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The Management of Macular Holes

By David T. Wong, MD, FRCSC

Macular holes are full-thickness retinal tissue defects centered at the fovea. They were first described by Knapp in 1869 in a case of ocular trauma.[1] For the next 100 years, there were further descriptions of macular holes and theories expounded on the cause for the problem, but no therapy was devised. However, much has changed over the last 20 years. In 1988, Gass conceived the theory of tangential vitreous traction[2] as a cause and, in 1991, Kelly and Wendel revealed that vitrectomy surgery could successfully treat this disease.[3] Today, modern diagnostic imaging enables earlier diagnosis and more accurate staging. In conjunction, modern surgical techniques, with the aid of adjunctive pharmacosurgical therapy, have increased the rate of surgical closure of macular holes, resulting in better visual outcomes. This issue of *Ophthalmology Rounds* describes the epidemiology, natural history, diagnosis, and treatment of macular holes.

Epidemiology

Data on the prevalence of full-thickness macular holes are limited and there have been few published population-based studies. The Beaver Dam Eye Study found the prevalence of full-thickness macular holes to be 0.3% in the general population. The prevalence increases from 0% in those aged ≤54 years to 0.8% in those aged >75 years.[4] Other studies have confirmed similar numbers.[5,6] Therefore, in Canada, with an estimated population of 32 million in 2004, there were possibly 96,000 people with macular holes. With the increasing age of the population, it is expected that the incidence of macular holes will increase. For reasons not yet fully understood, women have a 3-fold higher probability of having macular holes than men.[7] There is continuing debate about whether hormonal changes or demographics (ie, there is a greater proportion of women compared to men in the senior age bracket) are responsible for this difference. Of the total number of macular holes, idiopathic causes account for 85% compared to trauma-induced causes, 15%.[8]

Pathogenesis and staging

Various theories on the pathogenesis of macular holes have developed over the years. Originally, the explanation for the formation of a macular hole was trauma, with mechanical separation and necrosis.[9] Later, with further descriptions, macular holes were noted to occur without any trauma. The cystic degeneration theory evolved from the lack of an explanation for nontraumatic macular holes. Intraretinal cysts adjacent to macular holes were described and it was postulated that retinal degeneration was the mechanism for macular hole formation. It was believed that cystoid degeneration would occur due to the decrease in vascular flow associated with aging. As these cysts grew, they merged and formed macular holes. Various therapies to increase vascular flow (eg, vasodilators like nicotinic acid) were put forward, but without apparent success.

Knowing that vitreous traction was a cause of peripheral retina breaks, the concept of anterior-posterior vitreous traction as a cause for macular hole formation was first described in 1924. However, the lack of detection of vitreous traction over the macular hole created difficulties in accepting this theory. Others tried to unify the theories by suggesting a "combined mechanism," incorporating macular thinning with cystic

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changes from vascular insufficiency, followed by vitreous traction that pulled on the thin macular tissue, thus forming the hole.[10]

It was not until 1988, when Gass created a classification system, that attention shifted away from anterior-posterior vitreous traction to tangential traction along the vitreoretinal interface as a cause for macular holes. The result was a resurgence in interest in macular holes.[11] Gass suggested that tangential contraction creates photoreceptor displacement, with loss of photoreceptors.[12] Early histopathology of operculums revealed no photoreceptor loss; however, more recent histopathologies of the operculums from macular holes have shown some loss of foveal tissue, including photoreceptors.[13]

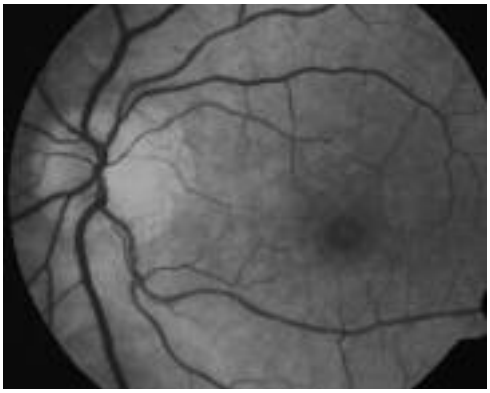
The transition of the stages in macular holes is related to various tractional forces.

