Disorders of the Vitreoretinal Interface

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15.1 Introduction

Vitreoretinal macular diseases are caused by abnormal cell migration and proliferation into or behind the posterior vitreous cortex or by vitreous traction of the macula. Posterior vitreous detachment (PVD) has an important role in the pathogenesis of vitreoretinal macular diseases. Indeed these disorders may arise from anomalous PVD, as the separation of the posterior vitreous cortex from the internal limiting membrane (ILM) does not occur in a clear fashion. Some remnants of the retina may remain attached to the vitreous cortex, as it will be discussed below for some cases of macular hole. In some instances during PVD, a layer of vitreous may remain attached to the macula, explaining some forms of premacular membrane. Moreover, a split with cavitation of the vitreous cortex (vitreoschisis) may be an important factor in macular hole formation [1].

Vitreoretinal interface syndromes may be divided into three categories:

1. *Maculopathy caused by traction due to incomplete posterior vitreous detachment*. A posterior vitreous detachment, starting in peripheral retinal areas, may cause traction on areas with anomalous vitreoretinal adhesion as well as many other retinal diseases, such as retinal distortion, tractional retinal detachment, avulsion or rupture of a vessel, or even a macular hole.
2. *Maculopathy caused by spontaneous contraction of the prefoveal vitreous cortex not involving PVD* (*at least at its initial stages*). This group includes the idiopathic macular hole.
3. *Maculopathy caused by contraction of the residual, adherent vitreous cortex after a posterior vitreous detachment*. After partial or total PVD, a translucent fibrocellular membrane may remain adherent to the internal retinal surface: the contraction of this membrane may cause various degrees of retinal distortion and edema. Such contraction may occur according to tangential centripetal forces, with the formation of cellophane and macular pucker, or centrifugal forces, leading to pseudoholes and full-thickness macular holes [2–4].

Microperimetry with a scanning laser ophthalmoscope (SLO, Rodenstock, Germany), and more recently with MP-1 microperimeter (MP-1, Nidek, Japan), has introduced new and more extensive information in the study of retinal function in a number of macular diseases, mainly of vitreoretinal interface syndromes [5–7].

Microperimeter allows an in-depth evaluation of the relations between anatomical and functional changes of macular-related disorders, through the direct correlation of fundus evaluation to retinal threshold, including retinal fixation parameters [8–16]. This approach allows the

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identification of absolute or relative defects in these areas which are full restricted to the central visual field [8, 16–18].

Because of these characteristics, microperimetry has become a relevant diagnostic method for the diagnosis, prognosis, and the follow-up of macular diseases of surgical interest, such as vitreoretinal interface syndromes [11, 13].

15.2 Microperimetry, Epiretinal Membranes (ERM), and Macular Pseudoholes

Epiretinal membranes (ERM) are fibrocellular membranes visible over the inner retinal surface in the macular area after partial or complete posterior vitreous detachment (PVD) [19]. ERM are considered a maculopathy secondary to the contraction of vitreous cortex still adhering to the retina in the macular area [20, 21]. They can be idiopathic or secondary to trauma, surgery, ocular inflammation, and other causes [22]. Mori et al. documented that secondary ERM are more likely to be characterized by focal retinal adhesion than primary ERM. Primary ERM differ because they are mainly globally adherent [23]. The pathogenesis of idiopathic ERM is not fully clarified, although PVD was observed in about 60–90 % of cases [2, 20, 21, 24–27]. After partial or total PVD, the contraction of a fibrocellular membrane still attached to the internal retinal surface may produce various degrees of retinal distortion as well as macular edema [20, 21, 28].

According to Gass, macular ERM develop as a consequence of tractional stimulation in the course of PVD through two mechanisms: (1) when a PVD with transitory vitreomacular traction occurs allowing migration and proliferation of astrocytes on the anterior internal limiting membrane (ILM) interface and (2) during the course of PVD, where separation occurs at the level of the vitreous cortex (vitreoschisis) with cortex residues and hyalocytes adhering to ILM. The proliferation, fibrous metaplasia, and the contraction of hyalocytes may favor the formation of ERM [29].

Gass classified ERM in three forms: cellophane maculopathy, wrinkling maculopathy, and pucker maculopathy [29]. Witkin et al. initially described two types of ERM using ultrahigh-resolution OCT [30]. The first type was ERM described as a thin highly reflective line anteriorly situated but separated from the retinal nerve fiber layer (RNFL), corresponding to previously reported ERM on OCT. The second type was unusual appearing ERM presenting as a highly reflective line with a moderately reflective material filling the space between the inner border of the ERM and the RNFL. This specific epiretinal tissue, removed during vitrectomy, had a yellow dense appearance and a fluffy consistency and could be classified neither as vitreous cortex nor as regular ERM [30]. Parolini et al., in a recent study concerning lamellar macular hole, redefined the two types of ERM as "tractional" (instead of "normal") and "dense" (instead of "unusual") [31]. The same authors correlated clinical and tomographic features with morphologic and immunohistochemical findings within these two types of ERM.

