SYMPTOMATIC VITREOMACULAR ADHESION

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Background: Symptomatic vitreomacular adhesion describes symptomatic loss of visual function as a result of vitreous traction at the macula.

Methods: Literature review.

Results: Symptomatic vitreomacular adhesion can occur in isolation as vitreomacular traction, which may lead to the development of a macular hole, or it may occur alongside epiretinal membrane. It is likely to be associated with age-related macular degeneration and possibly diabetic maculopathy, although this is less certain. The treatment depends largely on the cause, but options include observation, vitrectomy, and pharmacologic vitreolysis. Small uncontrolled trials have also explored the use of an intravitreal gas bubble as a means of releasing VMA. If all cases of sVMA are considered together, then the burden of illness is substantial, with a prevalence of ~0.35 per 100 population (excluding epiretinal membrane). Furthermore, there may be many more cases of undiagnosed sVMA.

Conclusion: The recent introduction of ocriplasmin is likely to increase interest in sVMA. Clinical trials suggest that it has a role in the treatment of vitreomacular traction and Stages 1 to 3 macular holes but not primarily as a treatment of epiretinal membrane. Its role in other diseases associated with VMA remains to be determined.

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Symptomatic vitreomacular adhesion (sVMA) describes abnormal vitreomacular adhesion (VMA) causing loss of vision. It is a relatively new term, encompassing a range of macular diseases, but they are all characterized by structural and functional foveal damage because of abnormal vitreomacular traction (VMT). In its purest form, VMT syndrome, these changes occur in isolation. Macular hole may be part of the same spectrum, but in this case, the traction leads to a full-thickness hole centered on the fovea. Symptomatic VMA has also been used to describe other conditions where VMA occurs alongside another primary disease. In this setting, the VMA may or may not be abnormal, but there is thought to be some deleterious interaction with the underlying disease. For some diseases, such as neovascular age-related macular degeneration (AMD), there seems to be an association with VMA, but it is difficult to establish how that interacts with vision or disease activity. In other conditions, such as diabetic macular edema (DME) and retinal vein occlusion, the link is uncertain.

Recently, intravitreal ocriplasmin has been introduced as a treatment to relieve VMA and with this comes the prospect of treating sVMA at an earlier stage or without surgery. This is likely to increase interest in sVMA, and this article therefore provides an overview of sVMA.

Method of Literature Review

The authors performed a MEDLINE search using PubMed and Ovid for articles published between 1966 and 2012. Search terms included the following: symptomatic vitreomacular adhesion, vitreomacular...
adhesion (and VMA), vitreomacular traction (and VMT), taut posterior hyaloid, vitreomacular traction syndrome, vitreomacular adhesion + macular hole, vitreomacular traction + macular hole, vitreomacular adhesion + epiretinal membrane, vitreomacular traction + epiretinal membrane, vitreomacular adhesion + age-related macular degeneration, vitreomacular traction + age-related macular degeneration, vitreomacular adhesion + diabetic macular edema, vitreomacular traction + diabetic macular edema. The relevant searches were repeated replacing vitreomacular adhesion with VMA, vitreomacular traction with VMT and macular edema with macular oedema.

**Posterior Vitreous Detachment**

The vitreous is an optically clear watery gel that fills the posterior segment of the eye. It is composed of >99% water and also collagen fibers and salts. In healthy eyes, the vitreous is adherent to the internal limiting membrane (ILM) of the retina. It has a particularly strong attachment at the anterior vitreous base and the optic nerve and less firm adhesion at the macula.

With age, the uniformity of the vitreous’ structure reduces, and subsequently, some areas become more liquid (synchysis) than others. A combination of a reduction in volume of the vitreous gel and a weakening of the attachment between the vitreous and ILM may lead to complete separation of the vitreous, defined as a posterior vitreous detachment (PVD). For most patients, PVD is part of the normal aging process. Typically, a PVD separates fully from the optic disk and macula, although it remains attached at the vitreous base. Notwithstanding the persisting vitreous base adhesion, this situation is referred to as “complete” PVD. In most cases, the vitreous separates first at the macula and then at the optic disk. Residual attachment at either the optic disk or macula is defined as an “incomplete” or “partial” PVD.