- In stage 1, Gass's classification described the separation of the retina from the retinal pigment epithelium (RPE) due to traction. However, recent data from optical coherence tomography (OCT) imaging studies suggest a modification in the location of the separation. In impending macular holes, perifoveal cortical vitreous detachment is present, with vitreous attachment at the umbo. This traction of the perifoveal vitreous at the fovea may separate Muller cells from photoreceptors in this location, initially creating a split in the intraretinal layers, and then, cystic cavitation.[14]
- In stage 1A, there is loss of the umbo with the intraretinal split and traction, creating the yellow dot, possibly representing xanthophyll pigment.
- In stage 1B, as the foveal retina elevates from the cavitation to the perifoveal retina level, there is complete loss of the umbo and the yellow dot merges to form a yellow ring.
- In stage 2, there is dehiscence of the roof of the cystic cavity, leading to a stage 2 macular hole with a retinal defect of <400 µm.
- Stage 3: Tangential traction causes the dehiscence to continue into the photoreceptor layer and leads to a full-thickness macular hole. This tangential traction also may form the operculum as it releases the roof of the cyst. This allows the posterior hyaloid face to separate from the retina, but attached to the optic nerve, creating a stage 3 macular hole (Figure 1). Further traction tangentially enlarges the hole.
- A stage 4 hole occurs when the posterior hyaloid has separated from the optic nerve.

Diagnosis

Patients with stage 1 rarely have visual complaints, whereas those in the other stages usually complain of a blurring of their central visual acuity or metamorphopsia. As the hole enlarges, the loss of vision is greater. Table 1 details the visual acuity of the various stages. Pin cushion distortion is common due to lateral displacement of the photoreceptors.[15]

Figure 1: Red-free photo of a stage 3 macular hole



A clinical examination is still the most common method to detect macular holes. The use of a contact lens in slit lamp biomicroscopy is superior in detecting and staging macular holes than the use of noncontact lens such as a 78D or 90D. If sufficient time is spent during the clinical examination, macular holes at all of the stages may be detected. Stage 1 holes depict yellow deposits, possibly indicating xanthophyll displacement. In stage 2, small microbreaks in the inner layer may be seen with adjacent vitreoretinal traction. In stage 3, there is round loss of retinal tissue >400 µm and an overlying operculum; yellow pigmentation may be seen at the level of the RPE in the hole. A surrounding subretinal fluid cuff may also be seen. A Weiss' ring usually depicts posterior hyaloid separation in stage 4.

Several chairside tests can help in the diagnosis of macular holes. The Watzke-Allen test, which is performed with slit lamp biomicroscopy, is commonly used. The technique is to direct a narrow slit beam into the fovea. A positive test is indicated when a gap or narrowing of the beam is perceived by the patient. The sensitivity of the Watzke-Allen test is 95% compared to clinical examination; however, when compared to OCT, the actual sensitivity drops to 60%.[16] A variant of the Watzke-Allen test is to direct the aiming beam of the laser at a 50 µm spot size in the

Table 1: Characteristics of the stages of macular holes

	Stage 1	Stage 2	Stage 3	Stage 4
Slit lamp bio-microscopy	1a - yellow dot 1b - yellow ring	Full-thickness hole diameter <400 µm	Full-thickness hole diameter >400 µm	Full-thickness hole diameter >400 µm
Posterior vitreous	Attached	Attached	Attached	Separated
Visual acuity	20/20 – 20/60	20/40 – 20/100	20/60 – 20/200	20/60 – CF
Spontaneous closure	60%	4%-33%	5%-12%	5%-12%
Surgical candidate	No	Excellent	Good	Fair

centre of the macular hole. The inability of the patient to detect the aiming beam indicates a full-thickness macular hole. It is a highly sensitive test. Another chairside test is the Amsler grid, which is highly sensitive, but nonspecific.[17]

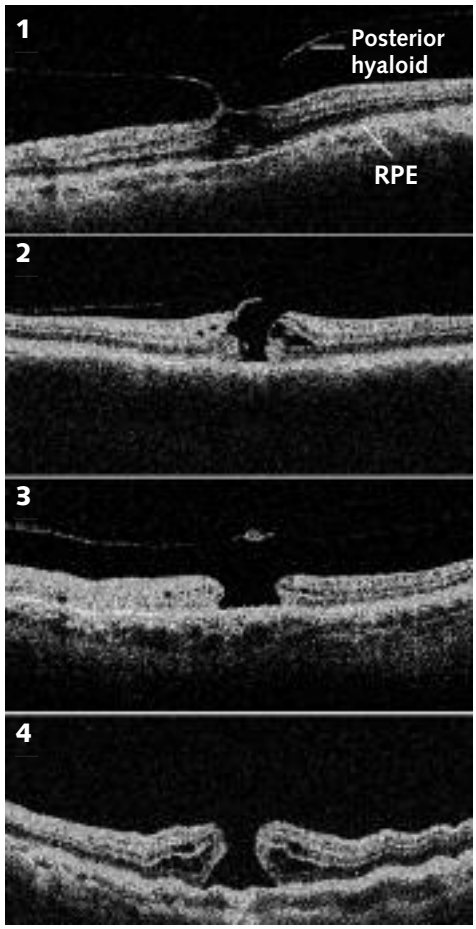
Fluorescein angiography is not sensitive or specific in detecting macular holes. In stage 2, 3, or 4 holes, there is a window defect with early hyperfluorescence in the hole due to the lack of xanthophyll and tissue. If the choroid is heavily pigmented, hyperfluorescence in the macular hole may be minimal or nonexistent. Hypofluorescence is sometimes seen within the hole due to the yellow deposits.