Transmission electron microscopy of "dense" membranes showed that native vitreous collagen is the major component of observed collagen. Compact fibrous long-spacing collagen (FLSC) was less frequently seen in "tractional" membranes compared with "dense" membranes, but it was surrounded by native vitreous collagen as well. An important difference between "tractional/normal" and "dense/unusual" membranes was shown by the immunolabeling of alpha-smooth muscle actin (α-SMA), the expression of which was more frequently demonstrated in "tractional" ERM than in "dense" ERM. Since the content of α-SMA in epiretinal membranes was demonstrated to be correlated with clinical contractility, the authors postulated that "tractional" membranes possess more potential to generate tractional forces on the retina than "dense" membranes [32].

OCT is certainly the most used diagnostic technique in ERM management. However, microperimetry provides numerous data which can allow to evaluate the degree of evolution of these diseases in the preoperative stage, to define

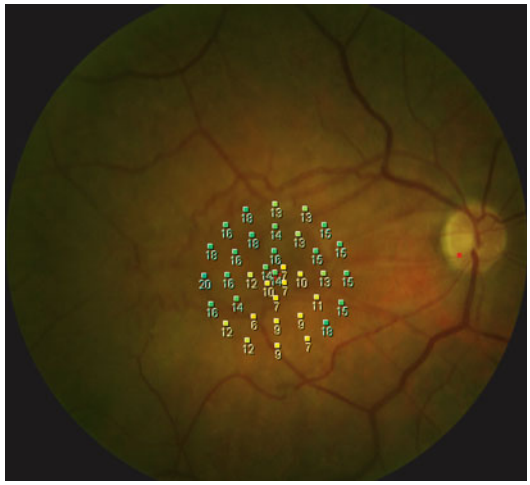

Fig. 15.1 Pucker maculopathy showing reduction in retinal sensitivity

operative timing, and to evaluate functional results in the postoperative stage (follow-up).

As general rule, microperimetry shows a preservation of macular sensitivity in initial stages of vitreoretinal interface diseases like macular cellophane (grade 0 ERM), whereas it highlights a quite evident reduction of macular sensitivity in the most advanced ones (pucker) [8, 28] (Fig. 15.1). Individual symptoms may be absent or may consist in visual loss in the initial or advanced stage, with or without metamorphopsia. Visual loss induced by ERM can be due to the presence of fibrous tissue distorting and covering the macula or to the formation of intraretinal macular edema caused by the leakage of fluids from vessels [2, 20, 26]. These conditions show variable reduction of sensitivity within the central visual field, causing different clinical manifestations.

Clinical observation is the correct approach for the majority of ERM of medium degree, without metamorphopsia, with fairly preserved visual acuity, and lacking functional decrease in retinal sensitivity, examined by microperimetry. When macular pucker causes persistent visual impairment or gradual decrease of visual acuity (associated or not to a reduction of macular retinal sensitivity, documented by microperimetry) or metamorphopsia, surgery needs to be considered. The isolated decrease of macular sensitivity, even in case of preservation of visual acuity, is also indication to surgery [28, 33, 34].

Better baseline retinal sensitivity represents a positive prognostic factor in eyes undergoing surgery and having the same preoperative visual acuity at baseline [8]. Negative predicting factors for postoperative visual prognosis of ERM are cystoid macular edema (CME), tractional retinal detachment, increased thickness of membrane, and long-standing visual dysfunction [35]. Too long observation period associated with the irreversible decay in retinal sensitivity worsens the postoperative prognosis. The presence of absolute scotoma is a fully negative predictive factor [8, 28].

An information of primary interest to any vitreoretinal surgeon is the possibility to identify retinal fixation area inside the macular area/s to protect the first one by intraoperative iatrogenic stress. This area which may not be restricted to fovea is the site of preferred retinal locus (PRL), and this is crucial to leave it unchanged in order to obtain a good postoperative functional result, since often as a consequence of iatrogenic stress, a deep scotoma may develop in areas previously used for reading (PRL) [29, 36–38].

As consequence, microperimetry seems mandatory to evaluate the clinical course of macular retraction syndromes, both before and after surgery, in conjunction with visual acuity assessment and morphological evaluation, provided by OCT.

Cappello et al. studied 41 patients with pucker and 18 patients with macular holes and reported improvement of visual acuity as well as retinal sensitivity and reading ability for up to 12 months after vitrectomy [39]. Instead, Richter-Mueksch et al., studying 19 patients with macular holes and 18 patients with macular pucker undergoing surgery, found that a higher number of patients showed greater improvement of retinal sensitivity than visual acuity. They concluded that visual acuity assessment without information supplied by microperimetry may underestimate functional benefit of surgery [40] (Figs. 15.2 and 15.3).

In eyes with ERM, structural changes in the photoreceptor layer, such as varying degrees of disruption of the photoreceptor inner and outer

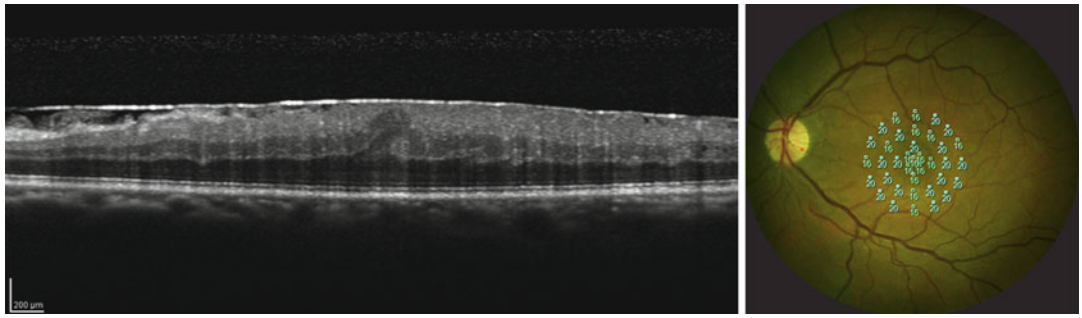

Fig. 15.2 Preoperative spectral domain OCT and microperimetry (MP-1) in a case of pucker maculopathy, with a mild reduction of retinal sensitivity

