Tractional Maculopathies in Age-related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD) is the leading cause of blindness among the elderly in developed countries. Much progress has been made in understanding the processes that lead to AMD, but much work needs to be done to improve visual outcomes for AMD patients. Much progress has been made in understanding the processes that lead to AMD, but much work needs to be done to improve visual outcomes for AMD patients.

Keywords

Age-related macular degeneration, tractional maculopathy, posterior vitreous detachment, macular hole, epiretinal membrane, Müller cells, and vitreoretinal adhesion

Vitreomacular Adhesions and Age-related Macular Degeneration

The current prevalence of tractional maculopathy is estimated to be 6.4% within the American population over the age of 50. Recent data have corroborated previous ultrasound findings that indicate abnormal PVD is more common than was previously thought and that associated posterior VMA seems to be more common among patients with AMD than in age-matched controls, placing prevalence at 22-36%. In particular, this seems to be the case more often in advanced exudative cases than in patients with non-exudative AMD. Frequently, vitreous attachment sites to the macula correspond to areas of choroidal neovascularisation (CNV), suggesting a direct relationship. Mojana and colleagues imaged VMA in AMD, showing 27.8% prevalence in exudative cases and 24.5% in non-exudative cases. In this study, traction was identified on OCT in 59 and 13% of patients in each group, respectively, suggesting a strong direct correlation between adhesion and traction. These abnormal vitreomacular interactions in AMD seem to be present in different populations in the world. In a cohort of Brazilian patients of 204 eyes with AMD imaged with time-domain OCT, 46.7% had VMA, 39.6% had ERM, 1% had macular holes and 12% had incomplete perifoveal PVD. When using spectral domain OCT imaging, the number of patients with VMA identified may increase up to 73%. Given that patients with AMD have a higher likelihood of partial PVD, it is often difficult to tell whether their visual symptoms and intra- or subretinal fluid are more likely to be related to the tractional component of VMA or to the anatomical distortion caused by the degenerative component of AMD, with the fortuitous discovery of a concurrent partial PVD (see...
Figures 1 and 2). Current knowledge does not indicate whether VMA in AMD is a cause or a result of AMD pathophysiology (see Figure 3). Several authors believe that although tractional maculopathy is not sufficient to induce AMD, it nonetheless has a key role in the natural history of AMD.\textsuperscript{24}

Patients with dry AMD and tractional maculopathy can go on to develop exudative AMD through the direct tractional effects on the retina and the RPE. This may lead to a chronic state of low-grade inflammation and ischaemia resulting from the obstruction of oxygen and nutrient diffusion, and an increase in pro-inflammatory and angiogenic growth factor load in the macular region, which can precede CNV (see Figure 4).\textsuperscript{13,15,16} In addition, a partial PVD leaves vitreous cortical remnants on the inner limiting membrane (ILM), which might later serve as a scaffold for cellular proliferation and traction.\textsuperscript{27} Therefore, understanding how these tractional forces arise and counter their evolution may be paramount in preventing the inexorable progression of AMD.

**Müller Cells and Reactive Gliosis**

A first step in developing a better understanding of VMA in AMD pathogenesis is to understand the changes at the cellular level that are different from those that occur in normal eyes. Although the end cascade event is always the loss of photoreceptors and RPE through different pathways of genetic, chemical or photic insults in accordance with other authors, the authors believe that Müller cells have a major role upstream in concurrent VMA and AMD.\textsuperscript{21,22}

Müller cells and astrocytes comprise the microglia of the retina. In the retina, Müller cells far outnumber glial astrocytes as the main support cells.\textsuperscript{19} In fact, only Müller cells are present in the normal foveolar centre. The Müller cells span all neurosensorial retinal layers, enabling them to provide an architectural scaffold that is essential for neuronal cell orientation, communication and information processing, to regulate ion concentrations, to limit the spread of cytotoxic neurotransmitters and to have a role in glycolysis and lactate metabolism.\textsuperscript{17,20}

Müller cells respond to damage to the retina in a graded manner depending on the extent and severity of the insult.\textsuperscript{23,24} This response is known as 'reactive gliosis'. Its primary function is one of neuroprotection through conservative gliosis, where chronic inflammation and the disruption of the RPE sets in, possibly activated through the recruitment of human leukocyte antigen (HLA) antigens, the complement cascade, microglia and circulating macrophages.\textsuperscript{18,25}

