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Epidemiology of Epiretinal Membrane in a Large Cohort of Patients with Uveitis

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Abstract

Objective—To identify clinical characteristics associated with the presence of epiretinal membrane (ERM) in patients with uveitis

Design—Case-control study

Participants and Controls—598 subjects seen in a single tertiary referral clinic between January 1, 2008 and December 31, 2011 who were diagnosed with uveitis.

Methods—Spectral domain optical coherence tomography (SD-OCT) images of all subjects were reviewed to assess for ERM. A multivariate logistic regression analysis was performed to compare characteristics of subjects with ERM (cases) to characteristics of subjects without ERM (controls). A second multivariate analysis assessed the relationship between ERM and visual acuity. Fundus photos were reviewed to compare SD-OCT ascertainment of ERM with photographic ascertainment.

Main Outcome Measure—Presence or absence of ERM on OCT imaging.

Results—Of 598 uveitic participants, 246 (41%) were found to have ERM in at least one eye on SD-OCT imaging. The prevalence of ERM by Standardization of Uveitis Nomenclature (SUN) anatomic subtype was 28.1% for anterior uveitis, 57.0% for intermediate uveitis, and 43.4% for posterior and panuveitis. Multivariate analysis showed that the following clinical factors were significantly associated with ERM: older age (3% increased risk per year of age; 95% confidence interval [CI] 1.02-1.05), intermediate uveitis (OR 3.41; 95% CI 1.67-6.96) and posterior and panuveitis (OR 1.81; 95% CI 1.09-3.01), male sex (OR 1.59; 95% CI 1.05-2.42), and history of cataract surgery (OR 1.78; 95% CI 1.13-2.79). When adjusted for covariates, eyes with ERM had a mean logMAR acuity of 0.58 (20/76) versus 0.48 (20/60) in non-ERM eyes ($P=0.039$). Thirty-eight percent of OCT-defined ERMs in this cohort were not detectable on fundus photos.

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Conclusions—ERM is a common complication of uveitis that is associated with patient age, intermediate, posterior, and panuveitis, male sex, and previous cataract surgery. It can independently contribute to vision loss in uveitic eyes. OCT is more sensitive than fundus photography for identification of ERM in uveitis.

Epiretinal membrane (ERM) is common in uveitis,¹ and it can cause loss of visual acuity, metamorphopsia, and micropsia. Large studies of ERM to date predominantly address idiopathic ERM, a condition associated with aging and posterior vitreous detachment (PVD).² ERMs that are specifically associated with uveitis appear to differ from idiopathic ERM in cellular composition, suggesting that they may emerge through a different pathogenic mechanism.³ Nazari and colleagues reported that most uveitic eyes with ERM did not lose vision over one to two years of follow-up and that thinner ERMs are associated with better visual acuity.^{4,5}

Studies of ERM have traditionally relied on gradings of color fundus photographs for the identification and characterization of ERM.⁶⁻¹⁰ In fact, some recent epidemiologic studies of ERM have maintained this approach.^{11, 12} However, it has been reported that optical coherence tomography (OCT) may be more sensitive for detection of ERM than color fundus photography.¹³ The use of OCT for ERM detection and characterization may have additional advantages in studying uveitic ERMs owing to the high prevalence of media opacities that can prevent clear visualization of fundus features on color photography.

In the current study, we employed an OCT-based definition of ERM to examine the prevalence of ERM in uveitis and to evaluate clinical characteristics that may be associated with its presence, including patient age, duration of uveitis, anatomic classification of uveitis based on standardization of uveitis nomenclature (SUN) criteria,¹⁴ and lens status.

Methods

The National Eye Institute (NEI) electronic medical record was queried for the signatures of physicians who see uveitis patients in order to compile a database of all patients with uveitis seen between January 1, 2008 and December 31, 2011. Each patient chart was reviewed by the investigators to confirm the diagnosis of uveitis. Masquerade syndromes, including primary intraocular lymphoma, were excluded. The Cirrus Spectral Domain OCT (SD-OCT) (Carl Zeiss Meditec, Jena, Germany) database was then reviewed for each patient to assess for the presence of epiretinal membrane, and subjects without SD-OCT data were excluded. Cases of epiretinal membrane and controls were thereby identified, and a retrospective case-control study was conducted. The study was done under an institutional review board (IRB)-approved clinical research protocol, and chart review was conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and the Declaration of Helsinki.

