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Vitreomacular Adhesion and the Risk of Neovascular Age-Related Macular Degeneration

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Purpose: To assess the prevalence of vitreomacular adhesion (VMA) in consecutive naïve eyes diagnosed with exudative age-related macular degeneration (AMD) in comparison with eyes with nonexudative AMD and age-matched controls, and to evaluate prospectively the incidence of vitreomacular interface changes over time and their influence on choroidal neovascularization (CNV) development.

Design: Retrospective cross-sectional analysis and longitudinal cohort study conducted at Sacrocuore Hospital, Negrar, Verona, Italy.

Participants: A total of 1067 eyes examined at Sacrocuore Hospital between August 2008 and June 2015 met the inclusion criteria and were evaluated in this study.

Methods: Eyes were classified into 3 groups: 403 eyes of 364 patients (mean [standard deviation; SD] age 77.8 [8.0] years) affected by exudative AMD; 350 eyes of 298 subjects (mean [SD] age 78.1 [8.2] years) with nonexudative AMD; and 314 eyes of 214 subjects (mean [SD] age 74.2 [8.2] years) with no signs of AMD enrolled as the control group. The vitreomacular interface status was evaluated by spectral-domain optical coherence tomography (OCT) and was graded according to the OCT-based International Classification System developed by the International Vitreomacular Traction Study Group by 2 independent masked observers.

Results: VMA was present in 101 (25.1%) eyes with exudative AMD, 84 (24.0%) eyes with nonexudative AMD, and 84 (26.8%) eyes with no signs of AMD (no statistical difference was found; $P = 0.3384$). Spontaneous release of VMA (RVMA) was found in 15 (15.3%) eyes with exudative AMD, 21 (28.0%) eyes with nonexudative AMD, and 10 (24.4%) eyes with no signs of AMD over a mean follow-up of 25.5, 25.9, and 24.1 months, respectively. The incidence of RVMA in exudative AMD eyes was significantly lower compared with nonexudative ($P = 0.0207$) and lower, but not statistically significant, with respect to eyes with no signs of AMD ($P = 0.1013$). In eyes with nonexudative AMD, de novo development of CNV occurred in 91 eyes (30.6%). There was no significant difference regarding the rate of CNV development in the presence or absence of VMA ($P = 0.0966$).

Conclusions: The present study found no significant difference in the prevalence of VMA in eyes affected by AMD compared with age-matched controls and no difference in the rate of de novo CNV development in eyes with or without VMA. Conversely, a lower incidence of RVMA over time was found in eyes affected by exudative AMD. The results of this study suggest that VMA might be a consequence rather than a causative factor in the development of CNV. *Ophthalmology 2017;■:1–10 © 2017 by the American Academy of Ophthalmology*

Age-related macular degeneration (AMD) is the leading cause of severe visual impairment in industrialized countries.[1–3] The pathogenesis is multifactorial and still not entirely understood. Several risk factors for the disease have been identified by large studies conducted on wide numbers of participants, such as age, cigarette smoking, heredity, and race.[4–7] Recently, vitreomacular adhesion (VMA) has also been hypothesized to be a further risk factor for AMD. This hypothesis has been derived from several studies that have reported a higher prevalence of VMA in eyes affected by exudative AMD compared with age-matched controls.[8–13] In addition, VMA was found to localize in the area of choroidal neovascularization (CNV).[9,11] However, the reported prevalence of VMA in eyes affected by exudative AMD differs substantially between the various articles, ranging from 12.2%[14] to 48.5%.[15] Moreover, several subsequent post hoc analyses have reported a much lower prevalence of VMA in eyes affected by exudative AMD than that reported in the previous literature. For example, in the large group of eyes enrolled in the Comparison of AMD Treatments Trials,[14] VMA was found remarkably infrequently. Similarly, the populations included in the EXCITE,[16] VINTREX,[17] and MONTBLANC[18] trials exhibited a much lower prevalence of VMA than that reported by previous studies. The reason for these differences remains unclear, and accordingly there is a lack of conclusive evidence on this matter.

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Furthermore, the association between VMA and CNV has raised speculation regarding the cause–effect relation. In fact, some authors have postulated that VMA might be a consequence, rather than a causative factor, in CNV development, because the exudative processes at the site of CNV could give rise to an abnormally strong adhesion between the posterior vitreous cortex and the area of CNV.

The aim of this study was to investigate the prevalence of VMA in a series of consecutive naïve eyes diagnosed with recent-onset exudative AMD, in comparison with eyes affected by nonexudative AMD and eyes with no signs of AMD. In addition, the incidence of spontaneous release of vitreomacular adhesion (RVMA) in the 3 groups over time, and the incidence of CNV development in the presence or absence of VMA in eyes affected by nonexudative AMD and with no signs of AMD, was evaluated.

Methods

Study Design

This study includes both a retrospective observational case series and cohort study conducted at a single Italian tertiary-referral center. The study was designed to evaluate the prevalence of VMA in all eyes affected by recent-onset, previously untreated exudative AMD diagnosed in the Sacrocuore Hospital, Negrar, Verona, Italy, from August 2008 to June 2015, in comparison with eyes affected by nonexudative AMD and eyes with no signs of AMD.

