FACTORS ASSOCIATED WITH SPONTANEOUS RELEASE OF VITREOMACULAR TRACTION

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Purpose: To analyze the factors that may predict the release of vitreomacular traction (VMT) and vitreomacular adhesion.

Methods: Retrospective case–control study of sixty-one patients with VMT imaged by optical coherence tomography over at least 3 months. Records from all patients seen at the University of Iowa from January 2012 to September 2013 were screened for the ICD9 code for VMT, vitreomacular adhesion, and epiretinal membrane (379.27 and 362.56). Release of VMT (R-VMT) was defined by resolution of patients' symptoms or traction by optical coherence tomography without surgical intervention or ocriplasmin injection. Individual factors or characteristics were evaluated by chi-square test. Using a binary logistic regression model, the potentially prognostic factors were evaluated for contribution to R-VMT.

Results: Of the 61 patients that met entry criteria, 21 (35%) developed R-VMT during optical coherence tomography follow-up, and 40 (65%) did not. Isolated inner retinal distortion without outer retinal involvement was significantly associated with R-VMT (P = 0.01). Vitreous injections were also associated with R-VMT (P = 0.02).

Conclusion: Eyes with VMT and isolated inner retinal distortion and those receiving vitreous injections are more likely to develop VMT release without the need for surgical intervention or ocriplasmin treatment.

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Vitreomacular traction (VMT) has been increasingly recognized as a cause of central vision loss and has attracted increased attention as a target for both surgical and pharmacologic treatments.[1] Both cause and severity of vitreous traction on the macula vary greatly among eyes, both in anatomical configuration and clinical course.[2] Isolated VMT with vision loss, also called VMT syndrome, may develop without associated retinal or other macular disease. In either setting, vitreous traction on the macula is due to a vitreomacular adhesion and may be associated with other conditions, such as age-related macular degeneration, diabetic macular edema, or retinal vein occlusion.[3–5] Vitreomacular traction can aggravate these concomitant retinal conditions but when to observe traction or relieve it surgically is not well established.

This study reports only on VMT that creates enough tractional force to induce structural changes to the macula, which are evident on optical coherence tomography (OCT). The structural changes include 1) inner deformation (i.e., "tenting") of the internal limiting membrane or inner retina, that is, often in a biconcave pattern,[6] 2) inner and/or, 3) outer retinal tissue distortion, and 4) localized neurosensory macular detachment. On OCT, VMT is usually associated with a partial posterior vitreous detachment.[7–9]

Serial observations have confirmed that the attachment of the vitreous to the macula will separate spontaneously in some cases.[10] It is not known however, what factors, if any, might predict or be associated with this spontaneous separation and resolution of

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the traction. This study assessed which factors might predict VMT separation in our population.

Methods

Patient Selection

We conducted a retrospective case–control study of patients who had a diagnosis of VMT between January 2012 and September 2013 at the University of Iowa. Subjects were initially selected by identifying patients receiving the ICD9 diagnosis of vitreomacular adhesion, VMT, or epiretinal membrane (379.27 and 362.56). Our study included new and follow-up patients but all subjects had received their initial diagnosis and treatment at our institution in an attempt to roughly synchronize the onset of VMT. All investigations of this study adhered to the tenets of the Declaration of Helsinki. Before data collection, the study received institutional review board committee approval.

Inclusion criteria were the presence of VMT as seen on OCT and at least 3 months of follow-up. Exclusion criteria included previous vitrectomy, ocriplasmin, or the lack of OCT imaging at all follow-up visits. The medical records and all fundus imaging (including OCTs) were reviewed for each subject who met the inclusion criteria. The specific data collected included medical history, ocular history, medications, ophthalmologic examination, fundus photographs, fundus fluorescein angiograms, number of anti-vascular endothelial growth factor (anti-VEGF) injections and the medication used, duration of follow-up observation, and anatomical findings on OCT.

