A Study of the Natural History of Vitreomacular Traction Syndrome by Optical Coherence Tomography.

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Abstract

Purpose: To examine the natural history of Vitreomacular Traction Syndrome (VMTS) in the absence of other ocular comorbidities.

Design: Retrospective clinical case series.

Participants: 183 eyes of 159 patients diagnosed with VMTS with no other ocular comorbidity.

Methods: Patients with VMTS were identified from an Optical Coherence Tomography (OCT) database at Moorfields Eye Hospital, London. Sequential OCT scans and patient notes were reviewed over a minimum period of 6 months. Data collected included patient demographics, best corrected visual acuity and OCT features of vitreo-macular adhesion. Contingency tests and binary logistic modeling were used to identify baseline predictors of stability and progression.

Main outcome measures: The rates of spontaneous resolution (defined by release of traction), progression to full-thickness macular hole or surgical intervention were analysed.

Results: Presenting visual acuity was 0.3±0.3 logMAR units. The mean length of follow-up was 17.4±12.1 months. During this period, VMTS persisted in 60% and

resolved in 20% (occurring on average at 15 months). Of the remainder, 12% developed a macular hole and 8% elected to proceed with surgery for symptoms. Focal adhesion of <1500 μm was present in 87%. A premacular membrane with macular pucker (PMM) was present in 20%. With persistent VMTS, vision and central foveal thickness remained unchanged. The relative risk of resolution increased in those cases with better presenting visual acuities, lesser foveal thicknesses and no associated PMMs; in those cases with resolution there was a significant improvement in vision.

Conclusion: VMTS persists in the majority of patients but despite this, visual acuities did not deteriorate significantly over the study period unless patients developed a full-thickness macular hole or required surgical intervention for symptoms. Resolution spontaneously occurred in 20%, with an improvement in vision.

Introduction

Vitreomacular traction syndrome (VMTS) forms part of a spectrum of diseases with abnormal vitreomacular adhesion. This condition was initially thought to be relatively uncommon, as only gross cases were identified by clinical examination. The development of optical coherence tomography (OCT) led to an increase in its diagnosis and revived interest in VMTS.

VMTS is characterized by anomalous posterior vitreous detachment (PVD) accompanied by anatomic distortion of the fovea. This may include the presence of

pseudocysts, macular schisis, cystoid macular edema and subretinal fluid. Clinically,

symptoms can vary from none to distortion and/or reduced visual acuity. In some

cases visual acuity may progressively deteriorate resulting in visions of 20/200

(logMAR 1.0) or less.[1] This may also be accompanied by macular hole formation.

More recently, the International Vitreomacular Traction Study group has developed

a classification system that aids in the characterization of this abnormal interaction

between the vitreous and macula.[2] In so doing, this has allowed more consistent

reporting of vitreomacular interface disorders.

There is a paucity of natural history data relating to VMTS within the published

literature. Controversy exists regarding the exact rate of spontaneous resolution in

eyes with VMTS. Some reports suggest that the rate of spontaneous PVD in this

condition is uncommon, with Hikichi *et al*. reporting a PVD rate of 11% over a five-

year period; other authors have observed a higher rate of approximately 50% in a

follow-up of around 9 months.[1,3,4] To further confound this issue of resolution,

Reibaldi *et al*. highlight a case with a ten year history of non-resolving severe VMTS

with no resultant anatomical or functional damage.[5]

The limited natural history data is surprising given that therapeutic interventions are

offered to patients with VMTS, including vitrectomy and more recently, enzymatic

vitreolysis.[6] In cases where spontaneous resolution of VMTS fails to occur,

vitrectomy may be offered to patients who complain of symptoms of reduced vision

and/or distortion.[7] Knowledge of the rate of spontaneous improvement is important

for patients making the decision regarding surgery, as well as providing doctors with sufficient information for informed consent. Following the advent of intravitreal injections of gas or pharmacologic agents such as ocriplasmin to induce vitreolysis, cases of mild yet symptomatic VMTS are now considered for intervention.[6,8] This further supports the need for more robust natural history data.

