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The design and validation of an optical coherence tomography-based classification system for focal vitreomacular traction

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Learning Objectives

Upon completion of this activity, participants will be able to:

- 1. Describe the design and features of a novel classification system for focal vitreomacular traction.
- 2. Discuss development and validation of a novel classifica- tion system for focal vitreomacular traction.
- 3. Assess the intended use of a novel classification system for focal vitreomacular traction.

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The design and validation of an optical coherence tomographybased classification system for focal vitreomacular traction

Abstract

Purpose To develop and validate a classification system for focal vitreomacular traction (VMT) with and without macular hole based on spectral domain optical coherence tomography (SD-OCT), intended to aid in decision-making and prognostication.

Methods A panel of retinal specialists convened to develop this system. A literature review followed by discussion on a wide range of cases formed the basis for the proposed classification. Key features on OCT were identified and analysed for their utility in clinical practice. A final classification was devised based on two sequential, independent validation exercises to improve interobserver variability. Results This classification tool pertains to idiopathic focal VMT assessed by a horizontal line scan using SD-OCT. The system uses width (W), interface features (I), foveal shape (S), retinal pigment epithelial changes (P), elevation of vitreous attachment (E), and inner and outer retinal changes (R) to give the acronym WISPERR. Each category is scored hierarchically. Results from the second independent validation exercise indicated a high level of agreement between graders: intraclass correlation ranged from 0.84 to 0.99 for continuous variables and Fleiss' kappa values ranged from 0.76 to 0.95 for categorical variables.

Conclusions We present an OCT-based classification system for focal VMT that allows anatomical detail to be scrutinised and scored qualitatively and quantitatively using a simple, pragmatic algorithm, which may be of value in clinical practice as well as in future research studies.

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Introduction

Advances in optical coherence tomography (OCT) and, in particular, the recent widespread adoption of spectral domain OCT (SD-OCT), have provided improved visualisation of the vitreoretinal relationships and retinal structure in vitreomacular traction (VMT) syndrome. $1,2$ This has enabled observers to differentiate between the focal variant of VMT sometimes called vitreofoveolar traction (VFT) and the more broadly adherent form of VMT, where the zone of attachment exceeds 1500 microns.[3,4](#page-9-0) The importance of this differentiation is because the latter has a lower probability of undergoing spontaneous separation and is also less responsive to ocriplasmin.[5](#page-9-0)

Although the diagnosis of focal VMT can be easily made on OCT, no study has yet been published detailing those OCT features that might have prognostic significance for either spontaneous remission or progression to a full-thickness macular hole. Equally it is not clear which eyes with focal VMT are best suited for intravitreal ocriplasmin. Indeed, published series report varying proportions of successful outcome with that treatment modality, as well as with spontaneous resolution or response to vitrectomy.^{6-[17](#page-9-0)}

The recently published report by Duker et al^{[18](#page-9-0)} has highlighted the OCT features of both the focal and broadly adherent subtypes as well as eyes with focal and broadly adherent interfaces where the retinal architecture is not disrupted, termed vitreomacular adhesion (VMA). They also detailed the presence and absence of macular hole in these cases. However, the most common presentation of VMT is the focal variant and there is a need for a more detailed classification of the OCT features that occur in focal VMT, with and without a full-thickness macular hole.

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315

CLINICAL

STUDY

316

In this study, we describe the creation and validation of a pragmatic, OCT-based classification system for focal VMT that can be used in clinical practice, future prospective studies, to select patients for therapy and evaluate the influence of a wide spectrum of OCT changes on therapeutic outcomes.

Methods

A group of UK consultant retinal specialists was convened with the aim of devising a SD-OCT-based classification tool for eyes with focal vitreomacular adhesions. A PubMed search for relevant published articles was performed, including only those written in English and published up to November 2013. Selected relevant papers were reviewed prior to the meeting.