Optical Coherence Tomography

Optical coherence tomography imaging was performed with the Spectralis Heidelberg spectral domain OCT (Heidelberg Engineering, Germany). All images were reviewed in real time to ensure they were of adequate quality. The VMT was characterized for each subject as either broad (>400 μm) or focal (<400 μm) based on horizontal OCT scans. Additionally, VMT was classified by the degree of inner only versus both inner and outer retinal involvement. Inner retinal distortion was defined as subjects with VMT causing abnormal inner retinal architecture up to, but not including, the outer nuclear layer along with a normal outer retinal anatomy, including a normal external limiting membrane and photoreceptor inner segment and outer segment junction. Subjects were classified as having combined inner and outer retina involvement if the outer retinal architecture was also involved.

Treatment History

Vitreous injection of an anti-VEGF agent was performed as part of clinical care for subjects with concurrent exudative age-related macular degeneration, diabetic macular edema, and macular edema associated with retinal vein occlusion. Anti-VEGF treatment decisions were made independently of the diagnosis of VMT. Anti-VEGFs were prescribed in accordance with activity of concurrent retinal disease as determined by the treating physician. As a general guide, anti-VEGF treatment included induction of 3 doses spaced 1 month apart followed by a treat-and-extend paradigm. Patients who had previous vitrectomy were excluded.

Definition of Vitreomacular Traction Release

The spontaneous resolution of VMT was defined as a release of the vitreomacular adhesion from all macular points seen on all OCT scans. Patients in the traction release (R-VMT) group continued on vitreous injections of anti-VEGF agents during the observation period as indicated for concurrent disorders. Patients who had nonrelease of their VMT (NR-VMT) were defined as study participants who still had attachments of the vitreous to the macula after at least 3 months of observation or who were suspended from observation because of vitrectomy or ocriplasmin injection.

Statistical Analysis

Data were analyzed using Statistical Analysis System (Cary, NC). For single comparisons (demographic characteristics, OCT descriptors, and treatment variables), we performed 2-tailed *t*-tests, calculated mean values, and 95% confidence intervals. We considered the finding statistically significant, if $P < 0.05$. All values were compared between the R-VMT and NR-VMT groups using *t*-tests. A binary logistic regression model was used to ascertain significance of variables, which correlated to R-VMT. Odds ratios, sensitivity, and specificity estimates for R-VMT and NR-VMT were calculated. Mean values are given with standard deviations.

Results

Sixty-one subjects with VMT met the inclusion criteria: 21 of these (35%) experienced VMT resolution (R-VMT), and 40 (65%) did not (NR-VMT) over the observation period. The groups were well balanced, and no significant difference in the baseline demographics, including age and lens status, were identified between the 2 groups (Table 1). Patients

Table 1. Demographic Data for All Study Patients

Demographic Variable	R-VMT Group (n = 21)	NR-VMT Group (n = 40)	*P*
Age (years ± SD)	70.3 ± 11.5	72.0 ± 8.5	0.8
Male, n (%)	10 (48)	13 (33)	0.3
Right eye, n (%)	12 (57)	13 (33)	0.2
Comorbid ocular history, n (%)			
None	6 (29)	22 (55)	0.3
AMD	7 (33)	10 (25)	0.2
DME	5 (24)	6 (15)	0.3
PDR	2 (10)	1 (3)	0.5
RVO	1 (5)	1 (3)	0.4

Associated values of *P* describe *t*-tests comparing R-VMT and NR-VMT.

AMD, age-related macular degeneration; DME, diabetic macular edema; PDR, proliferative diabetic retinopathy; RVO, retinal vein occlusion; SD, standard deviation.

were followed for a mean of 13.7 ± 11.4 months (range, 4–50 months) in the R-VMT group and 10.0 ± 6.6 months (range, 3–24 months) in the NR-VMT group.