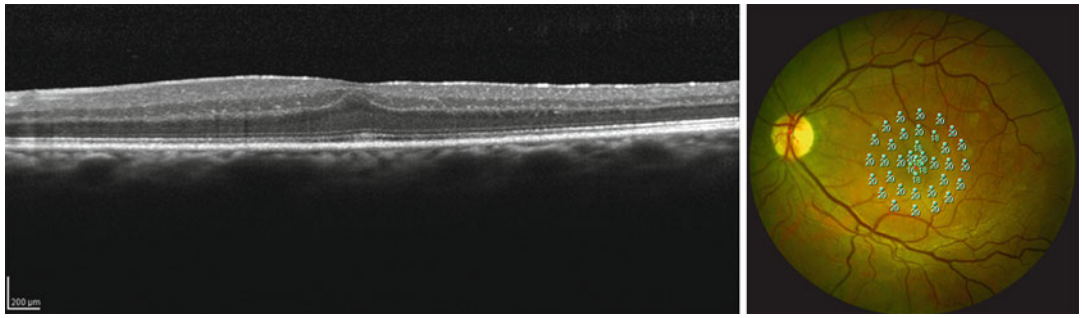

Fig. 15.3 Postoperative spectral domain OCT and microperimetry (MP-1) of the same case in Fig. 15.2 showing normalization of the macular profile with increased retinal sensitivity

segment junction (IS/OS) and increased foveal thickness, have been identified using both time domain and spectral domain OCT [41–44]. However, the studies using time domain or spectral domain OCT have not yet provided sufficiently clear images of individual foveal photoreceptor cells allowing to identify a specific structural abnormality able to explain metamorphopsia in eyes with ERM.

Pilli et al. studied 24 eyes of 19 patients with ERM in order to correlate morphologic changes (both time and spectral domain OCT) with visual function assessed by visual acuity and macular sensitivity. Macular sensitivity was evaluated using microperimetry in 15 eyes of 11 patients. To compare the macular thickness maps with macular sensitivity they overlaid microperimetry data over retinal thickness map, with retinal vessels and foveal center acting as reference points. Only 67 % of the eyes showed some qualitative correlation [45].

These data lead to hypothesize that the functional damage due to ERM could not be related just to the severity of macular edema, as previously suggested, but also to other morphologic changes in the macula. Electrophysiologic studies have shown both outer and inner retinal layer dysfunction associated with vision loss in eyes with idiopathic ERM [46, 47]. A recent case report showed that an adaptive optics flood illumination retinal camera, in association with spectral domain OCT images, can be used to visualize, in eyes with ERM, subtle changes within single retinal layers. Using adaptive optics system, the authors detected fine microstriae among the macular cone that resolved completely after surgical removal of ERM, with a complete visual recovery even if macular morphology on OCT never normalized [48].

This shows that current OCT and other imaging techniques such as scanning laser ophthalmoscopy fail to provide sufficiently detailed images of photoreceptor microstructure, primarily because of aberrations inside ocular optics. These aberrations can be compensated by using imaging systems that incorporate adaptive optics

consisting in a wavefront sensor to measure aberrations on the eye surface and a deformable mirror or a spatial light modulator to compensate for these aberrations. Ooto et al. used their adaptive optics-SLO system to investigate structural abnormalities in individual photoreceptor cells and changes in visual function, such as metamorphopsia and visual acuity, in patients with idiopathic ERM. On adaptive optics-SLO images, 96 % of eyes with ERM show many thin and straight hyporeflective lines in the cone mosaic. These lines, which they described as "microfolds," were not seen in any normal eye. In 83 % of the eyes, microfolds were localized in the fovea. These authors also checked metamorphopsia, using the Amsler grid. In all the eyes with metamorphopsia, microfolds were seen in the fovea. No microfolds were seen in 83 % of the eyes without metamorphopsia. Therefore, microfolds seen on adaptive optics-SLO can be directly associated to metamorphopsia. In 60 % of the eyes in which microfolds were visible in the fovea on adaptive optics-SLO images, the IS/OS appeared intact using spectral domain OCT images [49]. These data highlight how OCT alone is insufficient in the ERM management, but, thanks to microperimetry with future new tools using adaptive optics system, we will be able to have a more complete approach in the preoperative stage, to better define the operative timing and to better evaluate final functional results.

Macular pseudoholes (MPH) are macular lesions that have the appearance of macular holes, but without any loss of foveal tissue due to the centripetal contraction of an epiretinal membrane. Vice versa, lamellar holes (LH) are an abortive process to full-thickness macular hole formation characterized by loss of foveal tissue, but without a full-thickness foveal defect with intact foveal photoreceptors. Haouchine et al. identified in 40 patients with MPH a characteristic macular profile: a steepened foveal pit combined with thickened foveal edges and a small foveal pit diameter, a normal or slightly increased (167 ± 42 μm) central foveal thickness, and mean perifoveal thickness greater than normal [50].