Epiretinal membrane was diagnosed based exclusively on SD-OCT findings. Epiretinal membrane was defined as follows: hyperreflective signal at the inner retinal surface and evidence of contractility. Therefore, a hyperreflective signal that conformed to the natural contour of the inner retina did not qualify as ERM (Figure, part A). Evidence of contractility included any distortion, corrugation, or flattening of the inner retina (Figure, part B).

All ERMs were within the macula. The macula for the purposes of this study was defined as the full extent of the Cirrus 512×128 (6×6mm) macular cube. The full cube scan was reviewed for each eye. If the cube was decentered or captured the arcuate nerve fiber layer at the arcades, ERM that involved only non-macular portions of the scan were not included. Reviewers could refer to raster scans for additional data in the event of poor signal strength on the cube scan or to confirm signs of contractility. Reviewers were masked to the patient's chart and therefore to prior clinical assessment of patient features.

The NEI electronic medical record of each subject was reviewed for several parameters to assess for suspected risk factors for ERM in uveitis: age, gender, race, anatomic classification of uveitis, etiologic diagnosis, duration of uveitis, best-corrected visual acuity, presence of diabetes mellitus, systemic corticosteroid use, steroid sparing drug use, activity of intraocular inflammation on the date of the OCT, and lens status. Several additional parameters were recorded for subjects with ERM: OCT central retinal thickness (CRT), OCT macular volume, presence or absence of cystoid macular edema (CME), presence or absence of chorioretinal scarring on color photos, history of vitrectomy or other intraocular surgery, history of proliferative diabetic retinopathy, history of intraocular and periocular injections, and history of retinal laser treatment. All CRT and macular volume values were verified by the OCT graders and manual segmentation was performed when automated segmentation was inadequate.

Statistical Analysis

A multivariate logistic regression analysis was performed to assess for clinical characteristics associated with ERM. In this model, characteristics of subjects with ERM (cases) were compared to characteristics of subjects without ERM (controls). Variables for the model were chosen based on an exploratory age and gender-adjusted logistic regression analysis of 26 characteristics. Characteristics found to be statistically significant in this exploratory analysis were included in the multivariate analysis. This analysis was done by patient rather than by eye; therefore, inflammation was considered to be active if either eye was active, history of cataract surgery included those who had undergone unilateral or bilateral cataract surgery, and subjects were grouped by visual acuity based on acuity in the worse eye. No assumptions are required for categorical characteristics in logistic regression. For continuous variables such as age, the relationship between the logit and age must be linear. Nominal statistical significance was set at 0.05. All analyses were performed with SAS System software (SAS version 9.3; SAS Institute Inc., Cary, NC).

A second multivariate model was constructed to assess the effect of ERM on visual acuity. This analysis was done by eye rather than by patient. Because some subjects contributed both eyes to the analysis, it was necessary to account for the correlation between eyes within a person by specifying a compound symmetry covariance structure. The MIXED procedure of the SAS System was used. Mixed models assume normality of the continuous variables and that they have a linear relationship with the expected values. All eyes of subjects with ERM in one or both eyes (cases) were incorporated in this analysis. Variables affecting visual acuity were identified via an exploratory mixed effects regression analysis of 15

variables. Variables found to be statistically significant ($p < 0.05$) in this exploratory analysis were included in the multivariate mixed effects analysis.

The demographics of the case and control populations were compared using Student's t-tests, chi-square, or Wilcoxon rank sum tests where indicated. Chi-square testing was also used in secondary analyses of subjects with unilateral ERM in which eyes with ERM were compared to control eyes.

Results

The records of 701 patients with a diagnosis of uveitis seen between January 1, 2008 and December 31, 2011 were reviewed. Of these, 598 underwent SD-OCT imaging and were included in the study population for analysis. The prevalence of ERM in at least one eye in this cohort was 41% (246/598 subjects). The demographics of the ERM and no ERM groups are shown in Table 1. Subjects with ERM were significantly older (52 ± 17 versus 42 ± 18 years, $p < 0.0001$) and had a longer mean duration of uveitis (8.3 ± 9.0 versus 5.4 ± 6.5 years, $p = 0.0014$). In the case control analysis, patient age correlated with duration of uveitis ($p = 0.0027$). The prevalence of ERM by SUN classification was 28.1% for anterior uveitis, 57.0% for intermediate uveitis, and 43.5% for posterior and panuveitis.