B-scan ultrasonography is helpful in determining if a posterior hyaloid separation has occurred and may be useful in staging the macular hole in the later stages, but it is limited in determining the presence or staging of early macular holes. The presence of an attached posterior hyaloid increases the suspicion of macular hole formation in the future.

OCT has become the gold standard for detection of macular holes and has displaced most tests due to its noninvasive nature. It provides excellent definition of pathology and is helpful in the sizing and staging of macular holes. OCT is superior to the Watzke-Allen test in terms of sensitivity. Because of its ability to detect the posterior hyaloid, OCT has been invaluable in understanding the pathology of macular holes (Figure 2). Early detection of perifoveal vitreous traction can identify patients at risk of macular hole formation before any cystic changes occur. From a practical point of view, the graphic representation of a hole with OCT imaging is an excellent educational component for patients, allowing them to better understand their pathology. The advent of OCT has allowed observation of the etiology, as well as the outcome of treatment.

Other tests such as microperimetry and scanning laser ophthalmoloscopy may detect scotomas and better delineate the extent of affected photoreceptors. However, the impact of these new technologies remains to be seen.

Figure 2: OCT of Stages 1 to 4 macular holes.



RPE = retinal pigment epithelium

Stage 1 – Vitreous traction at perifoveal edge with formation of intratretinal cavitation.

Stage 2 – Inner retinal flap attached to posterior hyaloid face with full-thickness hole. Note formation of cystic changes.

Stage 3 – Full thickness hole with overlying operculum. Stage 4- posterior hyaloid separation and full thickness hole

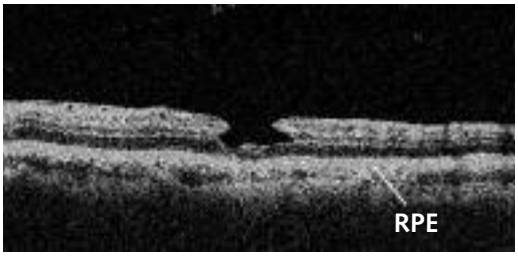
Differential diagnosis

Many macular diseases can mimic macular holes. Epiretinal membranes (ERMs) may create the false appearance of a hole (termed "pseudoholes"). The observation of the lack of a subretinal fluid cuff, the lack of yellow pigmentation dots within the hole, and the presence of relatively good vision, differentiates a pseudohole from a macular hole.[18] In addition, the Watzke-Allen test, as well as the laser aiming beam test, are negative with a pseudohole. An OCT easily differentiates a psuedohole from a full-thickness macular hole.

It is not uncommon for patients to have an epiretinal membrane (ERM) in association with a macular hole. Clinical observation of an ERM in a macular hole ranges from 25% to 65%, whereas, with histopathological examination, they may be observed in 73% of cases. Early studies could not determine if ERMs were a cause or a contributing factor in macular hole formation, or if they were the result of the open break. However, a study by the Vitrectomy for Macular Hole Study Group (VMHS) revealed that ERMs are more prevalent in larger macular holes, while the size of the ERM correlates with the duration of the hole.[19] This further supports the premise that ERMs develop after the formation of a macular hole.

Lamellar holes, a partial loss of retinal tissue, may also resemble a macular hole. The exact etiology of lamellar holes is unclear, but they are thought to be created by the sudden release of vitreous from the retinal surface in an impending hole. A pseudo-operculum may also be observed, making the diagnosis

Figure 3: Lamellar hole. There is still tissue above the RPE.



more difficult. A pseudo-operculum is thought to represent condensed vitreous. OCT will differentiate a lameller hole from a macular hole (Figure 3).

Other entities that may be confused with macular holes, especially stage 1 macular holes, include cystoid macular edema (CME), central serous retinopathy (CSR), age-related macular degeneration (AMD) with large central drusen, vitreomacular traction syndrome, and solar retinopathy.