**Definitions: Vitreomacular Adhesion, Vitreomacular Traction, and Symptomatic Vitreomacular Adhesion**

In healthy eyes, the posterior vitreous face lies in contact with the retina and so VMA does not necessarily represent a disease state. In usual clinical parlance however, VMA describes residual adhesion between the vitreous and macula, occurring in the context of an incomplete PVD (Figure 1A). Vitreomacular adhesion may not lead to any retinal abnormality, however VMA may exert traction on the underlying macula, causing distortion of the retinal architecture, so-called VMT. The distinction between VMA and VMT is sometimes difficult to define—gross traction is easily labeled as VMT (Figure 1C) but minor degrees of traction may be less easily classified. One method of defining VMT is to use a photographic standard to define VMT, such that distortion of this magnitude or greater can be labeled as VMT, whereas lesser degrees of distortion are considered as VMA. VMT can also occur in the context of other diagnoses, such as macular hole. The term sVMA is used to encompass VMT syndrome and cases where normal or abnormal VMA coexists with an associated ocular disease and loss of visual function. The severity of sVMA varies greatly, from
mild visual impairment through to more severe loss of central vision. Sometimes quite marked optical coherence tomography (OCT) changes are compatible with relatively minor symptoms and normal, or near normal, visual acuity.

Because of variations in terminology in the literature, the following definitions have been proposed by Jackson et al.1 and are used in this review:

Vitreomacular adhesion: focal adhesion of the vitreous face within the macular region.

Vitreomacular traction: VMA causing focal tractional distortion of the macula greater than of the macula greater than or equal to the Simpson standard.10

Vitreomacular traction syndrome: VMT associated with loss of visual function.

Symptomatic VMA: either VMT syndrome, macular hole, or cases where normal or abnormal VMA coexists with an associated macular disease in all cases, with symptomatic loss of visual function. (Figure 2).

Optical Coherence Tomography

Vitreomacular traction was appreciated on fundus biomicroscopy well before the advent of OCT; however, nowadays, OCT is central to diagnosis and has greatly increased the likelihood of detecting VMT. Optical coherence tomography shows focal adhesion of the vitreous with associated lifting of the inner retinal surface. This is often associated with intraretinal edema. Epiretinal membrane (ERM) may also be evident, as may features suggestive of an early macular hole, such that the diagnosis of VMT and impending macular hole often overlap. Vitreomacular adhesion, without associated macular changes, can be very difficult to detect clinically but is often evident on OCT. Although OCT is well suited to detect VMA and VMT, it may fail to detect a PVD if the detached posterior vitreous face lies anterior to the area imaged on the OCT. Likewise, a fully attached vitreous is seldom visible, as the posterior vitreous face is

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**Fig. 2.** Flow diagram shows the relationship between PVD, VMA, and VMT. Posterior vitreous detachment, VMA, and VMT can occur in isolation or in the context of other diseases. Isolated sVMT is often referred to as VMT syndrome (VMTS). The boxes in gray show diseases that have been reported to be associated with VMA, although the relationship is somewhat uncertain for retinal vein occlusion (RVO) and diabetic macular edema (DME). If this relationship is assumed then these diseases could be categorized as part of the symptomatic VMA spectrum, although that does not presuppose a causal relationship. RVO, retinal vein occlusion; MH, macular hole.
anatomically apposed to the ILM. Ultrasound and clinical examination are often useful to help diagnose PVD, if it is not visible on OCT.

