Perifoveal Vitreous Detachment Is the Primary Pathogenic Event in Idiopathic Macular Hole Formation

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Objective: To evaluate the relationship between the posterior vitreous cortex and the posterior retina in eyes with early stages of idiopathic macular hole formation.

Methods: Twenty-six eyes of 26 consecutive patients with stage 1 or stage 2 idiopathic macular hole underwent complete ophthalmologic examination, contact lens biomicroscopy, and B-scan ultrasonography or vitreoretinal surgery or both. In eyes that were operated on, the posterior cortical vitreous layer was meticulously examined with a silicone-tipped cannula prior to inducing a posterior vitreous detachment.

Results: In 25 (96%) of 26 eyes, one or more examination techniques revealed a shallow, localized detachment of the perifoveal vitreous, typically extending to the level of the vascular arcades. Among these 25 eyes, the posterior hyaloid membrane separation was detectable biomicroscopically in 4 (16%) of 25 eyes, ultrasonographically in 17 (74%) of 23 eyes, and intraoperatively in 23 (100%) of 23 eyes. Persistent vitreous adherence to the foveola was evident in 6 (100%) of 6 eyes with a stage 1 hole and in 12 (92%) of 13 eyes with a stage 2 hole but no operculum.

Conclusions: These findings suggest that localized perifoveal vitreous detachment (an early stage of age-related posterior vitreous detachment) is the primary pathogenic event in idiopathic macular hole formation. We postulate that detachment of the posterior hyaloid from the pericentral retina leads to foveal dehiscence by exerting anterior traction on the foveola and by localizing into the foveola the dynamic vitreous traction associated with ocular rotations.

PATIENTS AND METHODS

Twenty-six eyes of 26 consecutive patients with evolving (stage 1 or stage 2) macular hole underwent complete ophthalmological examination, including meticulous slit-lamp biomicroscopy of the posterior pole of the study eye with a fundus contact lens. Macular holes were staged biologically according to the updated classification proposed by Gass. An operculum was defined as a discrete tissue opacity suspended on the detached, typically invisible, posterior hyaloid membrane immediately anterior to the macular hole. Each patient underwent further evaluation of the vitreomacular interface with either B-scan ultrasonography alone (2 patients), vitreoretinal surgery alone (2 patients), or both ultrasonography and surgery (22 patients) (Table). Informed consent was obtained from each patient undergoing surgery. Most patients were accrued prospectively between July 1996 and January 1998. The patients visiting one of the authors (M.R.V.N.) had been evaluated earlier and were added to the series retrospectively (patients 1-3 and 24). Apart from 2 eyes with a stage 1 macular hole and poor visual acuity (patients 2 and 4), all eyes undergoing vitreoretinal surgery had progressed to a stage 2 macular hole prior to surgery.

B-scan ultrasound examinations were performed under topical anesthesia with the eyelids open and the probe placed directly on the ocular surface using methylcellulose as a coupling gel. Ultrasound studies were performed with the 1S-System-ABD unit (Innovative Imaging Inc, Sacramento, Calif) at medium- and high-gain settings. Early in our series, the studies consisted of longitudinal and transverse sections through the macula, obtained by positioning the probe on the nasal conjunctiva to avoid beam attenuation by the crystalline lens. After we discovered that absolute perpendicularity to the macula was necessary in most eyes for detecting shallow detachments of the posterior hyaloid membrane, horizontal and vertical axial views (through the cornea and lens) were routinely included in the ultrasound examination. Kinetic B-scan assessments were used as needed to help define the vitreomacular relationship. Localized vitreous detachment was diagnosed when a thin, smooth, continuous echodense membrane with minimal aftermovement was detected anterior to the retinal surface (Figure 1).