Natural history

Oblique vitreous traction has been identified as a precursor to macular hole formation. Macular holes generally progress from stage 1A to stage 1B within a few weeks to a few months. On average, the conversion to a full-thickness hole is 4.1 months, but it may occur in as early as 1 month. Patients with 20/50 to 20/80 vision have a 66% risk of progression, compared to those with better than 20/50 vision, whose progression is 30%. Over a 2-year period, 40% of stage 1 holes will convert to stage 3 holes.[19] Therefore, 60% of stage 1 macular hole patients abort conversion. Residual changes consistent with a lamellar hole are seen in some of the aborted cases.

Patients with stage 2 holes have a 67% to 94% risk of progression to stage 3 and 4 holes, and a 4% to 33% chance of spontaneous resolution that may take as long as 2 to 8 years.[20,21] Holes enlarge to >400 µm in 85% of cases, with a >70% chance of losing >2 lines of vision.

With stage 3 and 4 holes, further loss of visual acuity occurs with the increase of the subretinal fluid cuff, cystic changes in the retina, and photoreceptor degeneration. If the subretinal fluid cuff increases, the rest of the macula and, possibly, the peripheral retina may detach; however, this usually occurs with myopia >6 diopters.[22] Although uncommon, spontaneous closure of the hole occurs in 5% to 12% of cases.[23]

The risk of the fellow eye developing a macular hole ranges from 3% to 22%. Chew et al reported that the risk of development a macular hole in the fellow eye was 4.3% within 3 years, 6.5% in 4 to 5 years and 7.1% in over 6 years.[24] Using OCT in the fellow eye has helped to identify patients at higher risk. By finding an oblique insertion of the vitreous at the fovea, the chance that a patient will develop a macular hole increases by 6-fold.[25] Although the risk of bilateral development is low, close follow-up and patient education about the symptoms allows for earlier diagnosis and treatment.

Treatment

Prior to 1991, no therapies existed to treat full-thickness macular holes; however, by 1991, Kelly and Wendel described vitrectomy, membrane peeling, and gas tamponade as successful methods to treat macular holes. Since this original description, further refinements in technique have led to highly successful strategies in the treatment of macular holes.

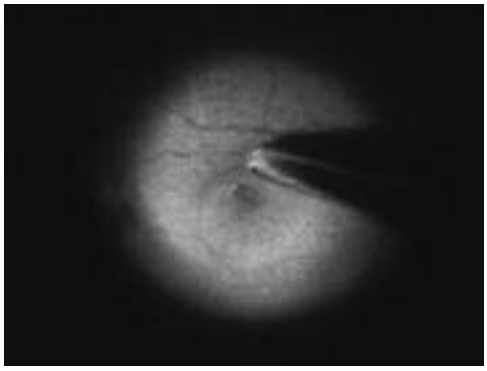
For stage 1 macular holes, a randomized multi-centre trial performed by the VMHS found that surgical intervention did not provide benefit. Furthermore, given the natural history of stage 1 holes – with at least 60% resolving on their own and conversion to full-thickness holes at 4 months on average – observation, with monitoring at 3 to 4 months, is the usual course. Amsler grid monitoring by the patient is helpful to determine progression between follow-up visits.

With macular holes at stage 2, 3, and 4, pars plana vitrectomy, posterior hyaloid separation, and tamponade have been highly successful in treatment. Kelly and Wendel originally described a 58% anatomic success rate of hole closure, with 42% of patients gaining at least 2 lines of vision with vitrectomy surgery. Success rates increased to 73% for closure, with 55% gaining ≥2 lines when patients were operated on within a 6-month window from the development of the macular hole.

The use of surgical adjuncts and peeling of the internal limiting membrane (ILM) are new areas of interest that may help to increase success rates. Previously, TGF-ß$_2$,[26] platelets, autologous serum, thrombin, and whole blood[27] were used to increase anatomic closure. Conceptually, after relieving vitreous interface traction, these adjuncts helped to close macular holes by creating a membrane to seal the hole. Although the success of closure appeared to increase, failures and late hole reopening fueled further investigation into other methods to close the hole.