This study describes the natural history of VMTS over a minimum period of 6 months. To our knowledge, this large series differs from others as it concerns VMTS in the absence of other ocular comorbidities and utilizes an independent accredited OCT grader to assess OCT features of VMTS, with a follow up of more than 6 months.

Methods

This is a retrospective cohort study which was approved by the local Ethics Review Board committee and adhered to the tenets set forth in the Declaration of Helsinki. 183 eyes in 159 patients with a diagnosis of vitreomacular traction syndrome (VMTS) were identified from a database containing all patients imaged with OCT between 2009 and 2011 at Moorfields Eye Hospital, London. The inclusion criterion was the presence of vitreomacular traction on OCT, as defined by the International Vitreomacular Traction Study Group: evidence of perifoveal vitreous cortex detachment from the retinal surface; macular attachment of the vitreous cortex within a 3-mm radius of the fovea; and association of the attachment with distortion of the foveal surface, intraretinal structural changes, elevation of the fovea above

the RPE, or a combination thereof, but no full-thickness interruption of all retinal layers.[2] Cases with lamellar macular holes were excluded from this study. All patients had a minimum follow up period of six months, unless there was either resolution, progression to a full-thickness macular hole or surgery for symptoms. Exclusion criteria included coexisting retinal disease; previous history of retinal detachment; ocular inflammation; and proliferative retinal disease.

The International Vitreomacular Traction Study Group grading system classifies VMTS into focal (< 1500 μm) or broad (≥ 1500 μm) groups dependent on maximal horizontal surface adhesion.[2] To complement this, we utilized a system described by John *et al.* to catalogue the intraretinal OCT findings on presentation (Figure 1). Here, grade 1 is defined as incomplete cortical vitreous separation with foveal attachment. The additional presence of intraretinal cysts/clefts denotes grade 2 and in grade 3 a foveal photoreceptor detachment is also present.[9]

The following data were collected on each patient at the time of inclusion: patient demographics, best corrected visual acuity and OCT features of VMTS, including macular thickness, maximal horizontal surface adhesion and intraretinal changes. Imaging was performed with either Topcon 3D-OCT (Topcon, Japan) or Spectralis OCT (Heidelberg Engineering, Germany). For the Topcon 3D-OCT, a macular volume scan was performed for each eye consisting of 128 horizontal B-scans, centered through the fovea. For the Spectralis OCT, a similar horizontal raster scan was performed, centered on the fovea and covering a 6x6 mm^2 area. Patients underwent a series of OCT scans spanning a period of more than 6 months. All OCT scans were

graded, then validated by a single, reading center-certified, OCT grader masked to all clinical information at the time of grading.

The rate of spontaneous posterior vitreous detachment (PVD), as defined by resolution of traction and improvement of anatomic distortion of the fovea, was documented. Over the study period some patients elected to have surgery. Surgery in this unit was offered for progression to macular hole or for symptoms of significant distortion and/or reduction of vision present with both eyes open. The Snellen visual acuity was documented at the final follow up visit.

Data analysis and statistic methods

Data were analyzed with descriptive and frequency statistics. Snellen visual acuities were converted to logMAR units for analysis. The application of parametric and non-parametric tests was dependent on normality, as determined by using the D'Agostino and Pearson test. The statistical distribution of groups was compared using either the unpaired t test (two-tailed), Mann-Whitney (two-tailed) and Kruskal-Wallis test (for comparison of more than two groups). The Wilcoxon test was used to compare paired groups while the Chi-squared test was used to compare categorical variables. The relative risk was used to calculate the strength of association between categorical variables, as the prevalence of VMTS is less than 10%.[10] A P value less than 0.05 was considered statistically significant. In graphs, the error bars depict standard deviation. Binary logistic regression models for different outcomes were fit

with potential baseline predictors: age, visual acuity, gender, grade, adhesion, PMM
and foveal thickness. The former two variables are continuous data while the
remainder are nominal data. Models were refined by using a stepwise backward
elimination of non-significant ($P \geq 0.05$) variables. A P value greater than 0.05 was
used to confirm the validity of the model using the 'goodness of fit' tests. Statistical
analysis was performed using Minitab 16 (Minitab Inc., USA) and Prism 6.0
(Graphpad Software Inc., USA).

