Idiopathic macular hole

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The idiopathic macular hole is a commonly observed retinal pathology. It had been generally considered an untreatable condition until 1991, when the first surgical successes were reported. Currently, the success rate of the surgical approach is very high. Surgical treatment includes pars plana vitrectomy, peeling of the internal limiting membrane, gas tamponade and face-down position. This approach is based on a better knowledge of the pathogenetic mechanisms underlying idiopathic macular hole formation. The aim of this review is briefly to describe the pathogenesis of the idiopathic macular hole, its natural history, the diagnostic approach and the current surgical treatment.

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Macular hole is a retinal disease characterized by a full-thickness defect in the neurosensory retina of the central fovea [1]. For a long time, this condition has been considered to be not only rare but also essentially untreatable. However, in the past decade, the first reports of success in surgical treatment have dramatically increased surgeons' interest in this disease [2].

Furthermore, the advent of new diagnostic tests, such as optical coherence tomography (OCT) and microperimetry, has provided new information regarding the pathophysiology of macular hole and they have been recognized as extremely useful in confirming macular hole diagnosis and in defining the stage of the lesion.

Epidemiology

This retinal disease is an important cause of central visual loss even if often misdiagnosed while patients are binocular. Macular holes usually occur in the sixth and seventh decades of life. The prevalence ranges from 0.9 to 3.3 per 1000 and affects women three-times more often than men [3,4]. This is not completely understood but it has been related to an estrogenic decrease with age causing a chemical change in the vitreous components and consequent adherence to the macula [4–8].

The macular hole is usually unilateral, although, according to different series, it could be bilateral in 1.2–22% of cases [9,10].

Pathophysiology

The fovea is a small region of the retina located on the posterior pole of the eye. It has a slightly elliptical shape, with a width of approximately 1.5 mm, or one disk diameter. Its central floor is the foveola (~0.35 mm in diameter) and it is the point of sharpest visual acuity (VA). In the fovea there is a high concentration of cone cells, which are smaller and more densely packed than in the rest of the retina, and virtually no rods.

In 1969, Yamada demonstrated that, in the central 200 µm of the fovea, the outer cone fibers are separated by Müller cells, which occupy the inner third of the retinal thickness [11]. In 1999, Gass hypothesized that Müller cells served as a plug to bind together the receptor cells in the foveola and were an important factor in the pathogenesis of retinal disorders and especially in macular hole formation [12].

The fovea is the thinnest part of the retina (ranging between 160 and 291 µm as measured with OCT) and, in this area, the layer of nerve cells, which are normally located above the receptor cells, is laterally displaced and in this way the photoreceptors are exposed to the direct impact of light rays [12,13]. Owing to its thinness, the fovea is particularly susceptible to macular hole formation.

The first full-thickness macular hole (FTMH) was described by Knapp in 1869 in relation to an ocular trauma, but recent clinical

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studies have shown that the great majority of holes are actually idiopathic [1]. Macular holes can also be seen in highly myopic eyes and in relation to macular pucker and to vascular or inflammatory diseases (cystoid macular edema) [8,14,15]. In traumatic macular holes, the most important event is an acute vasoconstriction in the macula area, followed by vasodilatation and edema. Cystoid spaces develop in the ischemic retina causing a retinal defect [16,17].

When the hole is of a vascular or inflammatory nature, the most likely pathogenetic hypothesis is a disorder of the hematoretinal barrier with an increased permeability of the macular microcirculation, followed by formation of microcysts, which later become bigger, causing substance loss [8,14]. These pathogenetic mechanisms cannot be considered valid for the idiopathic FTMH, whose formation involves tangential and anteroposterior vitreofoveal traction. In 1924, for the first time Lister defined anteroposterior traction as the key factor in the pathogenesis of idiopathic macular holes [18], while, in 1988, Gass and Johnson emphasized the role of tangential traction caused by a vitreous thickening [6]. According to this theory, the tangential traction parallel to the retina surface causes an anterior displacement and a change of the neuroepithelium, creating intraretinal cystoid spaces that evolve into a FTMH. In the early stages, when the traction is only tangential, the hole's edges are flattened, while in the later stages they are raised.

Gass used these theories to describe the evolution of the macular hole and divided its development into four stages:

- Stage 1. During this phase, also called 'impending hole', the posterior vitreous hyaloid is attached to the retinal surface and there is no sign of the hole. At this stage, there is a progressive loss of the physiological foveal depression and a yellow spot of approximately 100–200 µm appears on the fovea (stage 1a). This spot represents a focal serous retinal detachment and its yellow colour is probably due to greater visibility of the xantophyll, caused by the separation from the pigment epithelium, which is highly concentrated in this area. In this phase, the retinal receptor layer is stretched. When the foveolar retinal detachment progresses to the foveal retinal detachment, there is a redistribution of the xantophyll into a yellow ring configuration of approximately 200–350 µm (stage 1b, impending macular hole). After the yellow spot becomes a ring, there is a break in the continuity of the receptor cell layer at the umbo. Gass ascribed these histological changes to a thickening and contraction of the prefoveal vitreous cortex causing centrifugal tangential forces. The retinal receptors and the xantophyll retract centrifugally beneath the contracted vitreous cortex, the yellow ring enlarges and a well-defined central semitranslucent zone appears (stage 1B, occult macular hole). Metamorphopsia and blurring are the only symptoms and the VA is often good (FIGURE 1) [5,6,19,20].
- Stage 2. In this stage, the vitreous keeps thickening and it is still attached to the retina surface. The traction increases and can cause intraretinal tractional striae. The cystic spaces can open and cause a small full-thickness retinal defect. At this stage, two types of configuration can be distinguished. In the 'centric' configuration, the lesion begins in the centre of the fovea, while in the 'pericentric' configuration, the lesion begins in an eccentric position with respect to the fovea in a 'can opener' fashion. These holes are usually less than 400 µm in size. The VA usually deteriorates and there is an increase in the metamorphopsia (FIGURE 2) [5,6].
- Stage 3. In this stage, the typical FTMH develops. It appears as a full defect, well localized, with sharp margins, very often rounded by a cuff of subretinal fluid, which raises the adjacent retina. The neuroepithelium raising ring is determined by both neuroepithelium detachment and intraretinal edema. The intraretinal edema is due to an alteration caused by mechanical traction, which can also cause the pseudocystic volume to increase and break. Yellow–white precipitates can be seen at the base of the hole, probably formed by drusenoid material. It is associated with a typical localized foveal vitreous detachment and with the formation of an operculum, which is mobile with vitreous movements. This is described as a 'pseudo-operculum', as it has been observed that is formed by fibroglial structures and vitreous thickening. Nevertheless, other studies have demonstrated that it is possible to recognize photoreceptor cells in the operculum [4]. In this stage, the hole diameter may range from 400 to more than 600 µm. It is sometimes possible to see a nodular proliferation of retinal pigment epithelium (RPE) on the base of the hole. In this phase, metamorphopsia increases and VA can be very low [5,6].
- Stage 4. In this stage, the vitreous is completely detached from the retina surface and it is possible to see the Weiss ring floating inside it. The hole's enlargement decreases because there is no longer any vitreal traction. Metamorphopsia is invalidating and VA is very low (FIGURE 3). In this stage, intraretinal cystoid edema of the elevated margins is frequently observed [5].

Gass hypothesized that, in the first stages, the pathogenesis of the FTMH was due to tangential vitreomacular traction caused by vitreous cortex thickening and, especially, that it was due to a dehiscence and contraction of the glial membrane covering the macular surface. In fact, histological examination shows the presence of glial tissue and confirms the pseudo-operculum hypothesis. Its structure includes vitreous cortex thickening, inner limiting membrane (ILM), Müller cells, astrocytes and glial cells with miofibroblastic structure [21]. The presence of this contractile material might cause the retraction of the hole's edges and, consequently, its enlargement, including when there is a complete posterior vitreous detachment (stage 4) [22].

The Gass classification is the currently accepted classification for staging macular holes. However, this classification is based on biomicroscopic observation and interpretation and, since the advent of OCT, some substantial findings (especially in stages 1 and 2) have been recorded that are not covered by

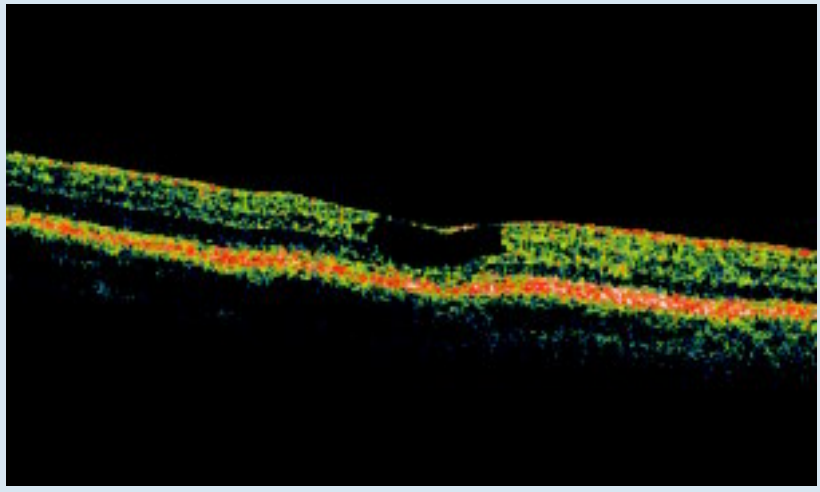

Figure 1. Stage 1 macular hole.

Gass's hypothesis. The most important findings concern the behavior of the vitreous, especially the posterior hyaloid and its relationship with the foveal retina and the neuroepithelium around the hole.

As a result of the OCT findings, Chan and colleagues have proposed introducing stage 0 macular holes in the Gass classification. In this stage, there is a normal biomicroscopic appearance of the fovea and OCT shows a normal foveal contour but an oblique insertion of the posterior hyaloid fibers on the fovea due to a partial detachment of the posterior hyaloid. The discovery of this stage in the fellow eye has been put forward as an important risk factor in the development of a macular hole in this eye as well [23].

Several papers based on OCT findings have highlighted the perifoveal vitreous detachment, with focal attachment of the vitreous to the foveola.

Hee and colleagues have demonstrated the existence of a small perifoveal detachment of the posterior hyaloid, suggesting that vitreofoveal tractions may lead to the formation of a foveal cyst [24].

Gaudric and colleagues have shown that the posterior hyaloid detachment begins around the macula but that the hyaloid remains adherent to the fovea. This causes the development of anteroposterior tractions that subsequently cause an intraretinal split evolving into a cystic space. This constitutes the 'impending macular hole'. The further vitreofoveal traction leads to the eccentric opening of the roof of this cyst, representing the evolution to the stage 2 macular hole [25]. Haouchine and colleagues have demonstrated that this foveal pseudocyst, caused by an incomplete separation of the vitreous cortex at the foveal center, may evolve into a lamellar hole and remain unchanged for several months or resolve spontaneously [26].