After initial moderate retinal stress, Müller cells are directly involved in the signal transduction of stress, doing so by releasing cytokines and vasoactive substrates such as vascular endothelial growth factor (VEGF), pigment epithelium-derived factor (PEDF), transforming growth factor (TGF)-β and activating extracellular signal-regulated kinases (ERKs), an early response to injury.\textsuperscript{18,26}

When the insult signal overwhelms the system, Müller cells undergo massive gliosis.\textsuperscript{19,27} They then contribute detrimentally to neuronal cell death through the excitotoxic pathway and dysregulated K+ conductance. In addition, they become reactive and re-enter the cell cycle to hypertrophy, forming gliotic scars such as the disciform scars seen in late exudative AMD (see Figure 5).\textsuperscript{28} Intermediate filament protein glial fibrillary acidic proteins (GFAP) within Müller cells, a universal hallmark of retinal injury, are also upregulated.\textsuperscript{29,30}

In pathological post mortem AMD specimens, GFAP expression was observed to be upregulated directly in regions overlying atrophic or drusenoid RPE changes. Similarly, VMA is also more commonly seen overlying areas of CNV. Both findings might indicate a direct localising relationship between retinal disease and Müller cell reactivity.\textsuperscript{30,31}
the Müller cells, with impairment of water transport across these glial cells contributing to macular oedema in addition to vascular leakage.\(^{27}\)

Thus, the presence of trans-differentiated reactive Müller cells at the vitreomacular and photoreceptor-RPE junction under the influence of vitreous growth factors might be a significant component explaining the frequent association of tractional maculopathy with AMD, as well as the underlying mechanistic forces destabilising the retina during tractional maculopathy surgery in AMD.\(^{46}\)

**Epiretinal Membrane and Age-related Macular Degeneration**

Most ERMs are associated with a high incidence of concurrent complete or partial PVD. ERM in AMD may develop as a result of VMT and inflammation causing ILM dehiscence and enabling migration of reactive Müller cells with myofibroblast transformation and astrocytes from the inner retina to the vitreal side of the ILM (see Figure 6).\(^{29,30}\)

Guidry and colleagues have clearly shown that Müller cells in normal retinas are not a component of the overlying ILM but have loose contact points. In a study of 44 peeled human ILM specimens analysed by phase-contrast microscopy and type IV immunofluorescent antibody staining, no Müller cell membrane or axonal components were found attached to the removed ILM.\(^{44}\) Another study of ILM-denuded pig retinas showed intact underlying Müller cell membranes.\(^{45}\) Both studies confirm that, in a normal eye, the ILM is separate from the underlying retina. In AMD, ultrastructural analyses of ERM with VMT showed that there is incorporation of Müller and glial elements into the ILM, with the presence of a fibrocellular multilayer interposed with vitreous collagen and directly on the ILM with predominant myofibroblasts.\(^{46}\) This corroborates the role that Müller and astrocyte glial cells have in reactive gliosis and traction, as previously stated (see Figure 7).

**Macular Holes and Age-related Macular Degeneration**

Macular holes in AMD arise from the same tractional pathologies that are active in ERM and AMD, and can be considered a progression and more severe clinical manifestation of the VMA forces at work in AMD (see Figure 8). In addition, tangential forces across the gap shown to be related to ERM and newly synthesised collagen fibrils within the cortical vitreous are also involved.\(^{47,48}\) Post-mortem specimens of macular holes often show the presence of subtle pre- and epi-retinal membranes in 30–75% of cases.\(^{49}\) This presence is no coincidence and the membranes are thought to evolve from gliotic reactions and to have an essential role in macular hole dynamics.\(^{50}\) Perpendicular focal anterior attachments have been shown on OCT, supporting the important role that vitreous traction has in the formation of macular holes.\(^{51}\) In addition, the alignment of the perifoveal Müller cells is also perpendicular, suggesting that the macular hole stages, as previously described by Gass, are initiated at the stage I level by inner retina layer Müller cell involvement.\(^{41}\) There is possibly an initial inherent inner retinal weakness and pseudocyst formation that is compounded by focal Müller glial cell proliferation in an unsuccessful attempt to repair and bridge the gap, creating secondary traction as cells migrate around the perifoveal denuded ILM.