Although OCT studies have added valuable information regarding the definition, pathogenesis, and progression of macular holes, the differential diagnosis between MPH and lamellar macular holes (LMH) is still unclear [51–55]. In particular, when there is residual retinal tissue at the bottom of the foveal defect, as occurs with OCT classification stage 2 according to Azzolini et al., OCT imaging cannot correctly determine whether or not there is loss of retinal tissue [54]. In this case, the diagnosis of MPH or LMH is often a matter of speculation. Bottoni et al. reviewed OCT and autofluorescence images of 50 eyes of 46 patients with stage 2 idiopathic macular hole with residual retinal tissue at the bottom of the foveal defect, classified as MPH or LMH according to OCT profiles established by Haouchine et al. [50, 54, 56]. After OCT image analysis, the corresponding autofluorescence images recorded with a confocal scanning laser ophthalmoscope were evaluated. Considering that foveal autofluorescence usually increases when there is a foveal defect, these authors found that the two groups showed similar foveal autofluorescence, demonstrating a similar loss of foveal tissue. In addition, they also found a lack of correlation between the amount of autofluorescence and the thickness of the residual retinal tissue at the base of both MPH and LMH. The absence of any difference in autofluorescence between the two groups and the lack of correlation between foveal autofluorescence and retinal thickness raises questions about the validity of distinguishing between macular pseudoholes or lamellar macular holes on the basis of OCT data alone.

The application of microperimetry to these disorders gives us a lot of new information to functionally differentiate macular pseudohole, the hole with partial thickness and the impending macular hole from full-thickness macular hole [11]. The full-thickness macular hole always corresponds to an absolute scotoma surrounded by a perilesional ring of relative scotoma, and fixation is located in a retinal area immediately adjacent to the scotoma. In MPH or LMH, we observe the presence of normal or slightly reduced foveal retinal sensitivity (Fig. 15.4). Therefore, the appearance of a central absolute scotoma detectable by means of microperimetry is the sign of a full-thickness macular hole. On the other hand, the

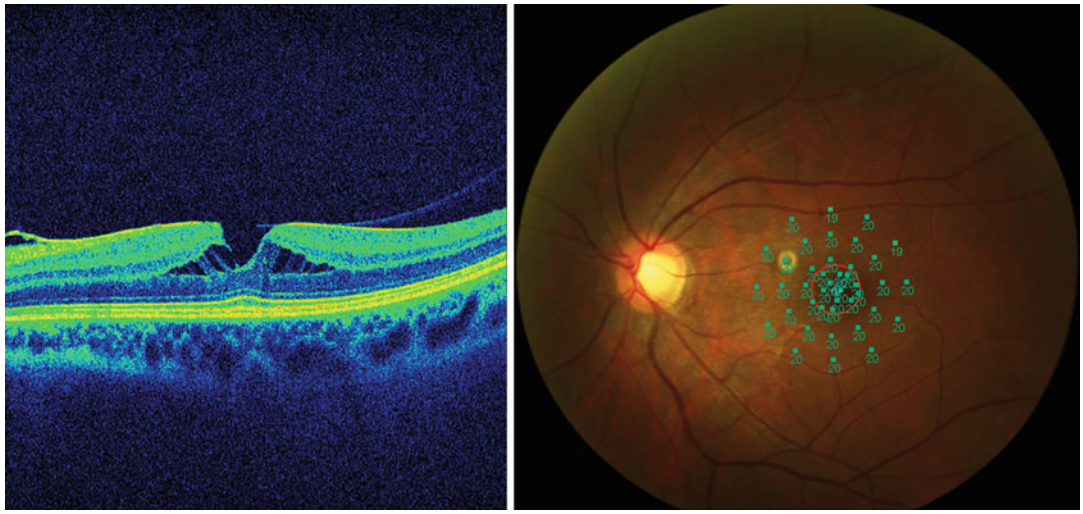

Fig. 15.4 Spectral domain OCT and microperimetry (MP-1) in a case of macular pseudohole with normal retinal sensitivity

presence of a normal or slightly reduced retinal sensitivity in macular pseudoholes and in lamellar holes results from the persistence of more external retinal layers [5, 7, 11, 57, 58]. In some cases a change of the site of fixation (PRL) could occur to better preserve reading function [59].

Macular pseudohole tends to remain stable and visual acuity is usually preserved [60]. Greven et al., in a survey dating back to 1998, observed in macular pseudohole, after 1-year follow-up, the tendency to maintain stable visual acuity [57]. Garcia-Fernandez et al. also recently documented as most idiopathic LMH and MPH do not anatomically progress and do not contribute to a significant loss of visual acuity during follow-up period (12–84 months) [61]. Considering this trend, attention must be paid before proceeding with surgery in patients with MPH.