In a recent study, Tornambe developed the 'hydration theory', according to which one of the main factors involved in idiopathic macular hole formation is the accumulation of fluid in the retinal tissue as a result of a defect in the inner retina. Accordingly, the closure of the hole following gas tamponade is due to the isolation of the hole from the vitreous fluid and the RPE pump activity [27].

Using OCT, it is possible to discriminate between different kinds of holes. In the lamellar hole the photoreceptor cells remain in their natural position while the operculum is constituted by thickening vitreous, Müller cells and astrocytes. Patients with this kind of hole may maintain a good VA. In the FTMH there are no photoreceptor cells at the base of the cystic spaces and it is possible to recognize them in the operculum, as Ezra has already demonstrated with his histological tests [4]. In these patients VA is decreased.

The ILM is another important factor in the pathogenesis of idiopathic macular hole. This basal membrane, derived from Müller cells, is particularly thin at the fovea, where there is an oblique disposition of these cells. The ILM can act as a scaffold to miofibroblastic cells' proliferation [28]. A contraction of these structures may cause a tangential traction that laterally displaces the photoreceptor cells and causes pseudocyst and macular hole formation.

Gordon demonstrated the formation of FTMH in eyes with a pre-existent complete vitreous detachment, therefore vitreous is not the only cause of traction in the hole's pathogenesis [22].

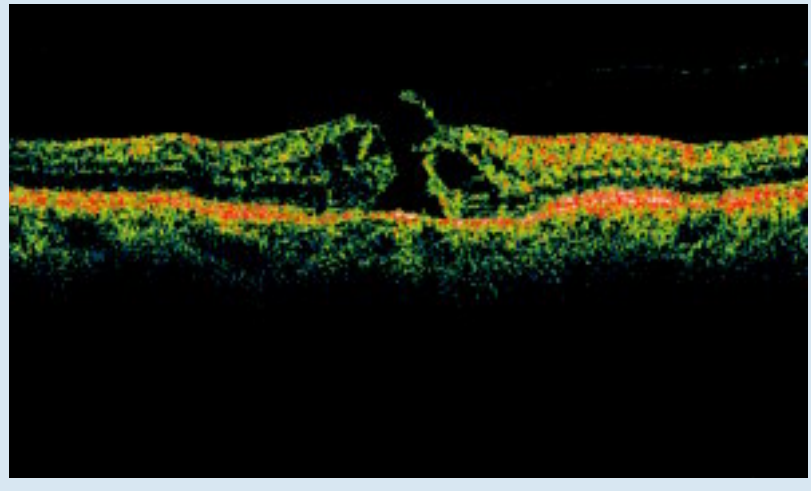

Figure 2. Stage 2 macular hole.

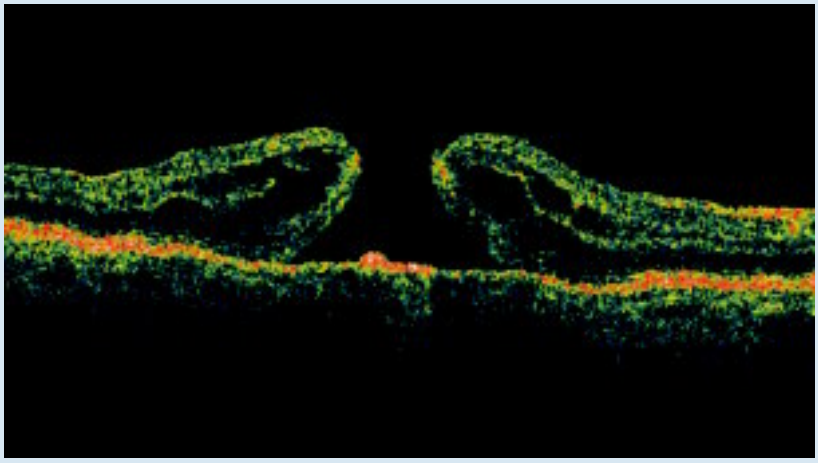

Figure 3. Stage 4 macular hole.

ILM is an anatomical substratum that permits the growth of the epiretinal membrane (ERM). It is known that remnants of posterior vitreous cortex may exist after posterior hyaloid detachment during surgery [29].

In a recent study, Schumann and colleagues analyzed the ultrastructure of the vitreoretinal interface after surgical removal of ERM and ILM in 100 patients operated on for stage 3 and stage 4 macular holes. They observed a fibrocellular proliferation, which was more severe in patients with stage 4 than stage 3 holes. This suggests that the remnants of the vitreous cortex attached to the ILM after spontaneous posterior vitreous detachment may be related to the formation of the ERM [30].

Another recent study by Hisatomy and colleagues examined the cellular proliferation and migration from ILM excised during macular hole surgery. Cellular activity was shown to develop after formation of the macular hole and so was not necessary for the initial formation of a macular break [31].

Their possible reappearance in the postoperative period is the major cause of the hole's recurrence and makes another surgery necessary. The ERM's presence in stage 3 and stage 4 holes and long-lasting holes supported this hypotesis [32].

Diagnosis

The most common tool that ophthalmologists may use to diagnose macular hole is the biomicroscopy along with a Goldmann or Volk's lens (Volk Optical Inc-Mentor, OH, USA). The Watkze-Allen test is an easy subjective test that can be coupled to biomicroscopic observation to confirm the clinical diagnosis. The patient is simply requested to observe the vertical line of light coming from the slit lamp and asked to note whether the line is complete or interrupted in the centre. This latter eventuality clearly indicates the presence of the macular hole. The sensitivity and specificity of this test have been demonstrated to be 75 and 100%, respectively [33].