There was a statistically significant difference in the degree of retinal involvement with 95% of patients in the R-VMT group having only inner retinal distortion compared with 65% in the NR-VMT group ($P = 0.01$) (Table 2). A typical example of a patient in the R-VMT is illustrated in Figure 1 with VMT affecting only the inner retina with subsequent spontaneous release. Vitreomacular traction with solely inner retinal disruption has been referred to as possessing the "column sign," owing to the outer retina being undisturbed in the configuration of 2 columns (Figure 2).[1] Conversely, combined inner and outer retinal distortion was significantly associated with a lack of VMT release (Figure 3).

Table 2. Analysis of Anatomical and Treatment Variables for All Study Patients

	R-VMT Group (n = 21), n (%)	NR-VMT Group (n = 40), n (%)	*P*
Anatomical variables			
Inner retina only	20 (95)	26 (65)	0.01
Inner + outer retina	1 (5)	14 (35)	
Focal VMT	14 (67)	26 (65)	0.9
Broad VMT	7 (33)	14 (35)	
Treatment variable			
Previous IVI	11 (52)	5 (13)	0.02

Associated values of *P* describe *t*-tests comparing R-VMT and NR-VMT for inner retinal involvement versus inner and outer retinal involvement, focal VMT versus broad VMT, and previous IVIs. Inner retinal distortion describes patients with VMT who were observed to have abnormal inner retinal architecture but a normal outer retinal anatomy, including a normal external limiting membrane and photoreceptor inner segment and outer segment junction. Patients with both inner and outer retinal distortions displayed an abnormal retinal anatomy in all retinal layers. Focal and broad VMTs define the degree of VMT adhesion and were defined as <400 μm or >400 μm, respectively, based on OCT horizontal linear measurements. The treatment variable was defined as patients who received IVIs for comorbid ocular disease at some time during the observation period.

There was no difference in the rate of R-VMT between focal and broad adhesions on the macula ($P = 0.9$). Approximately two thirds of each group had focal VMT (<400 μm), and this was evenly distributed across both R-VMT and NR-VMT groups (Table 2). Multifocal VMT was noted in a few cases and associated with a lack of VMT release (Figure 4); however, given the small number of patients with multifocal VMT, this was not statistically significant.

Previous treatment with intravitreal injections (IVIs) of anti-VEGF was associated with a higher incidence of VMT release ($P = 0.02$), and over half (52%) of the patients in the R-VMT received IVIs at some point

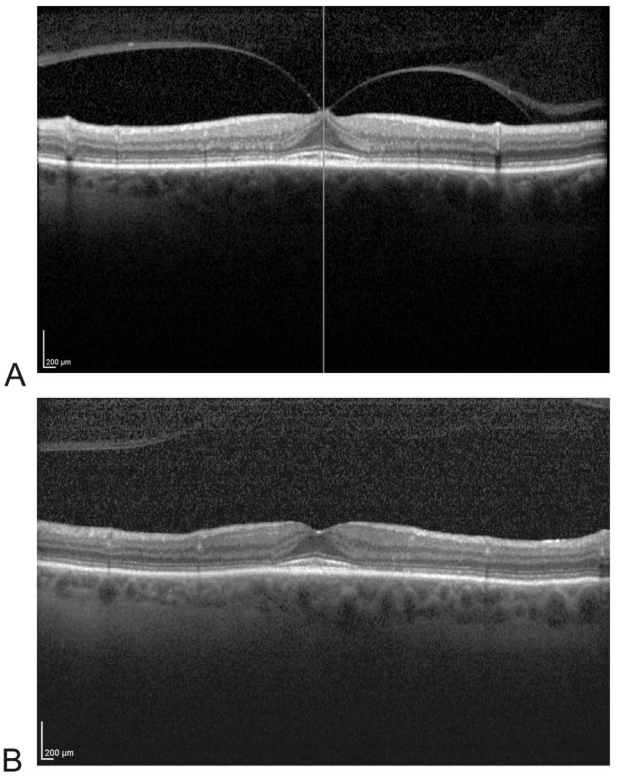

Fig. 1. A spectral domain OCT image of a 71-year-old woman with VMT and subsequent spontaneous release. **A.** There is a focal area of abnormal adhesion at the fovea with associated traction and distortion of the inner retina (the outer retina is unaffected). **B.** After 6 months of observation, the VMT spontaneously resolved with an improved foveal contour and normal inner retinal architecture. Visual acuity was 20/20 with a central macular thickness of 256 μm.