There can be an apparent discrepancy between the severity of VMT and visual function, in that severe OCT changes are not always associated with loss of vision. This usually occurs when the inner retina is distorted by traction, but the outer retina remains intact (Figure 3). As shown in the figure, there are commonly fluid-filled cysts. These may be traversed by columns of preserved tissue. The exact nature of these columns is unknown, but they may represent residual tissue held together by the Müller cells. The Müller cells pass from the inner to the outer limiting membranes and may resist tractional forces, as they contain mechanically robust intermediate filaments.\(^\text{11}\)

Early OCT studies have shown that abnormal VMA plays a substantial role in the development of many if not most macular holes.\(^{12-14}\) In many cases, there is clear VMT at the edge of the hole (Figure 4), and even in cases where this is not evident, it may be that previously VMT played a role in the development of the hole.\(^\text{12}\)

Optical coherence tomography of eyes with VMT will often show an ERM (Figure 5). Epiretinal membranes are comprised of glial and retinal pigment epithelium cells, with fibrous or myofibrobastic tissue and cortical vitreous.\(^\text{15}\) Whereas VMT typically exerts a predominantly anteroposterior traction, ERMs often exert tangential forces that cause corrugations in the retinal surface and distortion of the usual foveal contour.

**Observation**

Asymptomatic VMA or asymptomatic VMT does not require treatment. Vitreomacular traction syndrome causing loss of vision can be managed conservatively, as some cases will separate spontaneously. However, Hikichi et al\(^\text{16}\) reported that only 6 (11%) of 53 eyes developed a complete PVD over a median follow-up of 60 months. In addition, studies indicate that prolonged VMT may lead to progressive loss of vision, and increase the risk that subsequent intervention may be less successful.\(^{16-18}\) Therefore, persisting visual dysfunction is usually treated surgically.

The natural history of macular hole is somewhat uncertain, but a review by Ezra\(^\text{19}\) concluded that 30% to 50% of Stage 1 holes regress, whereas this figure falls to only 10% for Stages 2 and 3 holes. Furthermore, it is known that the longer the duration of the macular hole, the lower the chance of surgical closure,
such that prolonged observation may be inappropriate. For example, Jaycock et al\textsuperscript{25} found that holes present for \textless{}1 year had a 94\% closure rate versus 47\% for those of longer duration.

Epiretinal membranes tend not to resolve spontaneously, although this has been reported in the context of a PVD.\textsuperscript{21} This may be more likely to occur in young patients, perhaps because of firmer adhesion between the vitreous face and ERM, such that a PVD is able to pull the ERM from the retinal surface.\textsuperscript{22,23}

The natural history of VMT in the context of AMD, DME, and retinal vein occlusion is poorly understood.

**Surgery**

Pars plana vitrectomy (PPV) is the standard surgical approach for the treatment of sVMA occurring in the context of VMT, macular hole, and ERM. Many surgeons use an intravitreal injection of triamcinolone acetonide to visualize the vitreous, facilitating its complete separation from the ILM.\textsuperscript{25–27} Removal, or not, of the ILM depends on the underlying condition and surgical preference, but it is commonplace in the context of macular hole surgery, and to a lesser degree, ERM.\textsuperscript{28} Vital stains are often used to help identify the thin optically clear ILM.\textsuperscript{29,30}

The use of PPV to treat DME is more controversial. A meta-analysis of controlled studies investigating the effect of PPV on DME found that visual acuity improved by logarithm of the minimal angle of resolution 0.8 in 101 eyes after PPV compared with 0.04 in 83 controls (Jackson TL et al, unpublished data, 2013). Much of the literature was reported before the introduction of intravitreal drugs directed against vascular endothelial growth factor, and it is not certain how PPV would compare with anti–vascular endothelial growth factor therapy, and although they are not mutually exclusive, any benefit in terms of release of VMT has to be balanced by the potentially reduced half-life of intravitreal injections.\textsuperscript{31}

The role of PPV for the treatment of AMD is even more uncertain. A retrospective study of vitrectomy for breakthrough hemorrhage from wet AMD found that eyes with attached vitreous gained most, in terms of reduced disease activity, suggesting that VMA had an adverse effect of AMD.\textsuperscript{32} Another small case–control study of eyes with early AMD and macular hole or ERM found that eyes were less likely to develop choroidal neovascularization or geographic atrophy after vitrectomy compared with fellow eyes.\textsuperscript{33} Although these studies indirectly suggest PPV may be of benefit for eyes with AMD, neither were designed to quantify its therapeutic effect, and the question of its role is of interest, but remains unanswered.

