발견되었고(44/53, 83%), 유리체-황반 유착이 없는 눈에서는 드물게 발견되었다(6/53, 11.3%; P=0.0007). 유리체-황반 유착의
위치는 항상 삼출성 연령관련 황반변성 안의 맥락막 신생혈관
부위 위쪽에서 관찰되었다(50/50).
결론: 후유리체-망막 유착은 연령관련 황반변성에서 맥락막 신
생혈관과 연관되어 있다. 만성적인 유리체-망막 겉인이 삼출성
연령관련 황반변성 발생의 위험인자가 될 수 있다.

핵심되는 말: 후유리체-황반 유착, 연령관련 황반변성, 맥락막
신생혈관, 광간섭단층촬영