In eyes undergoing vitreoretinal surgery, meticulous examination of the posterior vitreous cortex was performed before surgically peeling the cortical vitreous from the posterior retina. First, the macular region was observed closely during the core vitrectomy for evidence of vitreoretinal adhesions. These were often apparent as small-amplitude movements of the inner retina owing to transient vitreous traction associated with the action of the vitreous cutter. Following the core vitrectomy, the posterior vitreous cortex was carefully engaged with a silicone cannula in several parafoveal locations. By gently, minimally, and repeatedly elevating the invisible and elastic cortical vitreous layer, areas of vitreoretinal adherence in the posterior pole could be observed prior to their surgical separation. When present, an operculum or pseudo-operculum attached to the posterior hyaloid membrane helped to define the position of the membrane during its gentle manipulation. Subsequently, the vitreous cortex was separated from the peripapillary retina and (if necessary) from the edges of the macular hole using aspiration through the silicone cannula or vitreous cutter. Observations were made as to the continuity of the posterior hyaloid membrane across the macular region, the relationship of opercula to the posterior hyaloid, and the existence of apparent vitreoretinal adhesions outside the posterior retina. Although the surgeon did not review the results of the ultrasound examination immediately prior to surgery, no masking protocol was followed with respect to ultrasound data.

RESULTS

The 26 patients comprising the study cohort ranged in age from 49 to 77 years (median, 68 years) and consisted of 17 women (65%) and 9 men. All 3 patients in our study who were younger than 60 years had myopia of 6 diopters or greater. Symptoms arising from the developing macular hole were of 2.1 months in mean duration (range, 1 week to 4 months). Snellen visual acuity (typically measured with glasses and pinhole) and macular hole stage at the time of initial visit are listed in the Table. The initial visual acuity ranged from 20/30 to 20/300, with a median acuity of 20/60. Five patients (19%) had a macular hole in the fellow eye at initial visit. Four patients (15%) without a macular hole in the fellow eye had a mobile prepapillary glial ring, indicating a presumed total posterior vitreous detachment (PVD).

In 25 (96%) of the 26 eyes in this study, one or more examination techniques revealed a localized, shallow detachment of the cortical vitreous from the perifoveal retina (Table). Among these 25 eyes, the vitreous separation was detectable with meticulous contact lens biomicroscopy in only 4 eyes (16%) and was completely invisible in the remainder. In 3 of these 4 eyes, the detached posterior hyaloid membrane was visible as a thin, transparent glistening interface, anterior to the retinal surface. The shallow vitreous separation could be traced out to approximately the level of the optic disc and temporal vascular arcades, and it remained adherent at the foveola. The posterior hyaloid membrane was slightly taut, showing minimal movement with ocular microsaccades, and had a flat trampoline-like configuration except where it was tethered posteriorly at the macular hole margins (Figure 2). In the remaining eye, visibility of the separated posterior hyaloid membrane was limited to a trace glistening interface immediately surrounding and in the plane of an operculum positioned 200 µm to 300 µm anterior to the central macular surface.
Opercula were identified biomicroscopically in none of the 6 eyes with stage 1 holes and in 7 (35%) of 20 eyes with stage 2 holes. The operculum was suspended a variable distance anterior to the macular surface, ranging from 150 µm to 600 µm on clinical estimation. Among the 13 stage 2 holes without an operculum, there was biomicroscopic evidence for subtle anterior traction on the edges of the hole in 6 eyes (46%), causing elevation of one or more small tissue flaps slightly anterior to the plane of the surrounding retina.

Of the 25 eyes with evidence of perifoveal vitreous detachment, B-scan ultrasonography was performed on 23. Shallow, localized perifoveal vitreous detachment was detectable echographically in 17 (74%) of 23 eyes (Table). Of the 13 eyes in which axial scans were included in the echographic evaluation, perifoveal vitreous detachment was detected in all of them (100%) and was visible only on the axial view in approximately two thirds. The detachment of the posterior hyaloid membrane typically extended nasally to the temporal optic disc margin and vertically to approximately the level of the vascular arcades (Figure 3). The temporal extent of vitreous detachment was variable, reaching the equatorial area in at least 4 patients (Figure 4). The extent of the vitreous separation was difficult to assess in some cases because the need for near-absolute perpendicularity of the sound beam to the detached posterior hyaloid membrane often precluded visualizing the entire membrane. In all cases, the separation was shallow, and the elevated posterior hyaloid membrane was somewhat taut and elastic.