Between November 2013 and March 2014, the group met on two occasions. At the first meeting, members presented a total of 46 cases of VMT using SD-OCT images from their own practices that helped define the proposed structure of the classification tool. Each feature of the retinal and vitreoretinal interface was systematically explored, before the key elements were identified and reviewed for their utility in assessing VMT in everyday practice.

The group agreed to confine the classification to isolated focal VMA and VMT and defined those entities as a circumscribed area of vitreofoveal attachment of $<$ 1500 μ m in diameter, with surrounding vitreoretinal separation, and without other retinal disease. VMT, as distinct from VMA, was defined as any associated retinal structural change that was attributed to traction. All retinal change associated with traction, including FTMH, could be included. Conversely, VMA was recognised as an adhesion between the hyaloid and macula but without any structural change in the latter. The minimum scan protocol to be used in grading images, in terms of orientation and position, was defined as a horizontal line scan using SD-OCT through the foveal centre.

The classification system was intended to be practical and user friendly, so data fields had to be easy to collate and quantify as well as having validity in clinical practice.

The tool was refined and progressed through a number of iterations via e-mail discussions and at a second meeting, a further 45 case studies were discussed and classified using the prototype tool. A number of exploratory values were added to the classification and a test set of 26 new images of focal VMT were collated and distributed. The 26 images were selected specifically to allow a range of representative features to be evaluated. Images were imported into an open-source image editor (GIMP version 2.8;<www.GIMP.org>) to allow linear and angular measurements to be made. The nine clinicians graded the images independently based on the initial

classification system. The original classification system used six domains with between two and six categories in each domain, namely:

- (1) The width of vitreous attachment: W
- (2) The nature of the interface between the vitreous and retina: I
- (3) The fovea shape: S
- (4) The presence of retinal pigment epithelium (RPE) changes: P
- (5) The elevation of the lowest point of vitreous attachment: E
- (6) The nature of associated intra-retinal changes separated into inner and outer retinal changes: R

Categories within each domain were designed to be used in a hierarchical manner. The acronym WISPERR was used as a simple reminder of the various domains. In this version of the classification, several additional parameters were also evaluated:

- (a) Subdividing the type of inner retinal change into two groups.
- (b) Measuring the angle of vitreous insertion into the retinal surface using the method described by Theodossiadis et al.[19](#page-9-0)
- (c) Defining the differences between three types of outer retinal change before the occurrence of an FTMH.
- (d) Evaluating the ability to discern interface hyperreflectivity in the zone of VMT.

The test results were analysed for interobserver agreement using intraclass correlation (ICC) for continuous variables and two-way analysis of variance to assess for any systematic bias between observers. In addition, we used the method of Jones et al^{20} al^{20} al^{20} to assess agreement between observers and to produce an estimate of the limits of agreement with the mean. Fleiss' kappa was used for categorical variables. Fleiss' kappa is a measure of the closeness of agreement between multiple raters employing a categorical scale. The data are considered categorical rather than ordinal, so no credit is given for close agreement as in a weighted kappa: the latter can only be applied to paired observations. The values of ICC and Fleiss' kappa can be interpreted as follows: 0 − 0.2 indicates poor agreement: 0.3 − 0.4 indicates fair agreement; 0.5 − 0.6 indicates moderate agreement; $0.7 - 0.8$ indicates strong agreement; and > 0.8 indicates almost perfect agreement. We were thus able to provide an overall measure of reliability and agreement between the ratings used and evaluate the reproducibility of the scale in each category of the proposed classification.

Disagreements were identified and definitions reviewed. Categories with high levels of disagreement where separate entities could not be consistently discerned were either merged or removed. In particular, the angular measurements and the subdivision of the inner retinal changes were removed because of low agreement, and the shape and interface classifications were simplified. The definitions of the outer retinal changes were also revised to provide greater clarity. Based on these results and discussions, a final classification was produced and named WISPERR ([Table 1,](#page-4-0) with illustrative figures defining the features used shown in [Figure 1](#page-5-0)). A further test set of 10 new cases was reviewed and agreement between group members was assessed again.

Results from both test sets are presented.

A series of examples of the classification using real images is shown in Supplementary Figure S1.