The laser aiming beam test is another clinic-based diagnostic test useful for discriminating the macular hole from the pseudoholes. A laser spot is moved from the normal-appearing retina to the center of the macular lesion and the patient must report whether the focal light disappears, looking for the presence of a scotoma. As noted by Martinez and colleagues, 100% of patients with macular holes could not detect the 50-µm spot, whereas 93% of pseudohole eyes could detect it [34].

Recently, many imaging techniques have been used to clarify the anatomic and pathogenetic characteristics that cause macular hole formation. OCT is the most important of these techniques and, in recent years, it has become the 'gold standard' in macular hole diagnosis. This is a new noninvasive diagnostic test introduced by Huang in 1991 [35] and afterwards used by Puliafito to study macular diseases [36]. Nowadays, the OCT is used largely to confirm the diagnosis and stage of the macular hole.

Microperimetry has also been proposed as a diagnostic tool for macular holes. Several studies have demonstrated its utility in defining the size and location of the central absolute scotoma and the parahole sensitivity [37–39].

The preoperative fixation point and the shift in the position of fixation after surgery can be defined. Preoperative assessment of the macular sensitivity pattern using microperimetry may be related to visual outcome after surgery [37,39,40]. Furthermore, asymptomatic paracentral scotomata can be observed in many patients after surgery. These scotomata did not change in size, density or shape over time and might be caused by a trauma to the nerve fibers during ILM peeling [41,42].

Natural history & indications for surgery

The natural history of this pathology is very variable. Stage 1 macular holes can remain stable and have been found to have a 50% chance of spontaneous resolution [43], while they progress to further stage in only approximately 15% of cases [44,45].

On the other hand, stage 2, especially if with a pericentric configuration and stage 3 FTMH, very rarely do not progress. Spontaneous hole closure is an exceptional event (>10% in stage 2 and 3) and it is favored by posterior vitreous detachment and fibroglial proliferation. Usually, macular hole evolution from the initial stages to the most advanced stages is quite slow but the worsening is certainly not automatic. In every stage, except for stage 4, an eventual posterior vitreous detachment involving the foveal zone may slow down or even stop the hole's evolution. Therefore, some authors have suggested introducing perfluoropropane (C3F8) to the vitreous chamber to cause the vitreous detachment and to stop the evolution of the pathology, as in the initial stages [46].

In a retrospective study, Guyer demonstrated spontaneous resolution in 79% of stage 1 holes, 33% of stage 2 holes and only 5% of stage 3 holes [10]. Statistics indicate that the mean evolution period from stage 1 to 3 lasted weeks or even months.

Johnson and Gass [6] and Kokame [20] have observed that 66% of holes at stage 1 keep evolving to full thickness. Other authors have obtained more optimistic results: Akiba [47] reports 37% and Guyer [10] reports as low as a little over 10%. The evolution from stage 2 to 3 is much more frequent: in Hikichi's opinion it is approximately 67% [48]. Other statistics add that this evolution may reach 100% if stage 2 can be referable to the pericentric configuration (can opener) while it drops to 55% for the centric configuration [49].

The risk of the occurrence of FTMH in the fellow eye is strongly related to the attached posterior hyaloid. If the posterior vitreous is completely detached, the possibility of a FTMH is expected to be 1% or less according to some observations, even though Schepens has stated that this situation should not even exist [50,51]. The indication for surgery is mainly vision loss in presence of a full-thickness defect. Other variables are further considered, such as fellow eye, hole duration and size and stage [52–57]. Concerning this latter aspect, there is quite a general agreement that vitrectomy is not advisable for stage 1 macular holes as they are often asymptomatic and can regress in 50% of cases showing spontaneous complete resolution when the posterior vitreous detaches [10].

On the other hand, stage 2 and especially stage 3 and 4 FTMHs rarely close spontaneously. For these cases, vitrectomy enables higher percentages of macular hole closure to be achieved, even if functional outcomes in larger and longer lasting holes appears to be poorer than in smaller and shorter lasting holes [58].

Surgical treatment

The tangential vitreomacular traction hypothesis and evidence of anteroposterior traction on perifoveal documented by OCT has increased the surgical interest in vitrectomy. In 1985, Kelly was the first person to perform a vitrectomy and a gas–fluid exchange in a patient with a macular hole. This operation was not successful. After 2 years, he realized the importance of removing the posterior cortical vitreous. Furthermore, observing that macular holes were often associated with ERMs, Kelly became convinced that it was necessary to remove them as well [59].

On the basis of this experience, in 1991, Kelly and Wendel proposed macular hole surgery and reported that it was possible to close FTMHs [2]. Their surgery included a vitrectomy, peeling of ERMs if present, a long-acting gas tamponade and 2 weeks spent strictly in a face-down position. They were able to achieve complete macular hole closure in 58% of patients. In 1993, they published a new case series where they achieved visual improvement of two or more Snellen lines in 42% of cases and anatomical success in 73% of cases [53].

Since the results of these studies, numerous attempts have been made to improve anatomical and functional results of macular hole surgery. If anatomical success is achieved a few days postoperatively, the foveal function is slow to recover after successful closure of the macular hole; complete visual improvement may only be achieved more than 1 year after surgery.

For a long time, the standard procedure included a complete vitrectomy with posterior hyaloid separation and gas tamponade. Anteroposterior traction is important not only for the hole's formation but also for its evolution. Ito demonstrated that the hole diameter increases when the vitreous detachment exceeds the vascular arcades but remains adherent to the foveal edge [60]. Chan proposed to fill the vitreous cavity with gas to induce the vitreous detachment, the release of foveal tractions and the macular hole closure [61]. The effectiveness of this procedure was documented by OCT studies proving the releasing of the foveal tractions [46,62].