**Pneumatic Release of Vitreomacular Traction**

Small studies have reported the use of an intravitreal gas bubble to treat macular holes based on the assumption that gas induces a mechanical PVD. Chan et al\textsuperscript{34} reported that 10 of 11 impending macular holes responded to treatment. Although there were only small numbers, the closure rate fell to 50\% in Stage 2 holes and neither of the 2 Stage 3 holes closed. Mori et al\textsuperscript{35} also reported a 50\% closure rate in 10 Stage 2 macular holes, with Jorge et al\textsuperscript{36} reporting the highest success rate (5 of 6 Stage 2 macular holes). Mori et al\textsuperscript{35} observed that 95\% of the cases developed a PVD, which indirectly supports the hypothesis that intravitreal gas works by release of VMT.

Intravitreal gas has also been used to induce a PVD in eyes with both diabetic retinopathy and diabetic maculopathy.\textsuperscript{37,38} Rodrigues et al\textsuperscript{39} recently reported a case series using intravitreal gas to treat VMT syndrome, and VMT occurring alongside DME, AMD, and impending macular hole. Of 7 cases of VMT syndrome, 2 resolved within 1 month of injection, a further 3 resolved within 6 months, and 2 failed to respond. All of the cases in the series were otherwise expected to undergo vitrectomy, and overall, only 33\% ultimately underwent surgery. There were no significant adverse events attributed to gas injection.

Although the studies of intravitreal gas injection are small and uncontrolled, they justify further investigation, particularly given that intravitreal gas is inexpensive, readily available, easy to adopt, and with well-established safety.

**Pharmacological Vitreolysis**

Pharmacological vitreolysis has been advocated as an alternative treatment option for VMT. Vitreolytic agents break down the peptide bonds in laminin and fibrinectin, molecules that maintain adhesion between the posterior vitreous face and ILM.\textsuperscript{40,41} Various vitreolytic agents have been investigated in animal models or early clinical trials, including collagenase, chondroitinase, hyaluronidase, dispace, nattokinase, plasmin, arginine–glycine–aspartate (RGD) peptides, plasminogen activators, and urea-based molecules.\textsuperscript{42} Autologous plasmin has been used in the past as an adjunct to vitrectomy to help induce a PVD at the time of surgery.\textsuperscript{43–45} Plasmin is a very unstable enzyme because of its autolytic properties and therefore has to be manufactured from the patient’s own blood immediately before its intravitreal injection. Ocirisplasmin, a recombinant DNA molecule, possesses the same catalytic properties of plasmin but is a far more stable product, and it has therefore emerged as the current vitreolytic agent of choice.
The MIVI-IIT trial was a randomized, double-masked, sham-controlled, dose ranging phase II trial evaluating single or repeated injections of ocriplasmin, given to release VMT. Complete PVD was seen 28 days after injection in 27% of the eyes, using the highest dose. Repeated injections increased the likelihood of a PVD occurring, up to 58%. Further studies of microplasmin are underway or have completed, including studies of DME (MIVI-II), prior to vitrectomy (TG-MV-006; TG-MV-007), and in wet AMD with VMA (MIVI-5).

The Microplasmin for IntraVitreous Injection—Traction Release without Surgical Treatment (MIVI-TRUST) group provided combined analysis of two large, randomized, double-blind controlled clinical trials. Patients with sVMA were eligible, including those with macular hole and VMT, with visual acuity in the range of 20/25 to 20/800. The presence of an ERM was not an exclusion. The treatment group received a single intravitreal injection of 125 μg ocriplasmin, and the control group received an intravitreal injection of drug vehicle/saline. The primary end point was resolution of VMA at Day 28. Other end points included total PVD, nonsurgical closure of a macular hole at 28 days, avoidance of vitrectomy, and change in visual acuity. The primary end point was met: of 464 eyes treated with ocriplasmin, 26.5% had release of VMA at Day 28 compared with 10.1% of 188 control eyes. This difference was statistically significant. There was also a greater chance of macular hole closure, PVD, and three-line visual acuity gain comparing the study eyes with the controls.