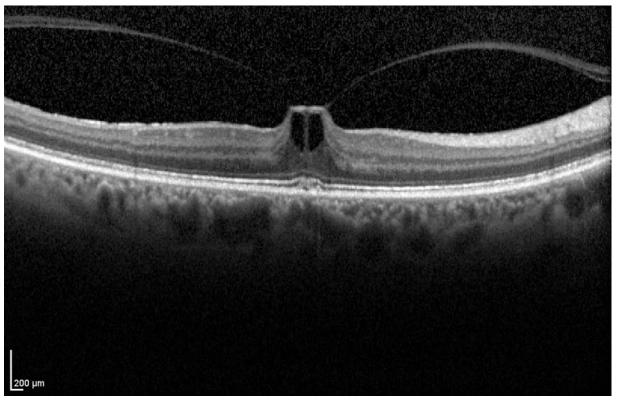

Fig. 2. A spectral domain OCT image of a 73-year-old woman with VMT depicting the column sign. There is a focal area of abnormal adhesion resulting in VMT distorting the subfoveal and perifoveal inner retina. The outer retina remains intact and resembles two columns; specifically, note the intact external limiting membrane and continuous photoreceptor inner segment and outer segment junction. Visual acuity was 20/30 with a central macular thickness of 370 μm.

during the observation period compared with only 13% in the NR-VMT group (Table 2). For those who received IVIs in the R-VMT group, the mean was 9.1 ± 8.9 injections (range, 1–31). In the

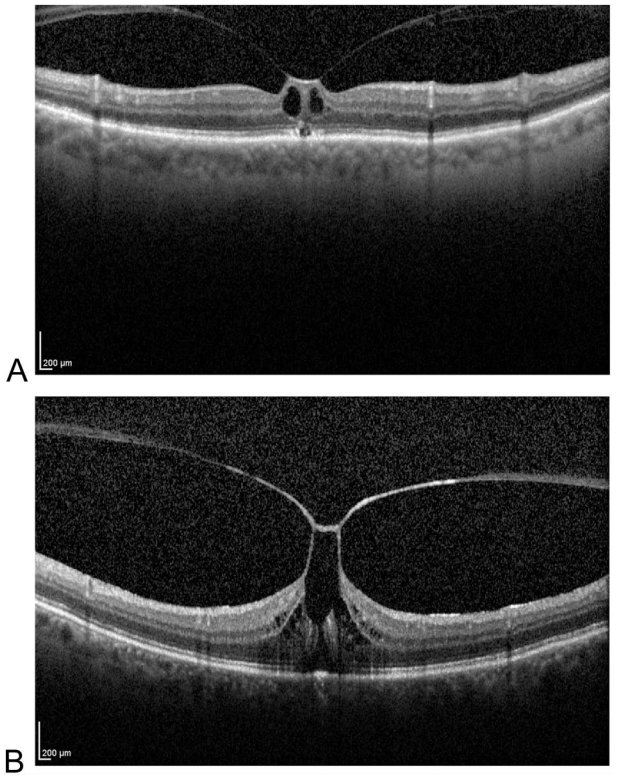

Fig. 3. Spectral domain OCT images of VMT with varying inner and outer retinal distortions. **A.** This 80-year-old man had abnormal VMT with a significant distortion in the outer retina and loss of the photoreceptor inner segment and outer segment junction. Visual acuity was 20/70 with a central macular thickness of 273 μm. **B.** A 73-year-old woman with marked VMT and significant traction on the inner retina; however, the outer retina is only mildly involved. Visual acuity was 20/30 with a central macular thickness was 304 μm.