Sakuma has recently proposed a single intravitreal injection of autologous plasmin or a combination of plasmin and intraocular gas without peeling the ILM to close idiopathic macular holes [63]. Trese has obtained the same results employing an enzymatic vitreolysis, applying the plasmin as a proteolytic substance towards laminin and fibronectin, which are responsible for the vitreous' adhesion to the retina [64].

The definition of macular hole closure has been the object of considerable controversy. Tornambe's classification is commonly accepted. He suggested a three-group classification of anatomical status after surgery [65]:

- Elevated–open: the edges are still elevated around the hole. This situation represents a surgical failure, but a visual improvement is not ruled out (FIGURE 4);
- Flat–open: the hole is not closed but there is a flattening of the cuff. In some cases, a hole can reopen with an aspect similar to elevated–open holes (FIGURE 5);
- Flat–closed: showing closure of the hole and flattening of cuff. Functional results are better than for the flat–open group (FIGURE 6).

The percentage of hole closures ranges from 58 to 100%, depending on the author and the technique used [2,66–69].

Several surgical variables have been proposed in order to enhance the closure rates. Gas tamponade and strict face-down positioning are believed to be associated with a higher percentage of hole closures, whereas adjuvant efficacy has not been fully demonstrated.

The functional outcome of macular hole surgery is influenced by several preoperative parameters; the extension of retinal detachment around the hole, hole duration and size, the presence of intraretinal cystoid edema in the retinal tissue around the hole and the site of the new fixation point.

It has been reported that more advanced stages and longer lasting holes are related to a worse anatomical and functional success as their closure, irrespective of surgical technique, is more difficult [53,66]. The size of the preoperative macular hole, determined with OCT, has proved to be useful in predicting the success rate after surgical intervention. Ip and colleagues have demonstrated a higher postoperative macular hole closure in stage 2 holes (diameter < 400 µm) compared with stage 3 holes (diameter > 400 µm) [70]. Furthermore, the predictive value of hole diameters for the anatomical and functional outcome of surgery for idiopathic macular holes has recently been

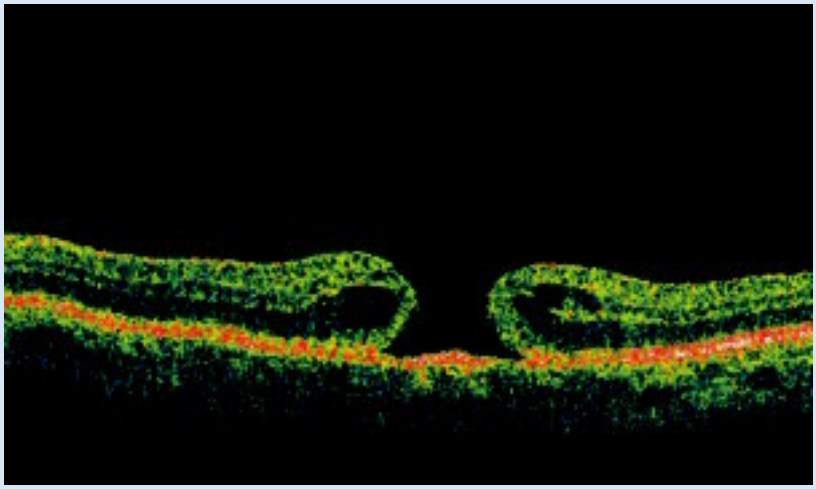

Figure 4. 'Elevated–open' aspect of the macular hole after surgery.

demonstrated [55,71]. In this study, it has been observed that the percentage hole closure after one surgical approach is significantly higher in eyes with macular holes with a small base and minimum diameter than in eyes with macular holes with a large base and diameter. Furthermore, significant negative correlation between both the base and the minimum diameter of the hole and the postoperative visual function has been demonstrated [60]. Paques reports that late reopening of initially successfully closed macular holes occurs in 10% of cases [72].

There are many factors that influence a reopening: the most important is the presence of ERM not removed during the initial surgery. He reports a high rate of macular holes reopening in patients who underwent cataract surgery after vitrectomy. The ILM peeling is associated with the lowest rate of recurrence and the highest rate of anatomical, and therefore functional, success.

In a recent paper, we reported the results of a retrospective evaluation of 1627 procedures for macular holes [58]. ILM removal proved to be crucial in obtaining anatomical success in stages 3 and 4 FTMH and in long-lasting holes, while it was not essential in achieving hole closure in stage 2 macular holes. Higher stage macular holes and longer duration of symptoms are risk factors for surgical failure.

ILM peeling

Recently, peeling of the ILM has been advocated as an important procedure to improve anatomical results [73]. The importance of ILM peeling for the pathogenesis of the idiopathic macular hole has been stressed by Yoon [74]. He hypothesized that, in the early phase of the pathology, the contraction of the vitreoretinal interface is the main factor in the pathogenesis followed by tangential traction generated by myofibroblastic cells formed on the ILM's surface. The first surgeon to peel ILM was Schultz, who reported interesting visual results of vitrectomy in the Terson syndrome [75]. Morris obtained similar results in a larger case series [76]. Encouraged by these results supporting Gass's hypothesis of tangential vitreomacular traction, a growing number of surgeons started to remove the ILM during surgery. Nevertheless, the identification of the ILM and its complete removal requires a precise surgical technique, longer surgery and the possibility of greater iatrogenic damages.