Results

Initial examination

A diagnosis of vitreomacular traction syndrome (VMTS) was identified in 183 eyes of
159 patients (Table 1), with a preponderance (70%) of women among cases. The
mean age at the time of presentation was 72 ± 10 years (mean ± standard deviation;
range, 45 - 95 years). Both eyes were affected in 28 patients (18%). Of the
remainder, 77 (48%) presented with VMTS in the right eye and 82 (52%) in the left
eye. The mean baseline visual acuity was 0.3 ± 0.3 logMAR units, with 18% of cases
having a visual acuity of 0.0 logMAR units or better at presentation. There was no
statistically significant difference in baseline visual acuity when the focal and broad
groups were compared (Mann-Whitney test) or between grades 1, 2 or 3 (Kruskal-
Wallis test) (Figure 2).

OCT Features at presentation

Patients were classified as having focal adhesion if the extent of vitreomacular adhesion was equal to or less than 1500 μm. Focal adhesion at the macula was present in 159 (87%) of the 183 eyes, with a mean width of 542 ± 270 μm (63 - 1407 μm). In the remaining 24 eyes with broad adhesion, the average width of adhesion was 2188 ± 375 μm (1623 - 2526 μm).

The mean foveal thickness at presentation was 317 ± 96 μm in the focal group, statistically significantly less than the initial foveal thickness of 410 ± 113 in the broad group ($P < 0.001$; Mann-Whitney test). When the intraretinal OCT findings were considered, similar measurements revealed average baseline foveal thicknesses of 313 ± 82, 333 ± 108 and 289 ± 100 for grades 1, 2 and 3 respectively, with a statistically significant difference between grades 2 and 3 only ($P < 0.05$; Kruskal-Wallis test with Dunn's multiple comparisons post hoc analysis) (Figure 3).

An premacular membrane with associated macular pucker (PMM) was present in 37 eyes (20%), with a statistically significant association with degree of adhesion ($\chi^2 = 44_{df = 1}$, $P < 0.0001$): cases with a broad adhesion have 5.6 relative risk (95% CI 3.5 - 9.1) of having a PMM when compared to those cases with a focal adhesion (Figure 4).

Outcomes

The average length of follow-up was 17.4 ± 12.1 months (range, 6 - 48 months). Of the 183 eyes included, there was no resolution in the majority (60%). Resolution of VMTS occurred in 36 patients (20%) with a mean time to resolution of 15 ± 14 months (range, 1 - 48 months); the incidence of resolution was 0.14/person-year. Over the study period, 23 patients (12%; incidence, 0.09/person-year) developed a full-thickness macular hole and 15 patients (8%; incidence, 0.06/person-year) elected to proceed with surgery for worsening symptoms. On average, this progression occurred at 19 ± 15 months and 13 ± 8 months respectively. There was no significant differences between the times to resolution, progression or surgery (Kruskal-Wallis test) (Figure 5).

The overall initial visual acuity of 0.3 ± 0.3 logMAR units was unchanged at the end of the study, with no statistically significant change in individual cases (Wilcoxon test). In cases with resolution of VMTS, the mean visual acuity was 0.1 ± 0.2 logMAR units, representing a significant improvement of 0.1 ± 0.2 logMAR units ($P < 0.01$; paired t test). In patients with stable VMTS at the end of the follow up period, there was no significant change in the visual acuity with an average visual acuity of 0.3 ± 0.2 logMAR units (Wilcoxon test). Development of a full-thickness macular hole resulted in a significant decrease in vision to 0.7 ± 0.2 logMAR units ($P < 0.001$; paired t test). Conversely, surgery for symptoms of VMTS significantly improved vision from 0.8 ± 0.8 logMAR units to 0.4 ± 0.2 logMAR units ($P < 0.01$; Wilcoxon test) (Figure 6).