The results of the multivariate analysis for clinical characteristics associated with ERM are presented in Table 2. Of the total 598 subjects, 110 were excluded from the multivariate analysis because of missing data for one or more covariates. Statistically significant odds ratios were found for anatomic classification of uveitis, patient age, visual acuity in the worse eye, male sex, and history of cataract surgery. Older age was associated with higher likelihood of ERM, with increased odds of approximately 3% per year of age (OR 1.03; 95% confidence interval [CI] 1.02-1.05). Intermediate uveitis (OR 3.41; 95% CI 1.67-6.96) and posterior and panuveitis (grouped for this analysis, odds ratio 1.81; 95% CI 1.09-3.01) were associated with ERM when compared with anterior uveitis. Male sex (OR 1.59; 95% CI 1.05-2.42) and previous cataract surgery (OR 1.78; 95% CI 1.13-2.79) were also associated with ERM. Subjects with best-corrected acuity $< 20/20$ - $20/40$ in the worse eye were more likely to have ERM (OR 2.41; 95% CI 1.19-4.89) when compared with those who were $20/20$ or better. Vitreous activity did not achieve statistical significance in the final model, but likelihood ratio testing indicated a better fit when vitreous activity was retained in the model. The likelihood ratio for the final model is 115.2 ($p < 0.0001$), and the R^2 value was 0.21. Variables excluded based on the exploratory analysis are noted in Table 2. Notably, there was a significant difference in disease duration and diabetes status in the univariate analysis, but these differences were not statistically significant in the exploratory multivariate analysis. Excluded subjects differed statistically from included subjects only in use of steroid sparing medications (those using steroid-sparing medications were more likely to be included, $p = 0.035$) (see Table 4, available at <http://aaojournal.org>).

In subjects with unilateral ERM ($n = 141$), several other potential associations were assessed by comparing eyes with ERM to the fellow eye. Eyes with ERM were more likely to have undergone vitrectomy (16/141 vs. 6/141, $p = 0.026$), retinal laser (15/141 vs. 6/141,

p=0.041), or intraocular injection (20/141 vs. 8/141, p=0.017). Histories of other ocular surgeries or periocular steroid injection were not associated with ERM in this analysis.

The results of the multivariate analysis of visual acuity in patients with ERM indicate that ERM has a statistically significant effect on acuity (p=0.039). This analysis was conducted on 349 eyes of subjects with unilateral or bilateral ERM after exclusion of eyes with media opacity and/or missing data. When adjusted for covariates, eyes with ERM had a mean logMAR acuity of 0.58 (~20/76) versus 0.48 (~20/60) in non-ERM eyes. This multivariate fixed effects model for the effect of ERM on visual acuity showed that vitreous activity (active vitritis), central retinal thickness on SD-OCT by group (i.e. <200 microns and >350 microns), anatomic classification of uveitis (posterior worse than anterior and intermediate), history of cataract surgery, and longer duration of uveitis had a significant impact on visual acuity (Table 3). The following variables were not found to have a significant effect on acuity: age, sex, anterior chamber activity, and presence of CME. Excluded eyes differed from included eyes in the following parameters: sex (eyes of female subjects were more likely to be excluded, p=0.02), anterior chamber activity (eyes with anterior chamber activity were more likely to be excluded, p=0.0001), and lens status (aphakic and pseudophakic eyes were more likely to be excluded, p=0.0015) (see Table 5, available at <http://aaojournal.org>).

Fundus photos were reviewed in 328/346 eyes with ERM on OCT. The 18 excluded eyes lacked fundus photos. Of the 328 eyes with OCT-diagnosed ERM, 55 had media opacities that precluded visualization of ERM on fundus photos. A further 69 eyes had clear media, but the ERM was not seen on fundus photographs. Thus, 38% of epiretinal membranes in this cohort would have been missed with traditional methods. The prevalence of ERM on fundus photos was 26% versus an OCT-defined prevalence of 41%.

Discussion

Epiretinal membrane has not previously been studied in a large cohort of subjects with uveitis, and this study confirms some impressions from previous studies while suggesting some novel conclusions. The relatively high prevalence of 41% for ERM in this cohort from a tertiary center is in line with the baseline characteristics from the Multicenter Uveitis Steroid Treatment (MUST) Trial (48% prevalence in subjects at tertiary uveitis centers with intermediate, posterior, or panuveitis).¹ Data from the present study suggest several significant associations with ERM, notably anatomic classification of uveitis (intermediate uveitis had a particularly high odds ratio, and the odds ratio for posterior and panuveitis was also statistically significant), male sex, prior cataract surgery, patient age, and duration of uveitis. Furthermore, our subgroup analysis of patients with unilateral ERM suggests that prior vitrectomy, retinal laser, or intraocular injection are associated with ERM in uveitis patients, and these factors require further study to determine whether they are independent risk factors. Our multivariate analysis suggests a statistically significant but modest effect of ERM on best-corrected visual acuity.