15.3 Microperimetry and Macular Holes

The term *lamellar macular hole* (LMH) was originally suggested by Gass in 1975, when he identified a macular lesion resulting from cystoid macular edema [62]. Since then, the term lamellar macular hole has been used to describe the abortive process of full-thickness macular hole formation, in which, clinically, the patient has relatively preserved visual acuity, usually 20/40 or better, and the macula contains a stable, round, and well-circumscribed reddish lesion [50, 52, 53, 55, 63–65]. Witkin and colleagues recently proposed distinct OCT criteria, based on qualitative image analysis without measurement of retinal thickness, according to which the diagnosis of lamellar macular hole (LMH) is based on (1) an irregular foveal contour, (2) a break in the inner fovea, (3) a dehiscence of the inner foveal retina from the outer retina, and (4) an absence of a full-thickness foveal defect with intact foveal photoreceptors [30].

As mentioned above, in LMH microperimetry shows normal or slight reduction in retinal sensitivity as a result of the persistence of more external retinal layers [66–68] (Figs. 15.5 and 15.6).

According to Bottoni et al. LMH monitored with spectral domain OCT and fundus autofluorescence seems to be a stable macular condition, and vitrectomy should be considered only when progressive thinning of foveal tissue and/or decrease of visual acuity is documented [69]. Moreover, microperimetry has become a very important method for the diagnosis, prognosis, and the follow-up of these macular disorders of surgical interest [11, 13]. Recently, several authors have stressed the importance of retinal

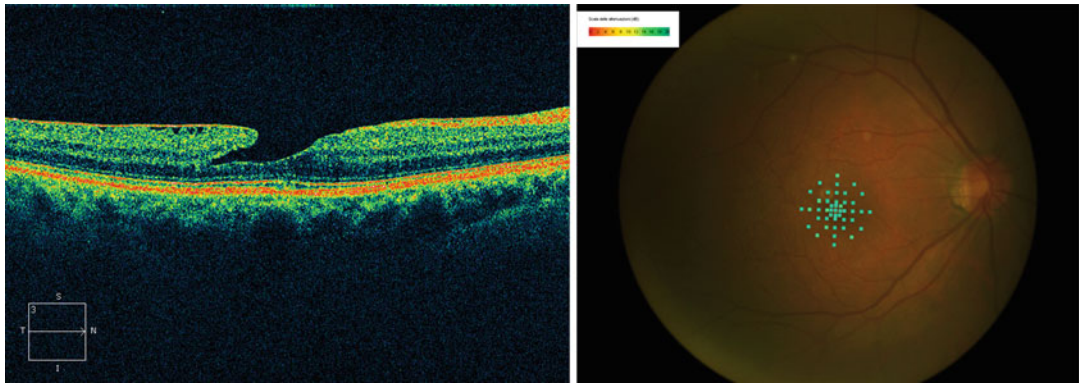

Fig. 15.5 Spectral domain OCT and microperimetry (MP-1) in a case of lamellar macular hole with preserved retinal sensitivity

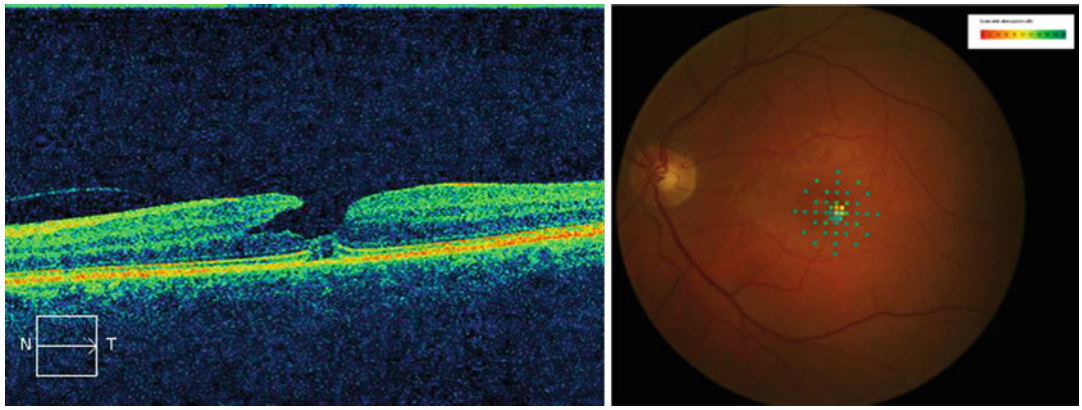

Fig. 15.6 Spectral domain OCT and microperimetry (MP-1) in a case of lamellar macular hole with mild reduction of retinal sensitivity

outer layer integrity for a good visual prognosis. Reibaldi et al. studied with spectral domain OCT and microperimetry 60 eyes of 60 patients with a diagnosis of LMH based on OCT characteristics and divided into three groups according to the integrity of the foveal photoreceptor layer, as proposed by Witkin et al. [30, 70]. The same authors found that integrity of the foveal photoreceptor layer, evaluated by spectral domain OCT, is closely associated with visual acuity and retinal sensitivity [70]. Only central retinal sensitivity was significantly different between the group with preserved inner/outer segment (IS/OS) and external limiting membrane (ELM) defect and the group with only IS/OS defect. This suggests that microperimetry is sensitive enough to identify early morphologic alteration of the photoreceptors layer before visual acuity is impaired in LMH patients. Furthermore, visual acuity was lower in eyes with disruption of ELM suggesting that preservation of ELM is mandatory in the potential preservation of visual acuity. In a personal survey concerning the functional and structural characteristics of LMH, we found that visual acuity and retinal sensitivity are reduced in LMH. Visual acuity, different from what was reported by Chen et al., was found to be unrelated to any of the morphological dimensions of LMH [71, 72]. Vice versa LMH depth was associated with macular sensitivity (Table 15.1). According to our results from 14 to 18 % of the variation of macular sensitivity within, the central 8° and 2° can be explained by changes of LMH depth. The discrepancy between visual acuity and mean