Presenting visual acuity

While the baseline visual acuity is independent of whether a case with VMTS remains stable or changes ($\chi^2 = 2_{\,df\,=\,1}$), there is a significant association between this baseline vision and either resolution or progression to a full-thickness macular hole or surgery, if there is change ($\chi^2 = 6_{\,df\,=\,1}$, $P < 0.05$) (Figure 7A). Here, those presenting with vision better than or equal to 0.3 logMAR units have 2 relative risk (95% CI 1.1 - 3.6) of resolution and 0.6 relative risk (95% CI 0.4 - 0.9) of progression than those with worse vision. In both groups, there was a significant improvement in vision with resolution (≤ 0.3: $P < 0.05$; Wilcoxon test; > 0.3: $P < 0.01$; paired t test). With progression, a significant decrease in vision was only noted in the group with presenting vision ≤ 0.3 logMAR units ($P < 0.01$; paired t test). Asymptomatic VMTS (visual acuity better than or equal to 0.0 logMAR units) was not a significant factor in determining whether a case either remained stable or resolved or progressed ($\chi^2 = 2.9_{\,df\,=\,1}$) (Figure 7B).

Presenting foveal thickness

Similar to presenting visual acuity, the foveal thickness at presentation did not influence the stability of the condition ($\chi^2 = 1_{\,df\,=\,1}$). If there was either resolution or progression to a full-thickness macular hole or surgery, the presenting foveal thickness was a significant factor ($\chi^2 = 8_{\,df\,=\,1}$, $P < 0.01$) (Figure 7C). Eyes with increased foveal thickening of less than 400 μm have 3.1 relative risk (95% CI 1.1 -

8.9) of resolution and 0.5 relative risk (95% CI 0.3 - 0.8) of progression than those with thicker foveas. Despite this association, there was no significant difference between presenting and final visual acuities in both groups (Wilcoxon test).

Mean foveal thickness at the end of follow up was 316 ± 105 µm. In patients with no resolution of VMTS over the study period, the average final foveal thickness was 334 ± 91 µm, indicating no significant change in the foveal thickness when compared to presentation (Wilcoxon test). Resolution of VMTS produced a significant improvement in foveal thickness with a reduced mean final foveal thickness of 242 ± 79 µm ($P < 0.05$; Wilcoxon test).

Vitreoretinal adhesion and retinal features

There was no significant association between the type of horizontal adhesion (focal vs. broad) and whether a case of VMTS either persisted or resolved or progressed (evolution to full-thickness macular hole or surgery for symptoms) ($\chi^2 = 1_{df = 2}$) (Figure 7D). Likewise, the presence of intraretinal cysts/clefts or foveal photoreceptor detachment (grades 1, 2 or 3) did not significantly influence persistence, resolution or progression in VMTS ($\chi^2 = 4.5_{df = 4}$) (Figure 7E). However, in this case series, a focal adhesion was present in all cases of VMTS that progressed to a full-thickness macular hole.

Presence of premacular membrane with associated macular pucker

Classically, VMTS exerts an anteroposterior or axial traction on the macula, whereas macular pucker is associated with tangential macular traction. Therefore, analysis was undertaken to determine whether the presence of a PMM with macular pucker (and the differing vector of traction) affected outcome in such cases, as compared to those with VMTS only. Although the presence of a PMM with macular pucker is independent of whether a case remains stable or changes (χ^2 = 2.4 $_{df\,=\,1}$), its absence becomes a significant factor if there is change (χ^2 = 7.1 $_{df\,=\,1}$, P < 0.01) (Figure 8). Those cases with isolated VMTS have 2.3 relative risk (95% CI 1.1 - 5.0) of resolution and 0.5 relative risk (95% CI 0.3 - 0.8) of progression than those cases with a PMM with macular pucker.

Independent predictors of differing outcomes in isolated VMTS

When the outcome of resolution is compared to those of stability, development of a full-thickness macular hole or requiring surgery for symptoms, the only significant baseline variable is age (Table 2). However, the effect of this variable was minimal, with increasing age reducing the odds of resolution by a factor of 0.94.

Age at presentation was also a predictor of stability, increasing the odds of stable VMTS by a factor of 1.07. In this model, baseline visual acuity had a greater impact of

whether a case remained stable. Poorer vision decreased the odds of a case remaining stable by a factor of 0.14.