In all 7 eyes in which an operculum was identified on biomicroscopic examination, the operculum was vis-
Visible ultrasonographically as a small echodense opacity suspended anterior to the foveolar area. In 5 of these 7 eyes, detachment of the posterior hyaloid membrane from the foveolar and perifoveal retina was echographically visible, and the operculum was attached to the membrane in each case (Figure 5). In the remaining 2 eyes, localized posterior hyaloid detachment was suspected based on the position of the operculum 200 µm to 300 µm anterior to the macular surface. However, detachment was not visible echographically, possibly because axial scans were not performed in either case (Figure 6). Each of the 12 eyes (stage 1 and stage 2 holes) with no operculum in which perifoveal vitreous detachment was visible by ultrasound was found to have persistent vitreofoveal adherence (Figure 7 and Figure 8).

Of the 25 eyes with evidence of perifoveal vitreous detachment, vitreous surgery was performed in 23. By intraoperative assessment, evidence for separation of the perifoveal vitreous cortex from the retina was present in all 23 eyes (100%). Although invisible, the elastic cortical vitreous layer could be gently elevated from the macular region with a flexible silicone cannula, and areas of residual vitreoretinal adherence could be determined by observing tractional effects on the retina. Opercula,
when present, were helpful in determining the position of the posterior hyaloid membrane during its manipulation. In all 23 eyes, adherence of the vitreous cortex to the immediate peripapillary retina could be demonstrated. In the 7 eyes with a biomicroscopically identified operculum, the posterior hyaloid could be elevated from the macular region (within the vascular arcades) with no detectable areas of persistent vitreoretinal adherence. In 14 of the 16 eyes with no preoperative operculum, gentle elevation of the posterior vitreous cortex demonstrated persistent vitreofoveolar attachment without other areas of detectable vitreoretinal adherence within the vascular arcades. In the remaining 2 eyes (patients 12 and 14), spontaneous vitreofoveal separation occurred between the initial evaluation and surgery, and no vitreomacular adherence was found intraoperatively (Table).

Once separated from the optic disc and (when necessary) foveola, the posterior hyaloid membrane could be readily elevated into the midvitreous cavity and visualized with oblique illumination as a grayish, faintly translucent interface that was continuous with the Weiss ring. The operculum, when present, was attached to the posterior hyaloid membrane in each case. In 18 eyes, the posterior hyaloid membrane appeared continuous across the macular region. However, in 1 eye, a discrete dehiscence was noted in the posterior hyaloid membrane near the operculum, and in 4 eyes, continuity could not adequately be assessed owing to poor visualization or surgical disruption of the hyaloid face. Apart from the fovea and immediate peripapillary retina, the only observed sites of focal vitreoretinal adherence were at the supertemporal arcade (2 eyes), in the superonasal midperiphery (1 eye), and in the inferior equatorial region (1 eye). In all other eyes, vitreoretinal separation out to the vitreous base region was apparent soon after induction of the glial ring and without further active vitreous peeling from the retina.

In 1 patient (patient 23), we found no convincing evidence for perifoveal vitreous detachment by any examination technique. However, axial views were not obtained on echographic evaluation of this patient. The intraoperative findings were equivocal in that no areas of persistent vitreoretinal attachment could be demonstrated in the macular area, but neither an operculum nor foveolar adherence were present to facilitate assessment of the position of the posterior hyaloid membrane.