Results

Initial test set of 26 images

The width of vitreous attachment in the image set ranged from a case of narrow VMT, which the observers measured at a mean of $22 \mu m$, to a case of broad VMT measured at a mean of $1040 \mu m$. The ICC between observers was 0.98 ($F = 0.84$, $P = 0.67$). The measurements showed no systematic relationship with width or image and the limit of agreement with the mean was $32.3 \mu m$, which we considered clinically acceptable.

The elevation of the lowest point of vitreoretinal adhesion ranged from a mean of $275 \mu m$ to a mean of 760 μ m. The ICC between observers was 0.84 (F = 1.07, $P = 0.38$). The measurements showed no systematic relationship with degree of elevation or image and the limit of agreement with the mean was 29.6 μ m, which was clinically acceptable.

For the purposes of the test evaluation, the base diameter of outer retinal dehiscence and FTMHs were measured. For outer retinal dehiscence $(n=7)$, the base diameter ranged from 128 to $820 \mu m$; the ICC between observers was 0.99 (F = 1.22, $P = 0.31$). For FTMHs ($n = 5$), the minimum linear diameter ranged from 160 to 346 μ m; the ICC between observers was 0.84 (F = 1.84, $P = 0.15$). The measurements showed no systematic relationship with width or image and the limit of agreement with the mean was $15.3 \mu m$ for base diameter and $26.2 \mu m$ for the minimum linear diameter.

The angle of insertion of the vitreous into the retina measured from 12 to 67 degrees on the nasal side of the VMT and from 11 to 69 degrees temporally. There was limited variation between the mean of observers for all measurements and variation between readers was

consistent, but the ICC showed only moderate agreement (0.69) and ANOVA suggested strong evidence of systematic bias between observers $(F = 5.21, P < 0.00001)$. The limits of agreement showed no obvious relationship with angle size but some angles showed tighter measurements than others, with the maximum variation in any one angle varying by up to 27 degrees between observers. The limit of agreement with the mean measured 9.6 degrees. We considered this to be clinically significant and hence excluded angle assessments, as they were too unreliable to be included in the classification.

Fleiss' kappa values varied between 0.61 for the vitreoretinal interface and 0.78 for the presence of RPE abnormality ([Table 2a](#page-6-0)).

Final test set of 10 images using final grading scheme

In this test set, only the categorical sections were reevaluated [\(Table 2b\)](#page-6-0), with improved Fleiss' kappa values of 0.76 − 0.95.

Discussion

The proposed classification system focusses on focal VMT (isolated VFT) rather than all types of VMT. The International Vitreomacular Traction Study Group recently published a classification system of vitreoretinal interface abnormalities, including VMT.[18](#page-9-0) Although comprehensive, it is not sufficiently detailed regarding focal VMT to allow the discovery of new prognostic indicators. Other classifications have also been proposed $4,8,21$ but none to date have included the wide range of features that clinicians use to assess focal VMT.

In a stepwise iterative process, we initially selected vitreoretinal features that were either previously known to be important or those that the group considered may influence VMT progression, resolution, or response to treatment. Importantly, these characteristics had to be easily assessable, with a clear definition to allow acceptable reproducibility in a real-world (rather than a grading centre) setting. This stepwise system allowed consensus to be reached and improved the classification's validity. The high agreement values in the final classification reflect this. We purposefully designed the classification to be hierarchical for ease of use. It should be noted that although only OCT features are included in the classification, non-OCT features remain important.