**Management of Age-related Macular Degeneration and Vitreomacular Adhesion**

Given that anomalous and partial PVD might have an important role in AMD progression, prophylactic surgical and pharmacological methods...
of traction release can be considered as an additional part of the treatment for AMD to improve retinal distortion. However, limited data (case reports, small case series, short follow-up) are available on surgical outcomes of tractional maculopathies in patients with AMD. OCT has revolutionised the detection of previously unrecognised cases of VMT and is now an indispensable tool in all cases of combined diagnoses.4

Pars Plana Vitrectomy

Pars plana vitrectomy (PPV) continues to be the mainstay treatment in releasing the traction on the retina induced by vitreomacular adhesions.14

Some researchers have postulated that PPV, as a form of artificial PVD alone, might be sufficient to simulate its beneficial effects in AMD. Alternately, vitrectomy might be beneficial through the release of tractional damages that ultimately lead to RPE atrophy, the reduction of inflammatory mediators from the milieu and the provision of a higher oxygen diffusion environment in areas that have localised ischaemia. In addition, ILM peeling to remove the scaffold for glial and myofibroblast cell migration into the vitreoretinal interface has also been advocated, as many authors have found this to correlate with higher anatomical and functional success in macular hole and ERM surgery, and lower recurrence rates.5,16,21 To facilitate visualisation during surgery, the use of intravitreal vital dyes, such as Trypan blue, triamcinolone acetonide, indocyanine green and more recently brilliant blue, is encouraged for staining the ERM and ILM. However, the risks of using these dyes in the presence of concomitant tractional maculopathies and AMD are unknown and therefore should be used with caution. In addition, endotamponade with an intracocular gas is recommended to ensure long-term surgical success after vitrectomy and membrane peeling for macular holes.4

Roller and colleagues recently conducted the first retrospective pilot study of paired eyes in non-exudative AMD patients who underwent vitrectomy in one eye for MH and ERM while the clinically similar AMD disease was observed in the fellow eye. Although the sample size was small (n=22), their results demonstrated that vitrectomised eyes did better than fellow eyes and that AMD did not progress.15

The authors conducted a prospective interventional small-gauge surgical series between 2005 and 2009 on the management of tractional maculopathy in AMD. In all, 12 patients with dry and exudative AMD were enrolled and followed up for at least 12 months post surgery. Ten patients underwent 25-ga vitrectomy and two patients underwent 27-ga vitrectomy. Two of two eyes with macular holes closed despite CNV reactivation (see Figure 8), four VMTs were operated on without any complications; of the six ERMs, three had no complications, two developed intraoperative RPE tears and one developed a new small subfoveal CNV one month post-operatively (see Figure 9). Overall, our results showed that after post-operative or new CNV, visual acuity improved in all eyes following small-gauge vitreoretinal surgery for tractional maculopathies in AMD. This was also the first time that intraoperative iatrogenic RPE tears were demonstrated to develop during surgery for ERM in AMD.4,5

Anti-Vascular Endothelial Growth Factor

Diseases that might be amenable to anti-VEGF treatment should also receive intravitreal injections first, as a concurrent vitrectomy might decrease the vitreous half-lives of such agents. Both ranibizumab and bevacizumab have been used as first line treatments in combined cases of AMD and VMT, although extended treatment is warranted to control exudative recurrences (see Figure 8).5 Interestingly, traction often worsens clinically and on imaging following intravitreal injections (IVI) and even macular holes have been described after anti-VEGF injection for exudative AMD.4 If eyes remain refractory to treatment despite IVI treatments, Mojana and colleagues recommended a surgical release of the traction. They performed surgery in five patients

Figure 6: Epiretinal Membrane in Exudative and Dry Age-related Macular Degeneration

A: Exudative age-related macular degeneration (AMD) shown using time-domain optical coherence tomography (OCT). B: Dry AMD shown using spectral-domain OCT.

Figure 7: Illustration of Reactive Gliosis in Age-related Macular Degeneration

A: The normal retinal microarchitecture highlighting only the retinal pigment epithelium (RPE) (brown), Müller cells (yellow), astrocytes (silver), retinal blood vessels (red) and inner limiting membrane (ILM) (transparent grey). B: Dry AMD with a close-up of drusen accumulation under the RPE and the proximity of Müller cells (yellow) over the RPE. C: Drusen inflammatory and oxidative stress (red staining of RPE and Müller cells) stimulus. D: Consequent reactive gliosis with Müller cells (orange) and astrocytes migration towards the ILM vitreal side. E: Epiretinal membrane formation in dry AMD.