Ocriplasmin had a favorable safety profile, with many adverse events likely to be because of release of VMA, including vitreous floaters and photopsia. There were more cases of blurred vision in the ocriplasmin group, but these were often transient, possibly suggesting that they may be because of aggravated VMT that occurs before release of VMA. A decrease of ≥3 line of visual acuity was experienced by 5.6% of the patients in the ocriplasmin group and 3.2% of those in the placebo group. This was not thought to be due to any manifest toxicity, but rather, the U.S. Food and Drug Administration concluded that a majority of these were because of progression of the underlying traction (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125422s000lbl.pdf, accessed 10 January, 2013).

A strength of the MIVI-TRUST study was its double-masked, randomized controlled design. The use of a placebo control, rather than sham injection, was both a strength and weakness. It proves that the difference between arms was drug related, but the control arm had VMA release in a greater than expected proportion of eyes compared with natural history studies. This will tend to erode the perceived benefit of ocriplasmin and also means it is difficult to extrapolate the control group to observation, the most relevant clinical comparison. This trial does not help determine if repeated ocriplasmin injections would add to the proportion of eyes with VMA release. The study was reasonably sized in terms of safety, but rare events such as endophthalmitis, expected in <1% of the cases, may not have been reliably detected. The magnitude of clinical effect was modest overall but varied substantially depending on baseline characteristics. For example, VMA associated with a large area of adhesion and ERM tended not to do as well as eyes with macular holes or a small area of VMA. Consequently, the OASIS study (ClinicalTrials.gov Identifier: NCT01429441, accessed 9 January, 2013) was initiated to see if more targeted case selection leads to higher success rates.

**Burden of Illness**

Given that VMA contributes, or may contribute, to the pathogenesis and clinical course of several macular diseases, an analysis of the burden of illness is intrinsically complex. Also, the quality and quantity of epidemiologic data available on VMT syndrome, macular hole, ERM, wet AMD, DME, and retinal vein occlusion varies widely. This is compounded by the fact that the relationship between VMA and some of these diseases is uncertain. At one end of the spectrum, VMT syndrome, abnormal VMA is clearly responsible for the disease, and all cases of VMT can be counted as sVMA; at the other, with DME, it is first uncertain what proportion of eyes with DME have VMA, and second, what influence VMA has on visual function.

A meta-analysis showed that eyes with wet AMD were 2.15 more likely to have VMA than controls. The same authors found that VMT was present in 28.7% of the eyes with DME in patients undergoing PPV, but it is not certain what this proportion would be in a nonsurgical setting.

Simpson and Jackson attempted to estimate the total number of affected cases using the data that were available. Their findings are summarized in Figure 6 and Table 1. This shows that ~1.5% of the population have eye disease that is caused by, or associated with, VMA. As shown by Table 1, ERM is responsible for a large proportion of these cases. As many of these cases were detected using fundus photographs, it is not known if they were associated with visual loss. As such they cannot easily be confirmed as sVMA, unlike the other conditions in the table, which are largely symptomatic. Furthermore, even if the
cases of ERM were symptomatic, relief of VMA may not resolve the patient’s symptoms given the structural changes imposed by ERMs. In terms of clinical utility, it may therefore be more meaningful to exclude ERM. If so, then the prevalence reduces to 0.35%. This remains a substantial burden of disease worldwide.

Future Research and Trends

There are several unanswered questions in relation to sVMA. One of the most interesting relates to the role of pharmacologic vitreolysis. Following the recent clinical trials in well-defined populations, it remains to be seen how ocriplasmin will be used in clinical practice, and it seems likely that it will be used to treat a range of diseases. It may also prove useful as a surgical adjunct to vitrectomy, to ease separation of the vitreous in situations where this may be difficult. Examples might include surgery in young patients and in those with proliferative diabetic retinopathy. It may also prove helpful for any eye with an attached vitreous if it reduces the risk of retinal breaks during vitrectomy. Other possibilities include use in vitreous hemorrhage if it is assumed that vitreous may entrap blood, and vitreolysis might then facilitate clearance. It is also not known if repeated injections enhance efficacy.