The effect of ILM peeling on functional outcomes in macular hole surgery is controversial. Some authors report significant functional improvement in patients who underwent ILM peeling compared with patients undergoing traditional surgery [77–79]. On the other hand, some surgeons reported a higher rate of functional success in unpeeled patients [66]. Byhr obtained good anatomical (98%) and functional results even without ILM and ERM peeling [80]. Brooks affirms that primary closure was significantly improved (100%) with ILM peeling versus holes without ILM peeling showing no reopenings during follow- up [78]. Different studies showed a reopening rate in patients who underwent vitrectomy without ILM peeling of 7–25% [78,81].

It is a common opinion that ILM peeling has to be performed in selected cases of macular holes: long-lasting holes, persistent and reopening holes, and stage 3 and 4 macular holes. On this last subject, Tadayoni has recently observed that ILM peeling does not appear to be useful for macular holes less than 400 µm in diameter [82]. The benefit of ILM removal is greater for larger macular hole sizes, for which the failure rate is also higher.

It has been suggested that the contraction of myofibrocytes contained in ILM around macular holes causes enlargement of the hole and prevents its closure. The ILM peeling may thus be a surgical adjunct that can promote gliosis and the closure of macular hole [66,79].

The importance of the ILM removal, especially in stage 3 and 4 macular holes, could also be related to the cellular proliferation on the ILM, which gradually increases after the appearance of the macular hole. A number of studies were performed to evaluate the possibility of anatomical and functional damage following the removal of ILM: only the electroretinogram's (ERG's) B-wave showed an important reduction in width [83]. This has been related to the attempts to remove ILM and to the difficulty in the intraoperative visualization. The incomplete removal of ILM may lead to the formation of secondary ERM and new tractional factors [83].

We have recently carried out a retrospective study whose main strength was the availability of a large number of patients and contributing surgeons, thus enabling results to be more generalizable than most single-surgeon, or low number of surgeon series. Considering the results for each macular hole stage, the percentage hole closure was higher in the ILM peeling group for stages 3 and 4. In stage 2 holes, the ILM peeling did not increase hole closure rates and this is consistent with previous literature, suggesting that stage 2 holes are not an indication for ILM peeling [35].

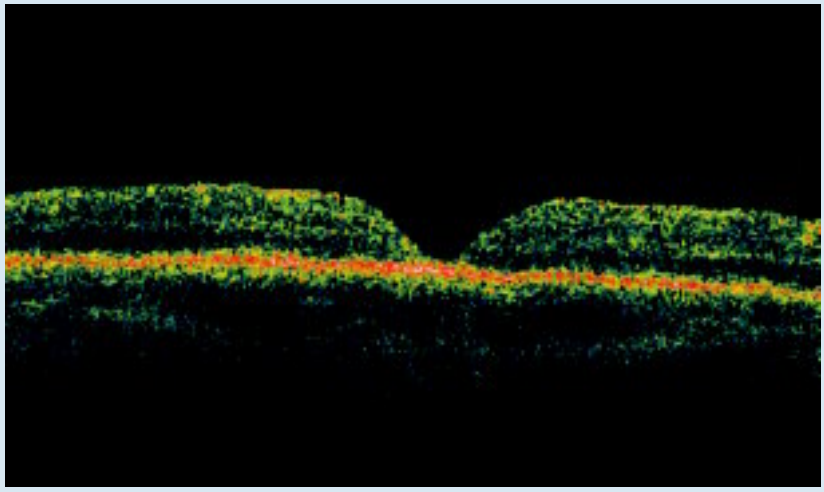

Figure 5. Flat–open aspect of macular hole after surgery.

Stainers

The removal of the ILM can be difficult even if indirect signs, such as a mild whitening of the retinal surface, can be observed on the peeled retina. Nevertheless, it has been pointed out recently that the dissociated optic nerve fiber layer appearance, featuring numerous arcuate striae, is not associated with the loss of optic nerve fibers. This clinical aspect of the retina surface is strictly related to ILM peeling and might be caused by cleavage of the optic nerve fiber bundles due to damage to the Müller cells [84,85].

Small retinal hemorrhages may also indicate that the ILM has been removed. Nevertheless, this should be considered to be a complication even if it hardly affects functional outcome. For these reasons, an incomplete peeling might occur owing to poor visualization. It has been shown recently that indocyanine green (ICG) stains the ILM, thus enhancing the visibility of this structure and greatly facilitating its identification and removal. The introduction of ICG-assisted ILM staining has made its removal much easier [86]. Since no standardized procedure has been assessed, different concentrations and times of exposure have been proposed, in air- or fluid-filled globes [86–88].

Even though several authors have reported a high rate of surgical success using this procedure [67,86,89], others have suggested possible ICG-mediated retinal damage [68,69,90–94]. Several experimental studies have demonstrated a direct toxic effect of ICG on the RPE [90,95–97]. Atrophic changes in the RPE at the site of the previous macular hole have also been described [94,98]. For all the above reasons, it is considered potentially dangerous to expose RPE and subretinal space to ICG. Therefore, many surgeons have suggested using different substances to protect the hole surface during staining. Perfluorocarbon liquid, high-viscosity viscoelastic substances, such as Healon 5®, and autologous blood have been put forward for this purpose [99–104]. Different studies have suggested that ICG staining may alter the cleavage plane between the ILM and the innermost retinal layers [68,69,91–93].

Gandorfer reported retinal elements, such as Müller cell plasma membrane, on histopathological sections of ILM specimens after ICG-assisted ILM peeling [93]. In 2005, La Heij and colleagues demonstrated that ILM peeled using ICG may contain remnants of Müller cell footplates, neural cells and ganglion cells [105]. On the other hand, Haritoglou demonstrated that only tiny retinal cellular fragments were observed after conventional ILM peeling without the use of ICG. This suggests a safe cleavage plane between the retinal surface of the ILM and Müller cell endfeet [106]. A possible photosensitizing effect of ICG at the vitreoretinal interface due to the spectral absorption properties of ICG has been reported [94]. This adverse effect may be influenced by the osmolarity, concentration and solvent medium of ICG [107,108].