Figure 8: Time-domain Optical Coherence Tomography showing the Presence of a Macular Hole and Choroidal Neovascularisation in Age-related Macular Degeneration

A: Macular hole and choroidal neovascularisation (CNV) in age-related macular degeneration (AMD). B: After vitrectomy and inner limiting membrane (ILM) peeling, the macular hole closed. C: However, despite the effects of higher oxygen availability to the retina post-vitrectomy the CNV reactivated and more frequent anti-vascular endothelial growth factor (VEGF) injections were needed compared to before the vitrectomy.
Figure 9: Subfoveal Classic Choroidal Neovascularisation Post-epiretinal Membrane Peeling in Dry Age-related Macular Degeneration

A, B: Classic choroidal neovascularisation (CNV); C: post-epiretinal membrane (ERM) (time domain optical coherence tomography [OCT] image) peeling in dry age-related macular degeneration (AMD).

Figure 10: Iatrogenic intra-operative Retinal Pigment Epithelium Tears during 25-gauge Epiretinal Membrane Peeling

The tears are indicated by arrows.

with persistent VMT, which they proposed is a mechanism that results in patients presenting with pharmacologic-resistant disease, possibly through tissue forces antagonising and limiting drug access to areas of macular disease. Others suggest that if vision improves with IVI alone, no further surgical steps need be taken to address VMT if the benefits of the latter do not outweigh the risks or if chronic atrophic changes have already set in. In all instances, spontaneous resolution of VMT from IVI treatment or a PVD is rare.

Vitreolysis

A future adjuvant therapy for tractional maculopathies in the presence of a partial PVD is the use of proteolytic human enzymes against the vitreoretinal protein matrix. An ideal pharmacological agent is one that induces complete liquefaction and dehisence of the vitreous simultaneously. Plasmin, a serine protease that can hydrolyze laminin and fibronectin glycoproteins at the vitreoretinal interface, has been suggested. More recently, ocriplasmin, a recombinant product containing only the catalytic domain of human plasmin has garnered interest, as it is molecularly more stable and easier to store and administer than its predecessor. This vitreolytic molecule has shown promise through the MIV-I (Microplasmin intravitreal administration in patients with vitreomacular traction scheduled for vitrectomy) and MIV-IIT (intravitreal injection of microplasmin for treatment of vitreomacular adhesion: results of a prospective randomised sham-controlled Phase II) trials and should soon be available; however, further research is needed as failure of complete chemical vitreolysis can result in anomalous vitreous dynamics and vitreoschisis, putting the eye at an increased risk for complications.

Exudative Age-related Macular Degeneration Progression following Tractional Maculopathy

In a few case reports, authors have established a clear sequence that CNV might develop post-ERM or macular hole repair. Two types of cause are proposed. In non-surgical cases, the CNV develops owing to the natural history of tractional disease, with subretinal fluid inducing inflammatory cytokines and mediators leading to Bruch’s membrane disruption. In surgical cases, despite the theoretical benefits of a vitrectomy inducing resolution of tractional traction and increase in oxygen tension, it appears that post-operative trauma and the surgical sequelae on the RPE may overpower the beneficial effects of surgery to incite neovascularisation.

This was the case in the authors small gauge vitrectomy series as described above, where the sole patient whose visual acuity did not improve was due to the result of development of de novo CNV post 25-ga vitrectomy for ERM removal (see Figure 9).

Management techniques advocate the sequential treatment of the CNV first followed by surgical hole repair (see Figure 8). The postulated reasoning is that pharmacological resolution of CNV might cause macular hole edges to regress. With these techniques and improved surgical instrumentation, improved visual outcomes can be expected. Photodynamic therapy in conjunction with vitrectomy has also been reported as a successful treatment, despite the evolution of anti-angiogenesis treatments.

Post-operative Complications

The surgical complications are the same as for general vitrectomy, and include intraoperative retinal breaks (5 %), intraoperative bleeding after tractional membrane removal and progressive nuclear sclerosis (12-68 %), retinal detachment (5 %), macular oedema, retinal pigment epithelopathy and recurrence of ERM (10 %). Submacular surgery in exudative AMD with forceful injection of subretinal tissue plasminogen activator (t-PA) has also been reported to induce occasionally an iatrogenic macular hole. However, with combined anti-VEGF and vitrectomy treatment for exudative AMD and tractional maculopathies, even if visual acuity improves and traction rarely recurs if surgery is successful, chronic irreversible RPE changes could have already set in. Most patients workers AMD require repeated and more frequent anti-VEGF injections despite release of tractional pathologies through vitrectomy.