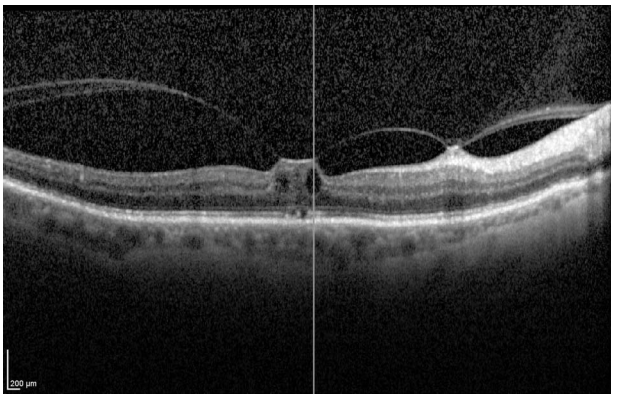

Fig. 4. A spectral domain OCT image of a patient with multifocal VMT. This type of broad VMT at the fovea center (>400 μm) was unlikely to undergo spontaneous release.

NR-VMT group, only 5 patients received IVIs (mean, 2.8 ± 1.8 IVIs), and none underwent spontaneous resolution. As a group, patients with spontaneous R-VMT were more likely to have had previous IVIs (Figure 5).

A total of seventeen patients (43%) in the NR-VMT group underwent pars plana vitrectomy for the indication of VMT. Conversely, no patient had to undergo pars plana vitrectomy in the R-VMT group. Three patients in the NR-VMT were prescribed ocriplasmin but failed to have resolution of their VMT with pharmacologic vitreolysis and underwent subsequent pars plana vitrectomy.

The significant, predictive anatomical (inner retinal involvement with no outer retinal involvement) and treatment (previous IVIs) variables were used to create

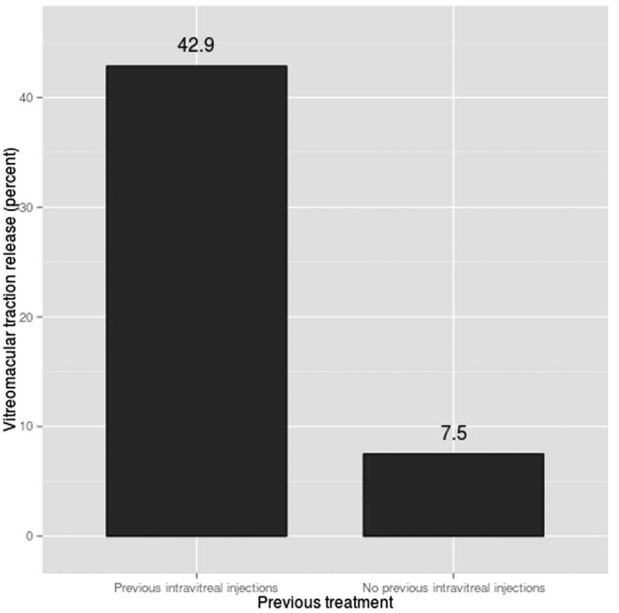

Fig. 5. Graphical representation illustrating the relative proportion of patients who experienced the R-VMT with a history of previous IVIs.

Table 3. Logistic Regression for Significant Variables Predictive of Spontaneous R-VMT

Predictive Variable	*P*	Odds Ratio	Sensitivity	Specificity
Treatment variable				
Previous IVI	0.002	7.39	0.52	0.88
Anatomical variable				
Inner retinal distortion with no outer retinal involvement	0.01	10.45	0.95	0.35
Combined prognostic variable				
Previous IVIs and inner retinal involvement	0.0002	16.28	NA	NA

Predictive variables include previous IVIs and VMT associated with an anatomical distortion of the inner retina only (normal outer retinal anatomy including a normal external limiting membrane and photoreceptor inner segment and outer segment junction). Binary logistic regression is displayed with associated values of *P*, odds ratio, sensitivity, and specificity for each predictive variable. An additional logistic regression model was computed with both treatment and anatomical variables as a single prognostic element for prediction of the spontaneous R-VMT.