The multivariate model to assess for the effect of ERM on visual acuity suggests that ERM is associated with approximately one line of visual acuity loss. This model adjusted for

central retinal thickness, lens status, vitreous activity, and anatomic classification of uveitis. Although cystoid macular edema was not independently associated with worse visual acuity, the adjustment for central retinal thickness (divided into three groups for this analysis: less than 200, 200-350, and greater than 350) likely accounts for some of the effect of CME on acuity. Pilli and colleagues also found that central thickness had a stronger correlation with change in visual acuity in ERM than other SD-OCT parameters.¹⁵ The mechanism of vision loss with ERM is thought to be related to distortion and thickening of the retina, and our approach of grouping retinal thickness into three broad categories does not account for mild or moderate ERM-related retinal thickening.

Given the moderate effect of the average ERM on acuity in uveitis patients, we typically avoid vitrectomy and membrane peel for ERM when possible. A study of six patients with uveitis and ERM showed that despite anatomic progression of ERM over two years follow-up, visual acuity did not worsen.⁴ Nazari and colleagues reported improvement in acuity over 12 months in a retrospective review of 80 eyes with uveitic ERM.⁵ The definition of ERM in the present study differs from the definition in these and other studies, but they collectively suggest that surgery can be reserved in cases of uveitic ERM until ERM-related vision loss has been clearly documented over time.

Most of the clinical factors associated with ERM and the variables associated with vision loss in this cohort can generally be considered surrogates for damage to the eye. Greater duration of uveitis and a history of significant cataract, for example, are intuitively related to overall morbidity. Possible exceptions to this generalization include male sex and anatomic classification. Intermediate uveitis may confer an especially high risk of ERM because of the direct local effect of vitritis on the vitreo-retinal interface. A relatively high prevalence of ERM in intermediate uveitis has been suggested previously: Raja and colleagues reported a series of 53 patients with pars planitis with a high rate of ophthalmoscopically-identified ERM (40%).¹⁶ Further study is warranted to determine the structural changes to the vitreous body in intermediate uveitis and the cellular composition of these membranes.

While nearly all large studies of ERM have used color fundus photos as the gold standard for identifying ERM, modern clinical practice has largely adopted OCT as the diagnostic tool of choice. In this study, 38% of ERMs would have been missed with a strictly photo-based approach. Milani and colleagues have reported a similar number: 37% of OCT-diagnosed epiretinal membranes were missed on biomicroscopy in 146 eyes undergoing cataract surgery.¹³ Our data shows that SD-OCT can provide useful data on the anatomy of the macula in some cases where no macular details are seen on fundus photography. This finding is particularly relevant for uveitis. The improved sensitivity and additional anatomic detail provided by OCT should guide future epidemiologic studies toward OCT as the gold standard in the diagnosis of ERM.

There are several limitations to this study of ERM in uveitis, beginning with the retrospective design and the fact that many subjects had years of care elsewhere before being referred to our tertiary referral practice. Some elements of their clinical courses were therefore not available for review. The uveitis database for this time period contained 701 subjects, and 103 had no SD-OCT scan. These 103 patients may have had less macular

pathology, and the true prevalence of ERM in this patient population may be lower than 41%. The study population is likely, on average, to have had a relatively severe and complicated disease course due to the tertiary nature of our clinic. The incidence of complications of uveitis including ERM may therefore be higher than would be expected in a population-based study. Lastly, OCT-defined ERM is likely a somewhat different entity than clinically or photographically defined ERM, and comparisons with past literature on ERM may therefore be limited.

This is, however, the first large study of ERM in uveitis, and it is among the few large studies of ERM in general that benefit from the availability of spectral-domain OCT. The size of this study has allowed for multivariate analyses to help determine the effect of ERM on visual acuity in uveitis and to identify factors that are independently associated with ERM. Risk factors for ERM in uveitis have not been previously characterized in detail, and enumeration of such factors may guide future studies aimed at preventing complications of uveitis such as ERM.