Retinal Pigment Epithelium Detachment and Tears

RPE tears and detachments in AMD have been described post-anti-VEGF IVI. Proposed mechanisms include the possibility of rupture of a previously present RPE detachment (PED), an iatrogenic tear from blunt needle insertion, vitreous incarceration causing VMT and vascular
membrane contraction, or the modulatory changes following the properties of the anti-angiogenic drug itself. All of these remain to be proven.\textsuperscript{11,12} Spontaneous RPE tears in patients with AMD have been previously reported in the literature, indicating the inherent fragility of this degenerated retinal tissue. Meyer and Toth suggested that chronic weak traction at the vitreoretinal interface induces excess shear and tangential forces applied and transmitted to the RPE, leading to mechanisms that make the RPE more susceptible to RPE detachment and tears, and even secondary macular holes.\textsuperscript{1,13}

In addition, Chan and colleagues linked PED and RPE tears in a study, where 2,785 injections in 1,064 patients demonstrated an incidence of 2.22 % RPE tears among all AMD eyes and 17.5 % among eyes with previous PED.\textsuperscript{14} However, RPE tears after ERM removal in patients with AMD, as seen in two of our own surgical AMD cohort, have previously been unreported (see Figure 10).

Previous authors have observed that spontaneous RPE tear can occur in patients with AMD secondary to the underlying PED.\textsuperscript{15} The authors suggest that in the absence of obvious predisposing factors, Müller cells and reactive glia are an important aetiological component by coupling inner and outer retinal movements and mechanotransduction forces (see Figure 11).

In AMD, Müller cells can directly form ERMs. Surgical removal or VMT on the ERM might directly transmit these forces along all retinal layers to create tears on the underlying photoreceptor-RPE junction. Given the similar composition of the vitreoretinal and the photoreceptor-RPE interface, one can assume that abnormalities in one can directly affect the other.\textsuperscript{16} By using atomic force microscopy to measure Müller cell elasticity in different underlying substrates in vitro, the authors demonstrated that Müller cells increase their mechanical stiffness 10-fold when grown on a stiff substrate, such as the ageing Bruch’s membrane in AMD (data not shown). It is hypothesised that these biophysical phenomena can account for the creation of an RPE tear in that a mechanically stiffer Müller cell can support the transmission of force from the internal limiting membrane to the outer retina and RPE (see Figure 11). The intercalation of Müller cells into adjacent photoreceptor structures predisposes them to the transmission of tractive forces so that when surgical instruments pull on the glial epithelial and VMA elements, the same force can be transmitted to the outer retina, directly damaging the already weakened and atrophic RPE. Therefore, extreme care must be exercised when performing ERM and ILM peeling in patients with AMD, and RPE tears should be recognised as a possible direct iatrogenic complication of these procedures in patients with dry or exudative AMD (see Figure 10).

\section*{Conclusion}

Superior imaging techniques and advanced biochemical analysis have provided clinicians and researchers with new understandings of the biomechanics of the vitreoretinal interface. There is now no longer a strict separation of the different aetiologies of disease. It is now possible to regard AMD and VMT pathologies as concurrent diseases that affect each other. At an early phase, partial anomalous PVD are often found in the presence of non-exudative AMD. With time and chronic traction, this can cause the AMD to degenerate into an exudative form, which in turn can trigger reactive glia, which will make the tractional disease worse. In addition, other environmental, genetic and inflammatory factors are likely to have a large role in AMD pathogenesis.\textsuperscript{17} These data should be considered once ocularlipase is used for.

With so many factors in play, possible future directions in the targeting of AMD and retinal maculopathies are limitless. Vitreous gel biomechanics and Müller cell glial reaction are excellent future targets for research.\textsuperscript{18} Controlling the potassium channels of Müller cells might also have a part in decreasing macular oedema (as corticosteroids can stimulate fluid clearance by Müller cells).\textsuperscript{19}

It would be interesting to know whether future imaging techniques will allow one to detect early and late AMD vitreomacular changes so as to detect early damage and follow cellular responses to treatment or even modulate and curb progression through the potential control of reactive glia. Already, findings relating to the role of melatonin in reactive glia modulation and opticin as a possible vitreomacular interface binding protein have garnered interest.\textsuperscript{20,21} This gives researchers hope for catching AMD pathologies early on instead of treating their downstream consequences.

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure11.png}
\caption{Illustration of Epiretinal Membrane Peeling and Secondary iatrogenic Retinal Pigment Epithelium Tear in Age-related Macular Degeneration}
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\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure12.png}
\caption{Trabecular Maculopathies in Age-related Macular Degeneration}
\end{figure}