Table 15.1 Correlation between functional (BCVA, MTRS, and MCRS) and morphological LMH parameters obtained by optical coherence tomography

Functional parameters	Morphological parameters	R^2	*p* value
BCVA	Base diameter	0.04	0.3
	Apex diameter	0.002	0.8
	Residual thickness	0.08	0.1
	Depth	0.05	0.2
	Mean nasal perifoveal thickness	0.006	0.62
	Mean temporal perifoveal thickness	0.002	0.76
MTRS	Base diameter	0.007	0.6
	Apex diameter	0.05	0.2
	Residual thickness	0.02	0.3
	Depth	0.18	0.006
	Mean nasal perifoveal thickness	0.056	0.10
	Mean temporal perifoveal thickness	0.09	0.05
MCRS	Base diameter	0.01	0.5
	Apex diameter	0.08	0.08
	Residual thickness	0.04	0.2
	Depth	0.14	0.02
	Mean nasal perifoveal thickness	0.04	0.14
	Mean temporal perifoveal thickness	0.06	0.078

BCVA best corrected visual acuity, *LMH* lamellar macular hole, *MCRS* mean central retinal sensitivity, *MTRS* mean total retinal sensitivity

central retinal sensitivity in relation to the depth could be due to the wider perifoveal area explored by microperimetry that is more likely to involve retinal locations functionally impaired by the presence of LMH and ERM. Moreover, as shown by Reibaldi, the impaired macular function is more pronounced in LMH eyes with outer retinal abnormalities [70].

The major pathogenetic hypotheses concerning the origin of macular holes are trauma, macular cystic degeneration, involutional macular thinning, and posterior vitreoretinal traction in the course of PVD [63, 73–76]. In 1988, the theory sustained by Gass and Johnson who recognized in the tangential traction the main mechanism for the pathogenesis of MH received large consensus [63, 77]. Johnson and others reported the presence of a perifoveal vitreous detachment in 96 % of the cases observed as the main pathogenetic factor in the formation of idiopathic macular holes at the initial stage [78].

In 1995, Gass revised his previous classification of idiopathic macular holes in four stages: stage 1, yellowish spot centered on the fovea; stage 2, yellowish foveal ring; stage 3, central full-thickness fault diameter >400 μm without Weiss ring; and stage 4, full-thickness central deficiency with Weiss ring [64]. The eye affected by macular hole (stage 2 and 3) may report visual loss (mainly for near vision), central scotoma, and metamorphopsia [79]. The Watzke-Allen test (interruption of the cleft of the biomicroscope in line within the hole) may be useful for the diagnosis and prognostic evaluation of full-thickness holes, but false-negative and positive results are quite common [80]. If information supplied by microperimetry about macular puckers and pseudoholes are important, this test becomes crucial in order to understand the natural history and surgical approach to macular holes. As regards microperimetry, a full-thickness macular hole always corresponds to an absolute scotoma surrounded by a perilesional ring of relative scotoma, with a secondary change fixation location in a retinal area immediately adjacent to the scotoma [8, 11, 36, 37] (Fig. 15.7).

The factors driving the site of PRL may be different, but the most important is the maintenance of adequate reading ability. According to our observations, the PRL is located, in most of cases, on the left side and immediately close to the scotoma. Such PRL is located in 75 % of right eyes in supratemporal areas from the fovea and in 85 % of left eyes in supranasal areas from the fovea [8, 59] (Figs. 15.8 and 15.9). This obviously occurs spontaneously in order to maintain reading ability. The possibility offered by microperimetry to exactly determine fixation location and to quantify its stability in patients affected by full-thickness macular hole and candidate for surgery is clinically very relevant in order to identify the retinal sites where manipulations should be avoided or performed in a very delicate way [9, 11, 36, 59]. Microperimetry evaluation is also useful in the early evaluation of functional