Epiretinal membrane (ERM) was confirmed to be a common complication of uveitis (41% prevalence) and to be associated with several clinical characteristics including anatomic classification. Visual acuity was significantly worse in eyes with ERM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure.

Defining epiretinal membrane. A hyperreflective inner retinal signal (A, arrow) that conforms strictly to the natural contour of the inner retina. This finding did not meet our definition of epiretinal membrane. To meet our definition, evidence of contractility was required, such as distortion of the inner retinal contour (B, arrow) and spanning of gaps in the inner retinal contour (asterisk).

Table 1
Demographics and clinical characteristics of uveitis patients with and without epiretinal membrane

	ERM group	No ERM group	P
n	246	352	
Mean age	51.9	41.9	<0.0001*
Mean duration of uveitis	8.3	5.4	0.0013 [†]
Female sex	57%	60%	0.33 [#]
Race			
-Black	34%	36%	0.31 [#]
-White	46%	49%	
-Other	20%	15%	
Site of uveitis			
-Anterior	20%	35%	<0.0001 [#]
-Intermediate	20%	11%	
-Posterior and panuveitis	60%	54%	
Mean best-corrected visual acuity in worse eye	0.46 (~20/58)	0.27 (~20/37)	<0.0001 [†]
Diabetes Mellitus	16%	7.4%	0.0018 [#]
Taking systemic corticosteroids	28%	21%	0.092 [#]
Taking steroid-sparing immunosuppressive drug	33%	30%	0.64 [#]
History of cataract surgery	50%	24%	<0.0001 [#]
Active intraocular inflammation at study visit			
-Anterior	30%	32%	0.38 [#]
-Vitreous	41%	28%	<0.0017 [#]
-Overall	53%	47%	0.20 [#]

* Student's t-test

[†] Wilcoxon rank sum test

[#] Chi-square

Table 2
Final multivariate model of clinical factors associated with ERM.*

Variable	Odds ratio	P value [†]
Age (years)	1.03 (1.02-1.05)	<0.0001
Male sex	1.59 (1.05-2.42)	0.030
Intermediate uveitis [‡]	3.41 (1.67-6.96)	0.0007
Posterior or panuveitis [‡]	1.81 (1.09-3.01)	0.021
Visual acuity <20/20-20/40 ^a	2.41 (1.19-4.89)	0.015
Visual acuity <20/40-20/200 ^a	3.97 (2.04-7.70)	<0.0001
Visual acuity <20/200 ^a	4.99 (2.29-10.9)	<0.0001
History of cataract surgery	1.78 (1.13-2.79)	0.013
Vitreous activity (active vitritis vs quiet)	1.52 (0.98-2.37)	0.062

* Variables excluded from final multivariate analysis based on lack of statistical significance in exploratory analyses include: prednisone use, steroid-sparing drug use, race, diabetes status, etiologic diagnoses (Behcet disease, birdshot chorioretinopathy, cytomegalovirus retinitis, HLA-B27-related uveitis, sarcoidosis, and Vogt-Koyanagi-Harada disease), anterior chamber activity, and overall activity.

[†] Multivariate logistic regression.

[‡] Anterior uveitis was used as the reference category.

^a Best-corrected visual acuity in worse eye. The reference acuity was 20/20 or better.

Table 4
Comparison of included and excluded subjects in the clinical characteristics multivariate analysis.*

Variable	Characteristics of excluded subjects	P value [†]
Anatomic classification	Excluded: 32% anterior, 18% intermediate, 50% posterior; included: 28%, 14%, 58%	0.27
Male sex	37% of excluded subjects, 42% of included subjects	0.38
Visual acuity, worse eye	Excluded: 24% <20/200, 37% 20/40-20/200, 13% <20/20-20/40, 26% 20/20 or better; included: 16%, 38%, 25%, 22%	0.057
Lens status	Excluded: 61% phakic in both eyes; included: 65% phakic in both eyes	0.37
Prednisone use	22% of excluded subjects, 25% of included subjects	0.47
Steroid-sparing medication use	23% of excluded subjects, 34% of included subjects	0.035
Diabetic	7.3% of excluded subjects, 12% of included subjects	0.19

[†] Chi-square

* Age (45.5±18.2 included vs. 48.6±18.1 excluded) and duration of disease (6.5±7.7 years included vs. 8.1±8.8 years excluded) were not statistically different between groups.