Similarly, presenting visual acuities were important significant variables when modeling the outcome of either development of full-thickness macular hole or the requirement for surgery. Poor vision increased the odds of these outcomes by factors of 12.89 and 15.52 respectively. However, the presence of a PMM with pucker at baseline had contrasting effects on whether a case developed a macular hole or required surgery for symptoms, reducing the odds by a factor of 0.08 in the former and increasing the odds by a factor of 15.63 in the latter.

Discussion

Here, we present natural history data of both symptomatic and asymptomatic patients diagnosed with vitreomacular traction syndrome (VMTS), as defined by the International Vitreomacular Traction Study (IVMTS) group.[2] In this study, the mean age of patients presenting with this condition was 72 years, with women comprising the majority (70%). On average, the baseline visual acuity was 0.3 ± 0.3 logMAR units. A PMM was present in 20% of cases. These characteristics are consistent with those noted in a slightly larger retrospective study (203 eyes with VMTS) by Stalmans.[11]

However, there are notable differences between our study and that published by Stalmans. Firstly, our paper analyses isolated VMTS in cases with no ocular comorbidity, while approximately 13% of cases with VMTS had diabetes in the latter study. Secondly, the degree of adhesion, foveal thickness and intraretinal changes were not analysed by Stalmans; in our study, these factors were independently assessed by a reading centre-certified OCT grader. This enabled us to statistically analyse the impact of the factors on differing outcomes for VMTS.

The similarity in baseline characteristics may have influenced the consistency in outcomes between the above studies. For example, the ReCoVit study cites an outcome visual acuity of 0.3 ± 0.4 LogMAR units in the VMTS only group, with 23% experiencing spontaneous resolution, 26% needing surgery for worsening symptoms and 5% developing full-thickness macular holes.[11] This compares favorably with our outcome data which shows a final visual acuity of 0.3 ± 0.3 and respective rates of 20%, 12% and 8%. The agreement of these two large independent studies, together with resolution rates of 20 - 30% in other studies,[9,12] suggests the possibility of a defined pattern for the outcomes of isolated VMTS.

This study also emphasizes the timing of resolution or progression of VMTS. On average, these events occurred after 12 months in both cases. The mean time of resolution is identical to that seen in a large pan-American retrospective case series.[12] Dimopoulos *et al*. analysed a subset of VMTS with focal adhesion and no PMM and found that 55% of cases resolved after more than 12 months, and highlighted this in relation to the final 6 month endpoint for resolution used in the

enzymatic vitreolysis trials.[6,13] Together, this data supports a more conservative temporal estimate of resolution when counseling patients.

Resolution of VMTS in our cohort of cases caused a statistically significant improvement in vision, in concordance with other studies.[11,12] Similarly, surgery for symptoms of VMTS resulted in an improvement in vision, while development of a full-thickness macular hole decreased vision. Others have used logistic regression modeling to identify cases which resolve or progress to vitrectomy.[11,14] We performed contingency tests to identify baseline characteristics associated with stability, resolution or progression in VMTS, with the latter being defined as the development of a full-thickness macular hole or surgical intervention for symptoms.

Interestingly, these tests showed that cases presenting with vision better than or equal to 0.0 LogMAR units did not have higher than expected rates of spontaneous resolution. Further analysis revealed that this 'threshold' was 0.3 LogMAR units, with those with better vision having higher rates of resolution and lower rates of progression than those cases with poorer vision. When this concept was applied to foveal thickness at baseline, another 'threshold' of 400 μm was discovered. Again, cases with thinner foveas have a higher relative risk of resolution and a lower relative risk of progression.

Other studies have not compared the natural history of focal and broad VMTS, as defined by the IVMTS group.[2] Randomized controlled trials investigating the therapeutic effect of enzymatic vitreolysis on VMTS resolution have shown a

differential in the rate of resolution between the focal (37%) and broad (14%) groups.[6] Our statistical analysis did not reveal an association between this variable and either rate of resolution or progression. In an attempt to classify the retinal architectural changes secondary to VMTS, John *et al*. devised three grades dependent on the presence of retinal cysts/clefts and foveal photoreceptor detachments on OCT. These authors, and Wu *et al*. subsequently, showed that there was no statistical difference in outcomes between the grades.[9,12] We graded our dataset using John *et al*.'s system and again failed to discern any differing outcomes, suggesting that the retinal architectural changes in VMTS are independent of outcome.

