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Macular Hole: From Diagnosis to Therapy

Lead Guest Editor: Claudio Azzolini

Guest Editors: Thomas Friberg, Steve Charles, Akihiro Ohira, and Francisco J. Rodriguez

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Contents

Macular Hole: From Diagnosis to Therapy
Claudio Azzolini
Editorial (2 pages), Article ID 1473763, Volume 2020 (2020)

Microscopic Observation of Proliferative Membranes in Fibrocontractive Retinal Disorders
Rino Frisina, Francesco Tessarolo, Ivan Marchesoni, Federico Piccoli, Emiliana Bonomi, Patrizio Caciagli, Edoardo Midena, and Giandomenico Nollo
Research Article (10 pages), Article ID 9647947, Volume 2019 (2019)

The Role of Single-Layered Flap in Temporal Inverted Internal Limiting Membrane Flap Technique for Macular Holes: Pros and Cons
Yasuyuki Takai, Masaki Tanito, Kazunobu Sugihara, and Akihiro Ohira
Clinical Study (8 pages), Article ID 5737083, Volume 2019 (2019)

Inverted ILM Flap for the Treatment of Myopic Macular Holes: Healing Processes and Morphological Changes in Comparison with Complete ILM Removal
Maurizio Mete, Alessandro Alfano, Emilia Maggio, Massimo Guerriero, and Grazia Pertile
Research Article (8 pages), Article ID 1314989, Volume 2019 (2019)

Idiopathic Macular Hole: A Comprehensive Review of Its Pathogenesis and of Advanced Studies on Metamorphopsia
Qi Chen and Zao-xia Liu
Review Article (8 pages), Article ID 7294952, Volume 2019 (2019)

Comparison of Anatomical and Visual Outcomes between Idiopathic and Myopic Macular Holes Using the Internal Limiting Membrane or Inverted Internal Limiting Membrane Flap Technique
Federico Peralta Iturburu, Claudia Garcia-Arumi, Maria Bové Alvarez, and Jose Garcia-Arumi
Research Article (7 pages), Article ID 6723824, Volume 2019 (2019)

Vertical and Horizontal M-Charts and Microperimetry for Assessment of the Visual Function in Patients after Vitrectomy with ILM Peeling due to Stage 4 Macular Hole
Dominika Wrzesińska, Katarzyna Nowomiejska, Dominika Nowakowska, Agnieszka Brzozowska, Teresio Avitabile, Michele Reibaldi, Robert Rejdak, and Mario Toro
Clinical Study (6 pages), Article ID 4975973, Volume 2019 (2019)

Morphology of Peeled Internal Limiting Membrane in Macular Hole Surgery
Mun Y. Faria, David C. Sousa, Bruna C. Almeida, Andreia L. Pinto, and Nuno P. Ferreira
Clinical Study (6 pages), Article ID 1345683, Volume 2019 (2019)

Pathogenesis and Management of Macular Hole: Review of Current Advances
Guzel Bikbova, Toshiyuki Oshitari, Takayuki Baba, Shuichi Yamamoto, and Keisuke Mori
Review Article (7 pages), Article ID 3467381, Volume 2019 (2019)

Comparative Study between Pars Plana Vitrectomy with Internal Limiting Membrane Peel and Pars Plana Vitrectomy with Internal Limiting Membrane Flap Technique for Management of Traumatic Full Thickness Macular Holes
Hammouda Hamdy Ghoraba, Mahmoud Leila, Hashem Ghoraba, Mohamed Amin Heikal, and Emad Eldin Mohamed Elgemai
Research Article (10 pages), Article ID 1959082, Volume 2019 (2019)

Lamellar Macular Holes: The Role of Microperimetry in Functional Assessment
Simone Donati, Paola Della Valle, Elias Premi, Marco Mazzola, Laura Lo Presti, and Claudio Azzolini
Research Article (8 pages), Article ID 9035837, Volume 2019 (2019)

Inner Retinal Layer and Outer Retinal Layer Findings after Macular Hole Surgery Assessed by means of Optical Coherence Tomography
Maria Vittoria Cicinelli, Alessandro Marchese, Francesco Bandello, and Michele Coppola
Review Article (11 pages), Article ID 3821479, Volume 2019 (2019)