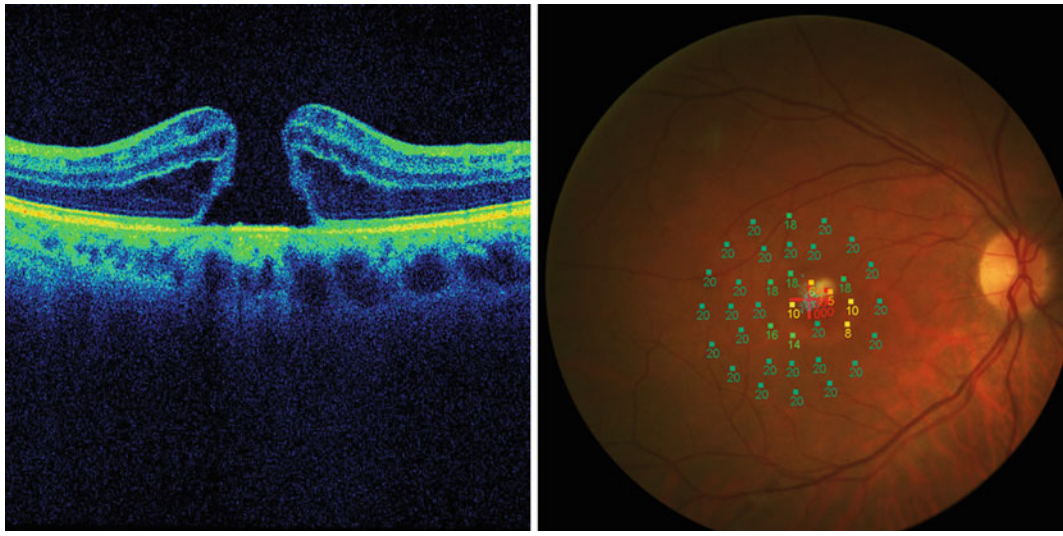

Fig. 15.7 Spectral domain OCT and microperimetry (MP-1) in a case of full-thickness macular hole. The presence of an absolute scotoma is clearly documented

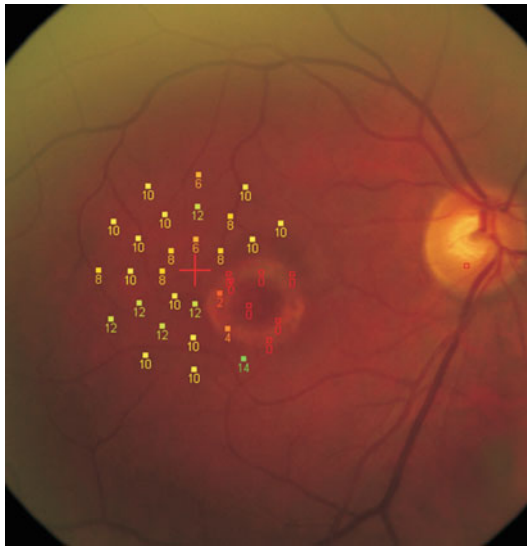

Fig. 15.8 Microperimetry of a macular hole. The PRL is located in the immediate proximity of the scotoma, in a supratemporal area with respect to the fovea (right eye)

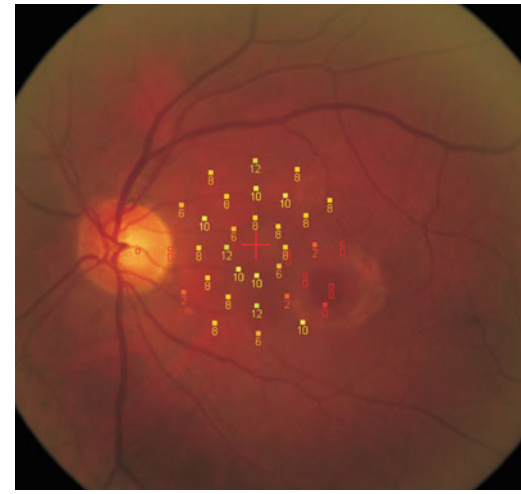

Fig. 15.9 Microperimetry of the other eye of the same patient showing macular hole in which the PRL is situated in a supranasal area with respect to the fovea

damage (absolute or relative scotoma) in the central and perilesional area, in the identification of negative prognostic factors, in establishing the location of the fixation area, and in predicting and monitoring, during the follow-up period, the functional effects of any surgical approach [8, 10, 11, 19, 36, 37, 58, 66, 81].

In a survey carried out in 2001, Amari et al. concluded that a better preoperative retinal (microperimetric) sensitivity is a positive predicting factor for better postoperative functional results [81]. Sjaarda et al., studying 30 eyes affected by full-thickness macular hole, also concluded that better postoperative visual acuity is related to the smaller size of the scotoma and to better perilesional sensitivity observed in preoperative phase, as well as

to the duration of the symptoms [13]. Tsujikawa et al. evaluated (with the old SLO microperimeter) 106 eyes with clinical diagnosis of full-thickness macular hole, macular pseudohole, and impending macular holes in order to qualify the relationship between scotoma characteristics (absolute or relative) and clinical data. In the 57 eyes having full-thickness macular hole, absolute scotomas were always found, while in the 49 eyes diagnosed with early pseudohole and impending macular hole, just relative scotoma but no absolute scotoma were found. They concluded that the presence of an absolute scotoma measured by means of microperimetry is able to detect the presence of full-thickness macular hole with 100 % sensitivity and specificity, while a relative scotoma displays the same level of sensitivity and lower specificity (98 %) [11]. More recently, Sun et al. studied 39 surgically closed idiopathic macular holes with microperimetry and spectral domain OCT (12 months of follow-up) in order to identify a method to foresee the long-term vision recovery of idiopathic macular hole [82]. They also studied the IS/OS junction. Eyes presenting continuous IS/OS junction at the 12-month follow-up were classified as group 1, and those presenting disrupted IS/OS junction were classified as group 2. These authors found that in all 39 patients preoperative mean retinal sensitivity and fixation location percentage were significantly correlated with the 12-month postoperative visual acuity. These results showed a strong relationship between microperimetry data with the visual prognosis, confirming that the value of microperimetry results in quantitatively predicting visual prognosis, just before surgery. Quantitative analysis indicates that the value of preoperative mean retinal sensitivity which prognosticates postoperative 0.50 logMAR visual acuity (Snellen equivalent 20/63) was approximately 12.56 dB. Any 1 dB increment compared to baseline value represents 0.034 logMAR improvement 12 months after surgery. Similarly, the value of preoperative fixation location percentage which predicts postoperative 0.50 logMAR visual acuity was around 29.1 %. Any 10 % increase compared to baseline induces visual acuity increase 0.058 logMAR unit. Evaluating fixation quality score, eyes with stable fixation before surgery had better visual recovery than those with relatively unstable ($p=0.001$) or unstable ($p=0.003$) fixation. It is interesting to note that preoperative measurements were found to be correlated with the recovery of IS/OS junction: Group 1 patients had better preoperative mean retinal sensitivity ($p=0.003$), better fixation location percentage ($p=0.008$), and higher fixation quality scores than did group 2 patients. Therefore, microperimetry results are useful in quantitatively predicting long-term visual prognosis in eyes with macular hole. Moreover, in this study, neither preoperative visual acuity nor macular hole size was predictive of postoperative visual acuity. Instead, visual prognosis after successful hole closure depends mainly on macular sensitivity, quantified by microperimetry.