**COMMENT**

These data demonstrate that localized perifoveal vitreous detachment is routinely present in the early stages of idiopathic macular hole formation. By one or more of the examination techniques employed in our study, separation of the posterior hyaloid membrane from the pericentral retina was detectable in 25 (96%) of the 26 eyes with stage 1 or stage 2 macular hole comprising this series. We suspect that the remaining eye had a broad vitreomacular separation without operculum that we failed to detect by ultrasound because axial views were not included in the assessment. Given sufficiently sensitive methods of detecting shallow separation of the poste-
rior hyaloid, we believe that perifoveal vitreous detachment is likely a universal finding in the earliest stages of idiopathic macular hole development.

It is common experience that shallow detachments of the thin, mildly echogenic posterior hyaloid membrane are difficult to render with B-scan echography. We found that despite a high-resolution ophthalmic ultrasound instrument and placement of the B-scan probe directly on the globe, the posterior hyaloid membrane was often undetectable in nonaxial echographic sections. Conversely, axial sections detected localized posterior hyaloid separations with 100% sensitivity in our series, probably because they allowed absolute perpendicularity of the sound beam to the macular region. Other investigators using similar ultrasound instrumentation and scanning techniques have demonstrated localized separations of the posterior vitreous face in 1 eye with a macular microhole, in 22 of 22 eyes with macular pseudo-opercula, and in 16 of 17 eyes with stage 2 or stage 3 macular holes. In contrast, ultrasound studies that do not use axial views (to avoid attenuation of sound waves by the crystalline lens) infrequently detect localized posterior hyaloid membrane separations in the macular region.

Optical coherence tomography is a new technique for high-resolution cross-sectional imaging of the retina and posterior vitreous. Although OCT scans were not performed on our patients, Hee et al and Gaudric et al have reported OCT imaging of localized perifoveal vitreous detachment in eyes with stage 1 and stage 2 macular holes, as well as in a significant portion of fellow eyes that were biomicroscopically normal. Other investigators have subsequently confirmed the ability of OCT to detect perifoveal vitreous detachment in the majority of eyes with early stage macular holes. However, it is probable that even OCT is unable to image the detached posterior hyaloid membrane with 100% sensitivity given several examples of eyes with known vitreous separations that were invisible on OCT images.

Based on our findings and those of the OCT studies cited in the previous paragraph, we believe that perifoveal vitreous detachment, as the initial stage of age-related PVD, is the primary pathogenic event in idiopathic macular hole development. The perifoveal separation of the posterior vitreous cortex demonstrated in these patients could be expected to exert traction on the foveola in at least 2 important ways. First, the elastic properties...
of a trampoline-like posterior hyaloid detachment with focal adherence at the fovea should exert anterior traction on the foveola toward the plane of the detachment (Figure 2). Because the plane of the posterior hyaloid detachment is slightly anterior to the plane of the inner retinal surface, such traction is more likely than pure tangential traction to generate the force necessary to cause a foveal dehiscence. Because the vector of anterior traction is small owing to the relatively shallow hyaloid separation, clinically obvious anterior displacement of the macular hole edges is not expected. Nevertheless, confirmation of this anterior vector is seen in the biomicroscopic and OCT finding of subtle anterior displacement of small flaps at the edge of stage 2 holes and in the position of opercula suspended anterior to the inner macular surface.7,8,16

Second, perifoveal vitreous detachment should localize to the foveola the dynamic vitreous tractional forces generated during ocular rotations.5 Although ocular rotations occur throughout life, associated tractional forces should be distributed evenly across the posterior retina until perifoveal vitreous detachment allows them to act focally on the fovea. This is analogous to peripheral retinal break formation, which occurs at a focal vitreoretinal adhesion after vitreous detachment from the surrounding retina. We believe that although dynamic traction and static trampoline-like traction both contribute to macular hole formation, dynamic forces are more likely to generate traction of the magnitude necessary to cause a foveolar dehiscence.