The emission spectrum of the different light sources used during vitrectomy may be another factor related to the retinal damage after ICG staining. An experimental study has recently demonstrated that the xenon light source induces only slight damage of the innermost retina compared with a halogen light source [109]. Furthermore, other studies have hypothesized that ICG causes direct toxic damage to the retina and the optic nerve [110–112].

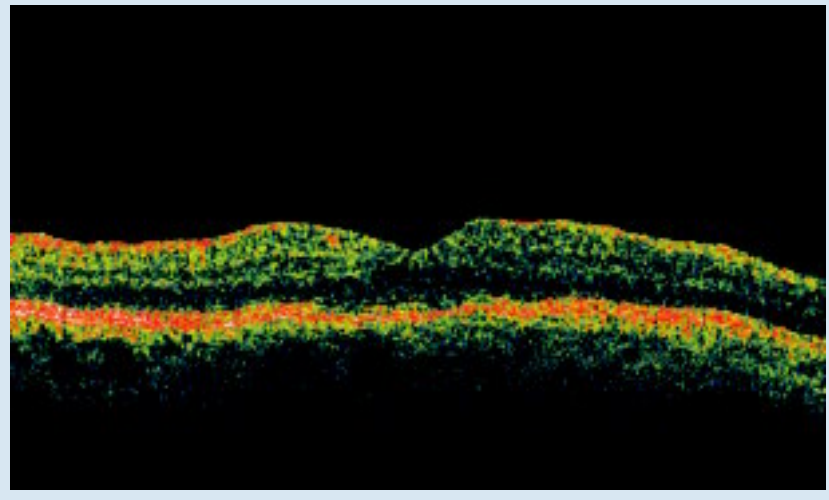

Figure 6. 'Flat–close' aspect of macular hole after surgery.

It has been observed that ICG can persist in the macular region for many months after surgery [113–115]. The presence of ICG on the retina surface and on the optic nerve head could potentially be related to damage to retinal axons, innermost retina layers and optic nerve fibers [111,116,117]. Uemura and colleagues have recently observed the occurrence of peripheral visual field defects after vitrectomy with ICG-assisted ILM peeling [118]. Yamashita and colleagues observed a reduction of retinal nerve fiber layer thickness in patients who developed visual field defects after the use of ICG to stain ILM in macular hole surgery [116]. Although the cause of these defects remains unclear, a potential role of ICG toxicity can be hypothesized. Over the past few years, several studies have reported worse functional results related to the use of ICG [68,119,120].

On the other hand, many authors did not observe any functional impairment with equivalent outcomes with and without the use of ICG; some of them even showed better functional results using the ICG staining of ILM [81,91,121–124]. Nevertheless, it has been observed recently that the multifocal ERG and the photopic negative response of ERGs can both be impaired after the use of ICG. This finding suggests possible clinically undetectable functional damage related to the potential toxicity of ICG [125–127].

Owing to these possible toxic effects, trypan blue has recently been proposed as an alternative ILM staining substance. Li and Perrier showed that the use of trypan blue (0.06%) as a vital stain in vitreoretinal surgery may address some of these issues [128,129]. It directly stains the ERM and, to a lesser extent, the ILM, and is not toxic for RPE cells. Several experimental studies have demonstrated the nontoxicity of trypan blue [128,130,131].

New dyes (patent blue and brilliant blue G) have been proposed recently for intraocular applications, as an alternative in chromovitrectomy. These dyes seem to be nontoxic and first uses have shown no adverse effects [132,133]. Finally, triamcinolone acetonide has also been proposed to visualize both the posterior hyaloid and the ILM during pars plana vitrectomy. This is not properly a stainer but it should be considered an enhancer as the triamcinolone crystals deposit onto the ILM surface, thus facilitating its visibility during the peeling [134].

Adjuvants

This is a broad category of substances proposed to enhance the hole closure rate. Many substances have been used, such as transforming growth factor (TFG)-β_2, thrombin, autologous serum and autologous platelets [135–138]. Many studies have shown that there is no statistically significant VA benefit from the use of these additives for the treatment of macular holes. In a multicenter study, Paques and colleagues observed no effect of autologous platelet concentrate in achieving hole closure [139]. Hoerauf showed that the use of autologous platelet concentrate is associated with high anatomic success rates without aggressive membrane removal, which may cause retinal damage. In most recent series of macular hole surgery, approximately 85% of macular holes were closed after vitrectomy and approximately 60% of patients achieved VA of 20/50 or better while only 20% had a VA of 20/200 or less [139]. Thompson found that the use of these 'biological glues' was associated with an increased risk of ophthalmitis and proliferative vitreoretinopathy [140].

Laser photocoagulation was also suggested as a potent adjuvant therapy that may improve anatomical and visual outcomes of surgery for macular holes [141]. However, this treatment has been completely abandoned. Today, interest in the use of adjuvants is declining as vitrectomy associated with ILM peeling and gas tamponade lead to percentages of hole closure approaching 100% of cases.

Tamponade

The tamponading effect of the gas bubble in the vitreous cavity appears to allow Müller cell processes and glial cells to form a plug within the hole, leading the edges to draw closer together and ultimately closing the hole. The effectiveness of tamponade has been widely discussed, but nowadays it is routinely used for enhancing hole closure. A strictly face-down position is required after tamponade and has to be maintained for a variable period (generally up to 2 weeks) according to different surgeons' preferences.