There are also many questions in relation to the burden of illness of sVMA. Despite attempts to estimate the number of affected individuals, data are incomplete. This is particularly so for the most common eye diseases, namely DME, retinal vein occlusion, and AMD. In the former two, the association is not yet proven, and in the latter, where the association seems likely, the effect of releasing sVMA has yet to be fully determined. Of particular interest is the unknown number of individuals with undiagnosed sVMA. Previously, when vitrectomy was the only treatment option, many cases with mild disease may have been left undiagnosed or not referred for review by a vitreoretinal specialist. Now that ocriplasmin is available, this may change, and increasingly patients may be diagnosed with sVMA. Consequently, the apparent incidence of sVMA may increase. This may be compounded by the introduction of OCTs into many optometric practices, as they greatly enhance the sensitivity of diagnosis, and by raised awareness, facilitated by industry.

Summary

The term sVMA is relatively new. It describes a wide range of macular diseases, all characterized by

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**Table 1. Prevalence and Annual Incidence of sVMA**

| Condition                  | Prevalence (per 100,000 Population) | Annual Incidence (per 100,000 Population)* | Proportion Associated With VMA (%) | Prevalence of Disease Occurring in Association With VMA (per 100,000 Population) | Annual Incidence of Disease Occurring in Association With VMA (per 100,000 Population) |
|----------------------------|-------------------------------------|------------------------------------------|-----------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Macular hole               | 149                                 | 8.8                                      | 72.8\(^{13}\)                     | 108                                                                             | 6.4                                                                             |
| ERM                       | 9,600                               | 3.2                                      | 12.7\(^{14}\)                     | 1,219                                                                          | 0.4                                                                             |
| VMT syndrome              | 22.5                                | 6.6                                      | 100 (by definition of disease)    | 22.5                                                                           | 0.56                                                                           |
| Wet AMD                   | 1,020                               | 143                                      | 16.7\(^{17}\)                     | 170.3                                                                          | 23.9                                                                           |
| DME                       | 320                                 | —                                        | 17\(^{17}\)                       | 54.4                                                                           | —                                                                               |
| Total                     | 11,111.5                            | 155.6                                    | —                                 | 1,574.2                                                                        | 31.3                                                                           |

The final row presents the combined incidence or prevalence of the conditions associated with symptomatic vitreomacular adhesion (sVMA), namely macular hole, epiretinal membrane (ERM), vitreomacular (VMT) syndrome, wet age-related macular degeneration (AMD) and diabetic macular edema (DME). Note that not all cases of ERM may have been symptomatic and that this disease contributes disproportionately to the final combined figure. The prevalence or incidence figures for each disease are then multiplied by the proportion thought to be associated with VMA, based on the literature, to give the figures shown in the final two columns.

*Adapted from Simpson and Jackson.\(^{49}\)
VMT or VMA combined with loss of visual function. In some diseases, the association with VMA is unproven, and in others, where it seems likely, the interaction with the disease state (and thereby the potential for treatment) remains to be fully determined. Despite these uncertainties, it seems likely that sVMA affects a large number of people. The treatment varies depending on the disease. For most patients with VMT syndrome, macular hole, and ERM, vitrectomy is the standard treatment. This may change with the recent availability of ocriplasmin. Ocriplasmin may allow for treatment of milder disease and avoid surgery for some patients who would otherwise require vitrectomy. It seems likely that there will be growing interest in sVMA as ocriplasmin moves from clinical trials to clinical practice, and as its role is explored and expanded.

Key words: age-related macular degeneration, diabetic macular edema, macular hole, posterior vitreous detachment, retinal vein occlusion, vitreomacular adhesion, vitreomacular traction.

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