The classification is designed to be used with SD-OCT and principally a single horizontal line scan through the foveal centre. Other scans, however, should be utilised to further define the extent of the VMA, aid in the detection of eccentric areas of macular hole and ERM, and to delineate the maximum values of the minimum linear diameters of FTMHs. It is important that the scan through

Table 1 The focal VMT classification tool: WISPERR

Abbreviations: ELM, exterior limiting membrane; ERM, epiretinal membrane; ETDRS, Early Treatment Diabetic Retinopathy Study, ILM, inner limiting membrane; IS, inner segment; OCT, optical coherence tomography; OS, outer segment; RPE, retinal pigment epithelium; SRF, subretinal fluid; VMA, vitreomacular adhesion; VMT, vitreomacular traction. ^aMany OCT systems measure this in an automated way but it is best measured manually to avoid segmentation errors. In cases where there is a partially avulsed flap of retina or an oblique highest point, the height to the lowest point of contiguous vitreoretinal adhesion should be used. ^bThe maximum base diameter should be measured horizontally from the two junctions of the outer retina with RPE. A dense scanning protocol should be followed to avoid missing small eccentric full-thickness macular holes. The maximum of the minimum linear diameter is measured—this is defined as the narrowest hole diameter in the approximate mid-retina using a line drawn parallel to the RPE. The narrowest part of hole should be measured other than that involving the hole operculum. To find the maximum measurement, the OCT slice with the widest macular hole width should be used—this can be facilitated by using a dense horizontal line scanning protocol or using multiple radial scans.

None

- without SRF, or dehiscence
- Sub-retinal fluid

Outer retinal dehiscence

Figure 1 Schematic representation of the focal VMT classification tool: WISPERR. (a) Width of vitreous attachment (W), interface features (I), and foveal shape (S). (b) Retinal pigment epithelial changes (P), elevation of vitreous attachment (E), and inner and outer retinal changes (R).

319

Table 2 Fleiss' kappa values

Abbreviation: RPE, retinal pigment epithelium.

the middle of the foveola is selected. This is defined as the area with no bipolar or ganglion cells and where the dark band of the outer nuclear layer extends to the foveal surface, without an intervening outer plexiform layer (Figure 2). Clinicians should be wary of using eccentric OCT slices as these will confound the assessment. It should also be noted when interpreting scans that, at the foveal centre on SD-OCT, the area between the ellipsoid zone and the RPE can appear slightly lucent and wider than adjacent areas. Furthermore, the inner retinal surfaces are brighter on the horizontal surfaces, especially nasally where the nerve fibre layer is the thickest (Figure 2).

The width of the VMA is the primary feature for differentiation between classically recognised VMT and VFT.[4](#page-9-0),[21](#page-9-0) Width has been demonstrated as predictive of treatment outcome with intravitreal ocriplasmin^{[9](#page-9-0)} and shown to be prognostic of spontaneous release. $22,23$ This feature of VMA exists as a continuum rather than a discrete value. $4,16$ $4,16$ $4,16$ and we therefore determined that it should be measured. The longest continuous length of adhesion is likely to be the most important in terms of release rather than the sum of discontinuous areas of focal VMT, and therefore this was chosen for the classification. Although the surface area of the adhesion has been evaluated as a prognostic measure of VMT separation,^{[23](#page-9-0)} measuring this in a clinic setting would necessitate a specified scan protocol, which varies between machines and centres.

Concerning the vitreoretinal interface itself, as ERM is known to be a feature of VMT and related to both the chance of spontaneous separation and separation induced by ocriplasmin, this was included. We separated retinal surface ERM from changes specifically at the area of VMT itself and further divided ERM that was contiguous with

Figure 2 Horizontal SD-OCT of a normal fovea. *Note pre-macula bursa.

the zone of VMT from non-contiguous ERM. Interface opacity at the zone of VMT, both hyper-reflectivity and increased thickness, was found to be a variable feature on the scans examined by the group and could be reliably detected. It has previously been shown to be prognostic of release with plasmin.^{[24,25](#page-9-0)} We did not observe any cases of VMT associated with the recently described entity of lamellar hole-associated epiretinal proliferation.^{[26](#page-9-0)}

Although the shape of the fovea is currently not known to be a prognostic factor, it is important in distinguishing VMT from VMA and correlates with the width of adhesion and elevation to suggest the extent of traction. In this study, we subclassified shape into normal, loss of inner retinal profile, or eversion of fovea. This simple categorisation of shape had good agreement between the graders. Eversion of the fovea may prove useful in future investigation of visual function in VMT, as found in recent studies on diabetic macular oedema.[27](#page-9-0),[28](#page-9-0)