Multifocal Electroretinography in Assessment of Macular Function after Internal Limiting Membrane Peeling in Macular Hole Surgery
M. Y. Faria, D. C. Sousa, S. Mano, R. Marques, N. P. Ferreira, and A. Fonseca
Research Article (7 pages), Article ID 1939523, Volume 2019 (2019)

Traumatic Macular Hole: Diagnosis, Natural History, and Management
Greg Budoff, Neelakshi Bhagat, and Marco A. Zarbin
Review Article (7 pages), Article ID 5837832, Volume 2019 (2019)

Characteristics and Risk Factors for Spontaneous Closure of Idiopathic Full-Thickness Macular Hole
Xida Liang and Wu Liu
Review Article (6 pages), Article ID 4793764, Volume 2019 (2019)

Sulfur Hexafluoride (SF6) versus Perfluoropropane (C3F8) in the Intraoperative Management of Macular Holes: A Systematic Review and Meta-Analysis
Idan Hecht, Michael Mimouni, Eytan Z. Blumenthal, and Yoreh Barak
Review Article (7 pages), Article ID 1820850, Volume 2019 (2019)

Macular Hole in Myopic Eyes: A Narrative Review of the Current Surgical Techniques
Chiara De Giacinto, Marco R. Pastore, Gabriella Cirigliano, and Daniele Tognetto
Review Article (10 pages), Article ID 3230695, Volume 2019 (2019)

An Internal Limiting Membrane Plug and Gas Endotamponade for Recurrent or Persistent Macular Hole
Fabrizio Giansanti, Ruggero Tartaro, Tomaso Caporossi, Daniela Bacherini, Alfonso Savastano, Francesco Barca, and Stanislao Rizzo
Clinical Study (6 pages), Article ID 6051724, Volume 2019 (2019)

Contents

Perspectives of Autologous Mesenchymal Stem-Cell Transplantation in Macular Hole Surgery: A Review of Current Findings
Raffaele Nuzzi and Federico Tridico
Review Article (8 pages), Article ID 3162478, Volume 2019 (2019)

Fundus Autofluorescence in Lamellar Macular Holes and Pseudoholes: A Review
Ferdinando Bottoni
Review Article (7 pages), Article ID 4948212, Volume 2019 (2019)

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Editorial

Macular Hole: From Diagnosis to Therapy

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Macular holes have attracted significant interest over the last few years due to the progress made in imaging and pharmacological and surgical therapies. The tractional interaction between foveal tissue and the vitreous has been extensively studied to identify vectorial forces, as well as the role of different cell subtypes in the pathogenesis and repair of retinal alterations [1]. At the same time, vitreoretinal surgery devices and instruments have advanced, increasing the safety, effectiveness, and repeatability of the surgical maneuvers [2].

This special issue encompasses cutting-edge research and review articles focusing on new perspectives on macular hole diagnosis and therapy. It includes novel research articles and reviews describing new insights into different types of macular holes, new instrumental OCT imaging, histopathology evaluations, and therapy. The main topics of the included manuscripts are summarized below to better classify and underline each topic.

In *idiopathic macular hole*, it is demonstrated that the dynamic forces caused by mobile posterior cortical vitreous with fluid currents exist already at early stages of macular hole development. A macular hole with a diameter of less than 250 μm may have more chance of closing spontaneously. In addition, these spontaneously closed macular holes possess some distinctive OCT characteristics. Metamorphopsia is significantly related to the deterioration of visual quality of life and can be used as an independent index to evaluate visual function before and after surgery. A systematic literature search was conducted to identify and review studies comparing SF_6 to C_3F_8 gases as a tamponade agent in the intraoperative management of macular holes, with no evidence found to support C_3F_8 gas as the tamponade agent of choice for macular hole surgery. Finally, several clinical studies evaluated different approaches applying the inverted flap technique for recurrent and large idiopathic as well as myopic macular holes [3–7].