Furthermore, evaluating the data of surgery in patients with macular holes Richter-Mueksch et al. found that postoperative visual acuity assessment, without the information supplied by microperimetry, may underestimate functional benefit of surgery [40]. To better understand the reason why microperimetry is so useful to predict final visual prognosis, it must be considered that with the development of the hole, photoreceptors might undergo centrifugal retraction toward the surrounding retina: the hole margin [64, 80]. Subsequently, patients' fixation will gradually shift to the hole margin and paracentral fixation will develop [59]. After tangential traction is removed by vitrectomy, the hole margin moves centripetally back to form a new foveola, along with the centripetal shifting of fixation toward the foveola [59, 63, 83]. This indicates that the hole margin might also affect the postoperative visual function. For this reason the analysis of the hole margin is central in predicting visual prognosis and microperimetry specifically gives fundamental information concerning the macular function, mainly regarding the function of the hole margins. As reported above for MH eyes, the typical microperimetric layouts show a central absolute scotoma representing the full-thickness retinal defect and a pericentral ring-shaped area of decreased sensitivity (relative scotoma) reflecting the dysfunction of hole margins. In addition, fixation stability and fixation location percentage evaluate the capability of gaze control and gaze

selection, respectively. They also evaluate the function of the hole margins where PRL is commonly localized [59, 84]. Another reason for the predictive role of microperimetry data is that they are correlated with IS/OS junction. Two factors determine IS/OS restoration: the diameter of IS/OS defect and the status of photoreceptors along the hole margin. As microperimetry measures both the IS/OS defect (the central absolute scotoma) and the photoreceptors (the pericentral relative scotoma) and fixation exam may be useful to check hole margins, they are effective in predicting the prognosis of IS/OS junction. About IS/OS defect, Chen et al. recently reported that central macular sensitivity, which reflects retinal function just over the area of the MH, correlates with IS/OS defects more closely and for longer duration than mean macular sensitivity [85]. Moreover, they found that IS/OS defect size is a good predictor value for postoperative macular sensitivity and that IS/OS defect area is more correlated to macular sensitivity than IS/OS defect diameter.

Many of the previous studies found a significant correlation between the extent of the foveal IS/OS defect and postsurgical visual outcome. However, this was not confirmed by other studies [86, 87]. Pilli et al. did not find a correlation between the size of the foveal IS/OS defect and visual outcome among the eyes that underwent ILM peeling [88].

Any surgical indication is determined according to anatomic characteristics of the lesion, symptoms, and microperimetry data, as well as to duration, stabilization, or vice versa progression of the retinal changes. As a general rule, when microperimetry indicates decrease in retinal sensitivity, even in case of apparent stability of visual acuity, long-term experience suggests to undergo surgery, in order to avoid any further retinal damage [66, 89]. On the other hand, attention must be paid to choose surgery, particularly vitrectomy with ILM peeling. In fact, some authors recently published data concerning the effects of ILM peeling for MH surgery. They showed that mean retinal sensitivity decreases after ILM peeling with increased rate of microscotomas, detected by microperimetry [90]. Moreover, sometimes spontaneous resolution of the hole (5–12 %) develops with anatomic closure and increase in central retinal sensitivity [67, 68, 91, 92]. Beutel et al. documented that there is no proof that using dyes may be better than ILM removal without staining [93]. The cause of the development of microscotomas after ILM peeling is still under investigation. The main hypotheses are direct trauma caused by the forceps when gripping the ILM and a toxic effect of dyes (indocyanine green is the only dye that has been demonstrated to have a toxic effect on ganglion cells). But these two hypotheses seem unlikely. Retinal sensitivity deterioration and microscotomas might be due to alterations involving mainly Müller cells, whose end feet are closely connected to the ILM and may be affected by ILM peeling [94]. Deterioration of other cells is also possible, either directly, due to the stretching caused by the peeling, or indirectly, due to Müller cell deterioration.

Conclusions

In conclusion, we highlight the importance of accurate retinal sensitivity checking, by means of microperimetry, in current clinical practice. Microperimetry allows us to better understand several aspects of the clinical behavior of many macular diseases, in particular those related to the vitreoretinal interface changes.

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