NA, not applicable.

a binary logistic regression model for prognostic prediction of VMT release (Table 3). Both anatomical ($P = 0.002$) and treatment ($P = 0.01$) variables were statistically significant in the logistic regression model. The odds ratio for the anatomical variable was 10.45 with sensitivity and specificity of 0.95 and 0.35, respectively. The odds ratio for the treatment variable was calculated at 7.39 with sensitivity of 0.52 and specificity of 0.88. A combined prognostic logistic regression model was calculated with both anatomical and treatment variables yielding an odds ratio of 16.28 ($P = 0.0002$) (Table 3).

Discussion

The prevalence of VMT causing or associated with ocular disease has been estimated to range from 0.35% to 1.5% of the population, suggesting large disease burden and a potentially large treatment need.[11] Factors that are associated with an improved natural history or spontaneous resolution of VMT would be useful on which to base rational therapeutic decisions. Our study suggests that patients who received anti-VEGF injections were 7.39 times more likely to have spontaneous R-VMT compared with patients who did not receive these IVIs. It is unknown whether this effect is due to mechanical disruption of the vitreous from the needle and injected fluid or the medication.

In our study, patients in the R-VMT received a mean of 9.1 IVIs (n = 11), whereas patients in the NR-VMT received a mean of only 2.8 IVIs (n = 5). From this data, we can calculate a VMT release rate of 69% postulated to be from posterior vitreous detachment creation secondary to multiple IVIs. The time course of the first year of IVIs is similar to the mean follow-up time in our study (13.7 months in the R-VMT group and 10.0 months in the NR-VMT group) and supports a period of VMT observation in these patients who may be actively receiving treatment with IVIs of anti-VEGF agents.

Additionally, we identify that patients who had VMT with only inner retinal distortion on OCT were 10.45 times more likely to have spontaneous resolution of traction compared with those who had both inner and outer retinal distortions. Conversely, patients with VMT with significant outer retinal involvement were unlikely to have spontaneous release.

The anatomical and treatment variables were independent of each other and may be used together to determine the likelihood of spontaneous release of traction. The sensitivity and specificity values for injections of anti-VEGF treatment were 0.52 and 0.88, respectively, and the values for the anatomy on OCT were 0.95 and 0.35, respectively. The low sensitivity of the first and the low specificity of the second limit their usefulness as a single variable in predicting the spontaneous R-VMT. However, the combination of high sensitivity (0.95 for anatomy) and high specificity (0.88 for treatment) is very useful in predicting VMT release. The high odds ratio of 16.28 for the combined anatomical and treatment variables illustrates this point.

These findings are especially important in the management of patients with age-related macular degeneration, diabetic macular edema, and retinal vascular disease who typically need and receive multiple anti-VEGF injections. If such patients have only inner retinal distortion on OCT, it would be reasonable to follow them for two reasons. One, the traction is likely to resolve spontaneously; and two, if the vitreous is removed, anti-VEGF agents will have a very short half-life and will not be as effective.[12] However, this study did not address patients who had vitreous attachment over the entire posterior pole with or without a thickened posterior hyaloid face.

There are several limitations to our study. First, it is a retrospective case–control study. Second, although our series is moderately large, a prospective trial with larger sample sizes could yield additional or even different results. "Big data" projects such as the American Academy of Ophthalmology Intelligent Research in

Sight registry or the American Society of Retina Surgeons community could be capable of adding additional information from large numbers of patients.

In summary, we present novel prognostic variables that can be used to predict patients likely to undergo spontaneous resolution of VMT. Patients with only inner retinal distortion on OCT and those receiving multiple IVIs are significantly more likely to have spontaneous R-VMT. These findings may be of value to the clinician in evaluating patients with VMT, especially in the setting of patients who have concomitant retinal diseases like diabetic macular edema, exudative age-related macular degeneration, and macular edema from vein occlusions, which require injections of anti-VEGF agents.

Key words: macular disease, vitreomacular traction, vitreoretinal interface.

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