From an anatomical perspective, it is not surprising that age-related PVD would begin as a localized perifoveal vitreous separation. The vitreous is thought to be most firmly attached to the retina at those sites where the internal limiting lamina is thinnest, including the vitreous base, along major retinal vessels, the optic disc, and the 500-µm-diameter foveola.4,17-20 Age-related PVD typically begins in the macular region,4,21,22 possibly related to the premacular liquefied vitreous pocket that is commonly present in older adults’ eyes.22-24 Gaudric et al8 recently demonstrated using OCT the initial stages of PVD, beginning in the periphery of the macula and gradually spreading throughout the entire macular area while remaining focally adherent to the foveola. This initial stage of PVD is usually asymptomatic and occult, as evidenced by the fact that posterior hyaloid separations from the perifoveal or entire macular area have been detected by OCT or ultrasonography in as many as 82% of asymptomatic eyes.7,8,25-27 In other eyes, the vitreous attachment to the foveola separates spontaneously prior to full-thickness hole formation, with subsequent resolution of the tractional changes in the fovea and with the frequent formation of a pseudo-operculum.10 In either case, the firm attachment of the vitreous to the peripapillary retina tethers the PVD, limiting it to the posterior retina in most eyes until further loosening of the vitreoretinal adhesion allows completion of the PVD with the development of a Weiss ring, typically months or even years later. Evidence for the weak vitreoretinal adhesion in these eyes with evolving PVD is found in our intraoperative observation that active peeling of the vitreous from the retina was rarely necessary except at the optic disc and foveola.

The theory that idiopathic macular hole is a complication of the initial (perifoveal) stage of age-related PVD explains the age and sex demographic profile of idiopathic macular hole, which is similar to that of age-related PVD.4,22,27 This profile is also seen in idiopathic epiretinal membrane, another condition considered to be a complication of age-related PVD.28 The cause of the female predominance seen in PVD and its complications is unknown, but may relate to the effect on vitreous hyaluronic acid concentration of low estrogen levels in postmenopausal women.22 The finding that the age of onset of PVD correlates with the degree of myopia22 may also explain our observation that the patients in our macular hole series who were less than 60 years old all had significant myopia (>6 diopters).

This modified theory of macular hole pathogenesis is simple in concept, has a pathoanatomical basis, and does not depend on hypothesized events such as Muller cell proliferation and migration or selective contraction of the prefoveolar vitreous cortex.1-3 Furthermore, we believe that the following observations are more consistent with the perifoveal vitreous detachment theory than with the tangential traction theory of macular hole development: (1) Macular hole opercula/pseudo-opercula are positioned above the plane of the surrounding retina (the height of which varies with the extent of the trampoline-like posterior hyaloid detachment from the curved macular surface).7,8 (2) With meticulous biomicroscopy and by OCT examination, there is often evidence for anterior displacement of small flaps at the margin of nonoperculated stage 2 macular holes.7,8,16 (3) Broad vitreous separations across the entire macular area have been demonstrated in our study and other ultrasound, OCT, and intraoperative examinations of the posterior hyaloid in patients with macular hole and pseudoperculm.7-11,16 None of these studies have shown localized vitreofoveal separation with persistent vitreoretinal adherence around the hole as illustrated in the tangential traction theory.1-2 (4) Slow progressive enlargement of the localized macular hyaloid separation has been documented by OCT,4 and macular hole maturity seems to be correlated with the likelihood of extensive vitreomacular separation or total PVD.11,29 Both of these observations support the idea of a slowly evolving PVD
causing macular hole formation in its early stages and sometime later separating from its firmest adhesion at the optic disc. (5) Fibrocellular and cellular membrane fragments were found in surgical vitreous specimens in only 10% of eyes with impending macular holes and were scant or absent in the majority of eyes with full-thickness macular holes. This suggests that mechanisms other than cellular proliferation are important in generating the traction that leads to macular hole formation.

Accepted for publication July 26, 2000.


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