Returning to Gass's concept of tangential traction, attention turned to the ILM as a potential cause of this traction. Some studies showed no benefit with ILM peeling, while others have shown benefit. Although the initial aim of ILM

Figure 4: Peeling of the internal limiting membrane (ILM) using indocyanine green (ICG)



peeling was to release traction on the edge of the macular hole, stimulation of gliosis may be a more important factor in the repair process.[28]

The ILM is thin and translucent, making it difficult to remove. This problem may be the reason why results have been variable with ILM removal. With the introduction of indocyanine green (ICG) as a method to stain the ILM, peeling of the ILM has become easier and safer (Figure 4).[29] Anatomic success rates have increased into the >90% range with one surgery;[30] however, concern for toxicity has emerged.[31] Patients with ICG-assisted ILM peeling appear to have a depressed recovery of visual acuity compared to those not using ICG. As well, pigmentary changes in the surrounding RPE have been noted after ICG-assisted ILM peeling. The exact mechanism as to why toxicity occurs is unclear. Mitochondria damage and osmolality are some of the factors that may contribute to the damage.

Studies have been performed to determine if using lower concentrations of ICG during surgery may be better tolerated by the eye. Concentrations of ICG that are <0.5 mg/mL have been shown to be non-toxic in cultures of RPE cells,[32] but the lower concentration results in less staining of the ILM than higher concentrations. Further in vivo study is required to determine the concentration of ICG that will not cause any damage.

The concern for ICG toxicity has sparked interest in other methods of improving visualization of the ILM. Kenalog may be used to help highlight the ILM. Although it does not stain the ILM, it does adhere to the posterior hyaloid, making it easier to detect. Furthermore, if an edge is created on the ILM, kenalog precipitates will help in highlighting this edge. However, the safety of kenalog is still in question. Long-term effects such as cataract formation, glaucoma, and RPE toxicity have not been well studied with kenalog used as a highlighting vehicle.

The use of trypan blue to highlight the ILM is promising. Although it does not stain the ILM, the counterstaining is similar to kenalog, enhancing the visualization of membrane edges, which is useful for ILM peeling. Studies to date have shown no toxicity. Although not yet approved in Canada, recent work in Europe shows promise.[33]

To aid in the closure of a macular hole, a tamponade of gas is often used to reduce the subretinal fluid cuff and to allow the recreation of a seal. The duration of "face-down" positioning varies from 24 hours to 3 weeks, with most surgeons selecting approximately 7-10 days and using perfluropropane (C3F8), in preference to sulfur hexafluoride (SF6). Another gas, C2F6, is ideal for macular hole surgery since its duration is between that of SF6 and C3F8; however, it has not been approved in Canada. Silicone oil, a long-term tamponade, may be used for patients who are unable to position face-down or for those with previous failures, but complications of glaucoma, corneal decompensation, requirement for another surgery for removal, and significant refractive shift, indicate that it is not the ideal tamponade for primary repair.

Self-sealing vitrectomy surgery, with either 23- or 25-gauge technology, is ideal for macular hole surgery. Patient discomfort and inflammatory response are minimized and patient recovery is faster with no sutures. Long-term complication rates have so far been no different from those with 20-gauge systems.[34]

Conclusion

Over 15 years ago, a macular hole was an incurable disease; however, today, established surgical treatments have changed the overall prognosis for these patients. Excellent closure rates are seen in over 90% of procedures and enhanced visualization techniques of the ILM are setting new standards in visual recovery. Further advancements with newer surgical techniques will continue to provide greater patient benefit. We have come a long way within a short period of time.

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Upcoming International Meetings

30 April – 4 May 2006
The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
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Fax: (240) 221-0370
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21-24 June 2006
Canadian Ophthalmology Society (COS) Annual Meeting and Exhibition
Westin Harbour Castle, Toronto, Ontario
CONTACT: Ms Kim Ross
Email: kross@eyesite.ca
Website: www.eyesite.ca/annualmeeting/2006/

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Upcoming events

April 6, 2006	**VPP** – Dr. Bita Esmaeli, Houston, Texas Oculoplastics
April 21, 2006	**17th Annual Jack Crawford Day** The Hospital for Sick Children Contact: Karen Martin – 416-813-8942 Registration Info: CME Office – 416-978-2719 or www.cme.utoronto.ca
April 27, 2006	**VPP** – Dr. Christopher J. Rapuano "Stepwise Approach to Management of ABMD and Recurrent Erosions"
May 18, 2006	TOS/U of T VPP rounds Vaughan Estates
May 25, 2006	**VPP** – Dr. Shaun Singer Quality Assurance
June 9, 2006	Departmental Research Day
Oct. 14, 2006	International Neuroprotection meeting Contact: Dr. Neeru Gupta 416-864-5444

Note: This year's (September 2005 to May 2006) VPP rounds will be held at:
The Hospital for Sick Children
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Main Auditorium, Elm Wing, 1st Floor, Room 1246,
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