In addition, the following were evaluated longitudinally: the incidence of spontaneous RVMA in the 3 groups over time; and the incidence of CNV development in the presence or absence of VMA in eyes affected by nonexudative AMD and eyes with no signs of AMD.

Secondary endpoints were correlation between VMA and CNV location, correlation between VMA and CNV area size, and correlation between VMA and angiographic subtypes of CNV.

This research adhered to the tenets of the Declaration of Helsinki. Institutional review board approval from the Sacrocuore Hospital was obtained to review patient data.

Patient Enrollment

Three groups of eyes were enrolled: eyes affected by exudative AMD; eyes affected by nonexudative AMD; and eyes with no signs of AMD. When both eyes of a patient met the eligibility criteria, they were independently included within 1 of the 3 groups according to the clinical features.

Exudative Age-Related Macular Degeneration Group. The Hospital Clinical Database of the Data Center of Sacrocuore Hospital was used to obtain a complete list of all patients treated with intravitreal anti-vascular endothelial growth factor (VEGF) injections in the Department of Ophthalmology from August 2008 to June 2015. Spectral-domain optical coherence tomography (OCT; Heidelberg Engineering, Heidelberg, Germany) has been available at the department since August 2008, therefore, patients treated before this period were not included in the research. From this list, all patients treated for diseases other than AMD were excluded. Then, patients' medical charts were reviewed to identify only eyes presented with newly diagnosed, recent-onset, and previously untreated CNV. Thus, eyes that had received any kind of AMD treatment, such as photodynamic therapy or anti-VEGF injections, were excluded, as well as eyes with late-stage disease and/or cases of long disease duration.

Nonexudative Age-Related Macular Degeneration Group. This group comprised eyes of patients diagnosed with nonexudative AMD in the Department of Ophthalmology between August 2008 and June 2015. It also included the fellow eyes of patients with unilateral exudative AMD with the other eye having nonexudative AMD.

The diagnosis of nonexudative AMD was made by experienced retinal specialists, paying particular attention to exclude cases of pattern dystrophy, alterations of retinal pigment epithelium secondary to central serous retinopathy, and other conditions that share some features of AMD. The Age-Related Eye Disease Study (AREDS) classification system was taken into account to categorize eyes in this group, as explained further below.

Group with No Signs of Age-Related Macular Degeneration. The control group comprised eyes of patients with no signs of AMD who were attending the clinic during the same period for other reasons, such as cataract, glaucoma, or routine eye controls. It also included the normal fellow eyes of patients with unilateral diseases, such as retinal vein occlusion, as well as the normal fellow eyes of patients with unilateral exudative or nonexudative AMD with the other eye having no signs of AMD.

Exclusion criteria for the 3 groups of eyes were as follows: younger than 55 years of age; presence of concomitant diseases that would have influenced the vitreoretinal interface, such as diabetic retinopathy, high myopia (>6 diopters), uveitis history, vascular occlusion, and macular holes; history of vitreoretinal surgery; inadequate imaging with lack of sufficient quality (i.e., severe media opacities, asteroid hyalosis, and synchysis scintillans), or with lack of essential details to define the vitreoretinal interface status (i.e., absence of OCT lines passing through the edge of the optic disc, preventing the detection of the adhesion of vitreous cortex in that area).

Evaluation Procedures

All patients underwent a complete ophthalmologic examination, including medical history, best-corrected visual acuity (BCVA) assessed with Snellen visual charts, slit-lamp biomicroscopy, dilated fundus examination with a 90-diopter indirect lens, and OCT. The same OCT was used between 2008 and 2015. Patients with exudative AMD also underwent fluorescein angiography (FA) and indocyanine green angiography (ICG) with the Heidelberg Retina Angiograph (HRA), as a part of the routine practice for all patients diagnosed with exudative AMD, except those with a history of severe drug allergy or a known systemic problem. OCT was performed with the spectral-domain OCT-SLO (Heidelberg Engineering, Heidelberg, Germany). The routine scanning protocol at the Sacrocuore Hospital consisted of both an 8-mm cross-hair scan (with 2 sections perpendicular to each other) and a posterior pole series consisting of 128 horizontal B-scan images, each image composed of 512 axial scans, covering an 8×8 mm area of the posterior pole.

In addition to the routine protocol, further scans could be acquired at the physician's discretion.

As a routine practice for all patients diagnosed with exudative AMD at Sacrocuore Hospital, eyes with CNV were treated with 3 monthly intravitreal injections of anti-VEGF and then periodically underwent standardized examinations for subsequent pro re nata injections, including BCVA, fundus examination, OCT, and, at physician's discretion, FA/ICG.

Vitreomacular Interface Configuration Grading

All scans obtained from the eyes of each group were analyzed to define the vitreomacular interface status by 2 independent, masked observers (E.M., G.P.). OCT images were graded separately and then compared with regard to vitreomacular interface finding. In case of any discrepancy, agreement was reached upon subsequent re-examination of the OCT images by both investigators and a third observer (A.P.) and further discussion.