Our data also shows that the presence of a PMM is significantly associated with broad VMTS. This observation was noted by Odrobina *et al*., who postulated that the extent of the vitreous attachment could influence spontaneous regression of vitreofoveal traction.[3] While not conclusive, results from the previously mentioned randomized controlled trials suggests that the presence of a PMM affects outcomes: among patients without a PMM, VMTS resolution occurred in 37% of the enzymatic vitreolysis group and in 14% of the placebo group. In patients with a PMM, these rates reduced to 9% and 2% respectively.[6] These findings are supported by contingency tests on our outcomes, which show that cases without a PMM and macular pucker have a higher relative risk of resolution and a lower relative risk of progression.

Vitreoschisis is an abnormal split in the posterior vitreous cortex; a PVD in this setting results in the outermost layer of split vitreous cortex remaining attached to the retina. It can be identified using OCT combined with scanning laser ophthalmoscopy by the 'lambda' or 'Y' sign and was present in 53% and 42% of eyes with macular holes and pucker respectively.[15] Using similar criteria, vitreoschisis occurred in 6% of our cases. Of the 11 cases of VMTS with vitreoschisis seen, only 1 case resolved and 4 required surgery for symptomatic pucker.

In our analyses, while age was a significant predictor of whether a case of isolated VMTS resolved, remained stable or progressed to a full-thickness macular hole, it had minimal effect on these outcomes. In contrast, visual acuity at baseline had a profound effect on whether a case remained stable or required surgery for symptoms. This reflects clinical practice, where patients with poorer vision are more likely to require surgery for symptoms. However, it is notable that a worse presenting visual acuity increases the odds of a case developing a macular hole. The presence of a PMM was associated with a greater odds of requiring surgery for symptoms. This predictor also decreases the odds of developing a full-thickness macular hole.

There are limitations to our study, which include its retrospective nature; additional prospective data on long-term outcomes is still required. Visual acuity is used as measure of visual function, and does not reflect metamorphopsia due to retinal distortion. The latter is often a major symptom in VMTS and can be objectively measured using either three-dimensional threshold Amsler grid or M-charts.[16] This

study did not evaluate natural history of VMTS with regards to this symptom. It should be noted that the number of patients with asymptomatic VMTS that present to clinics appears low. This raises the possibility of creating a reporting bias, where this potentially 'milder' part of the VMTS spectrum is under-represented, skewing outcomes towards the more severe symptomatic cases.

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Figure legends

Figure 1. Retinal OCT scans depicting John *et al*.'s grading of retinal architecture in

VMTS: 1 (A) vs. 2 (B) vs. 3 (C). (D) shows an example of a broad adhesion subtype of

the International Vitreomacular Traction Study group subtypes.

Figure 2. Graphs showing presenting visual acuities for International Vitreomacular

Traction Study group subtypes (focal vs. broad adhesions) and John *et al*.'s grading of

retinal architecture (1 vs. 2 vs. 3).

Figure 3. Graphs showing initial foveal thickness for International Vitreomacular Traction Study group subtypes (focal vs. broad adhesions) and John *et al.*'s grading of retinal architecture (1 vs. 2 vs. 3) (*** $P < 0.001$ using Mann-Whitney test; * $P < 0.05$ using Kruskal-Wallis test).

Figure 4. Graph showing number of cases with either focal or broad adhesion presenting with a premacular membrane with associated macular pucker (PMM).

Figure 5. Time taken for cases to resolve, develop full-thickness macular holes (FTMH) or require surgery.

Figure 6. Graph showing the initial and final visual acuities for groups in which VMTS remained stable, resolved and progressed to either full-thickness macular hole (FTMH) or surgery (** $P < 0.01$ and *** $P < 0.001$; Resolved and FTMH using paired t test; Surgery using Wilcoxon test).

Figure 7. Graphs showing number of cases which either persist / change or resolve / progress to full-thickness macular holes or surgery, in relation to various baseline factors.