The classification was not designed to be used with for VMA in conjunction with other diseases, such as wet agerelated macular degeneration, diabetic maculopathy, or retinal vein occlusion. However, we frequently noted that some cases of otherwise isolated VMT had concomitant features of ageing, including RPE atrophy and small drusen. Additionally, in chronic VMT there can be changes in the uniformity of the RPE pigment with pigment migration, $29,30$ $29,30$ $29,30$ so a simple categorisation of the presence or absence of RPE changes has been included.

Elevation is an objective measure of the severity of VMT. Many OCT machines provide an automated measure of maximum foveal height, but with tenuous focal VMT we found that segmentation errors were common using automated protocols. We therefore included a manual measurement of the height from the RPE to the lowest point of VMA to allow for cases with partially avulsed inner retinal flaps.

It is well established that there is a positive relationship between the tension exerted by differing widths of VMT

Figure 3 Examples of minimum linear diameter measurements using SD-OCT slice with maximum hole dimensions. In (a), the minimum linear diameter is on the inner side of the hole and in an eccentric slice without vitreomacular traction, while in (b) it is on the outer retinal side of the hole. (c) A case of apparent outer retinal dehiscence but with a tiny para-central full-thickness macular hole seen on one more eccentric OCT slice in (d). When measuring minimum linear diameter, the area of the retinal operculum should not be included (shown in (e) and (f)).

and alterations in retinal architecture.^{[16](#page-9-0),[19,31](#page-9-0)} Observation of cases has shown that inner retinal changes are more common and that outer retinal changes can range from subtle alterations at the level of the outer segments of the photoreceptors to outer retinal dehiscence and FTMHs.^{[32](#page-9-0)} Recently, however, Almeida et al^{22} al^{22} al^{22} noted that eyes with isolated inner retinal distortion but without outer retinal changes have an apparently higher incidence of spontaneous vitreomacular separation than those with outer retinal changes. We therefore separated inner retinal change recording from outer retinal change.

A variety of inner retinal changes have been described and named in tractional maculopathies. Some authors have also attempted to differentiate between inner retinal changes that may be associated with VMT (variously described as foveal cavitation, foveolar cysts, foveal cystoid spaces) 33 33 33 vs cystoid macular oedema^{29,33} and retinoschisis.[2](#page-8-0) We found, however, that the observers could not reproducibly differentiate these entities, so a single division of present or not present was included. A measure of the degree of inner retinal change is also coded within the classification by the elevation measurement.

Similarly, a large number of outer retinal changes have been described, including a localised opalescence of the ellipsoid zone termed the 'cotton ball' sign, thought to be due to traction at the foveola, which disappears upon vitreoretinal release.[25](#page-9-0)[,34](#page-10-0) Other changes reported include

localised defects of the ellipsoid zone and/or external limiting membrane, which can be associated with the presence of ERM.35–[38](#page-10-0) These are all included in one category as distinguishing between them was inconsistent between observers. We differentiated subretinal fluid from more subtle outer retinal changes and also from outer retinal dehiscence seen in impending macular holes. The latter occurs as a result of tractional forces on the outer retina[.39](#page-10-0),[40](#page-10-0) It has been shown that, following treatment of VMT, while intraretinal cystic changes resolve quickly, subretinal fluid resolves more slowly during longer follow-up.[41](#page-10-0)

When considering the assessment of FTMH, measurement of the maximum of the minimum linear diameter is included, as this measurement has been used in the majority of publications to date. It is defined as the width of the narrowest hole diameter using a line drawn parallel to the RPE. The narrowest part of the hole should be measured, other than that involving the associated retinal operculum—the exact location of the narrowest part of the hole varies with the hole configuration ([Figure 3](#page-7-0)). To find the maximum measurement, the OCT slice with the widest macular hole width should be used—this can be facilitated by using a dense horizontal line scanning protocol or using multiple radial scans. Base diameter of macular holes is, however, a more reproducible measurement 42 and was included to quantify the extent of outer retinal dehiscence in cases without FTMH. It is important that in cases of outer retinal dehiscence the presence of an eccentric fullthickness defect is not missed by utilising a dense scanning protocol as with FTMH ([Figure 3\)](#page-7-0).