In a recent study, Krohn demonstrated the crucial importance of the first 3 days of the face-down position in obtaining a higher rate of hole closure [142]. This study has been confirmed by Wickens and Shah who found that macular hole surgery with ILM peeling and a shortened period of face-down positioning achieves excellent anatomical closure and is not associated with significant adverse outcomes [143].

The most common tamponades in this surgery are perfluoropropane (C_3F_8), hexafluoroethane (C_2F_6) and sulfur hexafluoride (SF_6). Different percentages of gas–air mixture are used according to the gas type; lower for C_3F_8, higher for SF_6. Some surgeons use air tamponade alone. Silicone oil has been proposed as tamponade as well, but it requires further surgery for removal. The use of silicone oil as tamponade in macular hole surgery is mainly reserved for patients who may be unable to maintain the postoperative face-down position. This tamponade could also be useful for monocular patients and its use has also been advanced in cases where the macular hole reopens after primary surgery. It is not commonly used, owing to its well-known cataractogenic effect and the need for reoperation to remove the silicone oil.

Complications

Macular hole surgery could be associated with several complications. Cataract formation or progression is the most common postoperative complication. Most patients develop a cataract within 2 years of surgery [144]. Lens opacities can obstruct a clear vision of the retina during vitrectomy so many surgeons prefer to combine pars plana vitrectomy and phacoemulsification for the treatment of macular hole and cataract. Sheidow does not recommended combined cataract and macular hole surgery owing to the risk of developing a cystoid

macular edema [145]. As a result, patients should consider cataract surgery either in conjunction with, or subsequent to, vitrectomy [78,144,146,147].

New peripheral retinal tears are not unusual (5.5–20%) and could be treated at the end of the procedure. They can be connected to sclerotomy-related damage or to the vitreoretinal tractions occurring during the induced posterior hyaloid detachment. Retinal detachment should be expected in 3–25% of cases [148]. An accurate peripheral retinal examination is required at the end of vitrectomy to find retinal tears or holes and to prevent retinal detachment during follow-up. Reopening of the macular hole occurs in approximately 5–20% of cases, depending on the author and surgical technique. Some authors have described instances of the macular hole reopening after cataract surgery [72,149].

Other complications included a transient increase in intraocular pressure, cystoid macular edema, ERM, choroidal neovascular membrane and endophthalmitis [147,150–154]. In addition, the possible presence of RPE alterations (25–30%) and postoperative visual field defects have been described, the latter probably being related to dry air infusion under high pressure during fluid–air exchange [155].

Conclusions

An idiopathic macular hole is the result of tangential and anteroposterior tractions exerted on the foveal retinal tissue. The surgical removal of all these tractions may lead to hole closure in almost all cases with excellent anatomical and functional results. Essential surgical steps during vitrectomy include ILM peeling for stage 3 and 4 holes and gas tamponade with strict face-down positioning for all cases. Adjuvants do not appear to be useful in achieving surgical success. Macular hole size and duration are the main negative prognostic factors for both the anatomical and functional success rates.

Expert commentary & five-year view

There has been significant activity in the past years in the fields of macular hole surgery. However, we need to develop new techniques and instruments to improve visual outcome and diminish surgical time and complications. The peeling of the ILM has been recommended by several authors as an effective means of reducing tangential traction on the retinal surface in order to achieve better anatomical results. These tractions are likely to originate from the contraction of the ILM derived from the cell proliferation on its surface. Moreover, ILM removal avoids secondary membrane formation starting from undetected vitreous cortex remnants on ILM surface after posterior hyaloid removal [30].

It has been demonstrated that ILM peeling should be performed, especially in stage 3 and 4 macular holes, to improve the closure rate [35,58]. Although the use of ICG makes ILM peeling easier, its potential toxicity has been debated. The use of infracyanine, different concentrations, times of light exposure and 5% glucose dilution have been proposed in air- or fluid-filled globes in order to reduce the potential toxicity [10].

In addition, the use of adjuvants, such as TGF-β2, autologus serum and autologous platelets, has been discussed. Nevertheless, as no clear advantages seem to be related to these substances, their use is decreasing more and more [139,156].

The current trend has been towards shorter lasting tamponade and shorter face-down positioning, as suggested by OCT. It has been demonstrated that the crucial period of tamponade for hole closure to occur is within the first 3 days of surgery [157–159].

The use of 25-gauge transconjunctival sutureless vitrectomy has been proposed recently for macular hole surgery. This technique is associated with faster visual recovery and reduced postoperative inflammation. The main concern with the use of this minimally invasive technique in macular hole surgery is possible gas leakage through the sclerotomies. The oblique sclerotomy technique has been proposed recently to avoid gas leakage and to enable tight incisions to be made [160–162].

Finally, the use of new diagnostic instruments, such as ultra-high resolution OCT and microperimetry, promises to lead to a better knowledge of the pathogenesis of macular holes, the timing of surgical repair and the evaluation of anatomic and functional outcomes [163].

Key issues

- Idiopathic macular hole is a full-thickness defect in the central fovea.
- The prevalence ranges from 0.9 to 3.3 per 1000.
- Its pathogenesis involves tangential and anteroposterior vitreofoveal traction according to clinical and optical coherence tomography classifications.
- Standard surgical treatment includes vitrectomy, epiretinal membrane and internal limiting membrane (ILM) peeling for stage 3 and 4 holes and gas tamponade with strict face-down positioning.
- The use of indocyanine green to enhance ILM visibility has been debated owing to possible toxic effects.
- The use of adjuvants to enhance the hole closure rate did not prove successful and nowadays has been almost discontinued.
- The use of 25-gauge transconjunctival sutureless vitrectomy has been proposed recently for macular hole repair.

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