We initially included the angle of vitreous insertion into the VMT relative to the RPE. Theodossiadis et al^{17} al^{17} al^{17} described an increasing angle of vitreous insertion as being predictive of VMT spontaneous resolution. However, this was subsequently removed from the classification owing to the high variability of measurements between observers. Furthermore, although angles may be useful in a research setting their measurement is confounded by a number of variables, including scan orientation and the aspect ratio the scan is viewed at. Furthermore, OCT scans are typically presented with the retina viewed as a planar surface rather than the reality, which is a concave curved surface,^{[43](#page-10-0)} which will also alter the VMT angles measured.

In conclusion, we present a novel classification system for focal VMT with details of its design and validation. We hope it will serve as a pragmatic system that clinicians could use in routine clinical practice and in collaborative research studies to investigate new prognostic features related to functional and anatomical outcomes, either with treatment or observation.

Summary

What was known before

- Isolated vitreomacular traction (VMT) has previously been classified based on the width of vitreous attachment and the presence of a macular hole.
- Other associated features of VMT are known to occur, but no unified classification system exists to describe them.

What this study adds

- A simple validated classification system for focal VMT intended to aid in decision-making and prognostication is described.
- It is based on optical coherence tomography and hierarchically classifies seven features of VMT, namely, width, vitreoretinal interface changes, shape, pigment epithelial changes, elevation, and inner and outer retinal changes, under the pneumonic WISPERR.

Conflict of interest

This study group was convened by Alcon, which distributes ocriplasmin in the UK on behalf of Thrombogenics. Neither Thrombogenics nor Alcon had input in the design of the study, manuscript preparation, or editorial review and neither were invited to review the manuscript prior to submission. Steel DHW is a consultant to Alcon and advisor to Novartis and Bayer. Jackson TL is a consultant to Thrombogenics and advisor to Alcon, Bausch & Lomb, and DORC. Yang Y is a consultant to Bayer and Alimera Sciences and advisor to Alcon, Thrombogenics, Allergan, and Novartis. Downey L, Laidlaw DAH, Koshy Z, Heimann H, Wickham L, and Greiner K have acted as advisors to Alcon and Thrombogenics regarding ocriplasmin.

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322

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Supplementary Information accompanies this paper on Eye website (http://www.nature.com/eye)

The design and validation of an optical coherence tomographybased classification system for focal vitreomacular traction

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- 1. You are considering use of a novel classification system for focal vitreomacular traction (VMT). According to the report by Steel and colleagues, which of the following statements about the design and features of a novel classification system for focal VMT is correct?
	- A It does not require optical coherence tomography (OCT).
	- B It classifies only five features of VMT.
	- C It does not use hierarchical classification.
	- D It classifies foveal shape and retinal pigment epithelial changes.
- 2. According to the report by Steel and colleagues, which of the following statements about development and validation of a novel classification system for focal VMT is correct?
	- A A panel of general ophthalmologists developed this system based only on consensus opinion.
	- B Final classification was based on a single validation exercise.
	- C Intraclass correlation between graders ranged from 0.84 to 0.99 for continuous variables, and Fleiss' kappa values ranged from 0.76 to 0.95 for categorical variables.
	- D The stepwise system reduced the classification's validity.

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- 3. According to the report by Steel and colleagues, which of the following statements about the intended use of a novel classification system for focal VMT is correct?
	- A It is intended solely as a research tool.
	- B System characteristics are easily assessable; clearly defined; have acceptable reproducibility in a real-world setting; and may reflect VMT progression, resolution, or treatment response.
	- C Scans other than spectral domain OCT are unnecessary.
	- D Clinicians should use eccentric OCT slices.