In *lamellar macular hole*, a clinical study which evaluated the two different subtypes of LMH found peculiar functional aspects due to their morphological features; tractional lamellar macular holes revealed higher visual acuity and retinal sensibility due to the relative preservation of the outer retinal layers compared to degenerative lamellar macular holes. Another clinical study demonstrated that an accurate diagnosis of full thickness macular hole, lamellar macular hole, and myopic macular hole is important to determine the most appropriate surgical treatment of these lesions. Different options may be selected according to the OCT and fundus autofluorescence imaging findings [8].

In *traumatic macular hole*, a review on its etiology and management discusses about the role of tangential and anteroposterior vitreomacular traction. This macular hole may also result from foveal photoreceptor atrophy following commotio retinae. Spontaneous closure can occur; however, vitrectomy combined to the induction of posterior vitreous detachment and inner limiting membrane (ILM) peeling (with or without an ILM flap to cover the macular hole) is associated with anatomic success rates of up to 100%. Another research paper evaluated the outcome of surgery with and without an ILM flap, underlining the benefits of the ILM flap technique.

In *myopic macular hole*, an interesting review on surgical techniques underlines how myopic eyes still remain a challenge for vitreoretinal surgeons. Several and complex tractional mechanisms are implicated in the development of macular holes. The introduction of significant innovations for the treatment of myopic macular holes has allowed vitreoretinal surgeons to perform safe and effective surgery in these complicated eyes. Another research article on ILM

peeling and inverted flap, which investigated the microstructural changes after successful myopic macular hole surgery, underlines that the inverted ILM flap technique did not affect the myopic macular hole healing processes compared to complete ILM removal [6]. Thus, the presence of the ILM plug did not interfere with the restoration of both external limiting membrane and ellipsoid zone, which correlated with functional recovery [5, 9].

In a research article on *the histology of epiretinal proliferative tissue*, the authors investigated the morphological characteristics and cell composition of various types of surgically excised proliferative membranes and internal limiting membranes. Cell components such as myofibroblasts, macrophages, and polymorphonuclear cells were recognized as the expression of cell migration and differentiation that induced an inflammatory process and a fibroproliferative repair process. The detection of pigments in specific types of epiretinal membrane suggested that retinal pigment epithelium cells might have a role in the development of these vitreoretinal disorders.

In a review evaluating *new experimental approaches in autologous cell transplantation as a new therapy*, the application of mesenchymal stem cells (MSC) described an adjuvant treatment for refractory and late-stage macular holes to be considered a promising direction. The combination of pars plana vitrectomy and MSC injections or MSC exosome application appears feasible, but the evidence regarding their safety needs to be expanded. Long-term clinical trials featuring control groups are still required in order to compare the efficacy of MSC applications with pars plana vitrectomy and other adjuvant techniques.

In summary, this special issue offers an overview of different types of macular holes, as well as providing new findings that may offer directions for new research in this important field.

Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this Special Issue.

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Claudio Azzolini

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Research Article

Microscopic Observation of Proliferative Membranes in Fibrocontractive Retinal Disorders

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Proliferative membranes of fibrocontractive retinal disorders are extensively studied from the morphological and evolutive point of view. Despite this, little is known of their cellular composition. In this study, the authors investigated the morphological characteristics and cell composition of various types of surgically excised proliferative membranes and internal limiting membranes (ILMs), in order to provide new data supporting or challenging the pathogenic theories proposed until now. Sixty-nine specimens from 64 eyes of 64 consecutive patients were collected at surgery and subjected to a multilevel analysis by means of optical and electron microscopy. Membrane samples were semiquantitatively evaluated for the amount and distribution of cell nuclei and pigment. Immunohistochemical staining was performed with antibodies to alpha smooth muscle actin and CD68. Data were analyzed after grouping according to the following tissue types: ILM (20 specimens), epiretinal membrane (ERM) (22 specimens), ILM + ERM (20 specimens), and proliferative vitreoretinopathy (PVR) (7 specimens). The cell components found in the ERM specimens, like myofibroblasts, macrophages, and polymorphonuclear cells, were recognized as the expression of cell migration and differentiation that induced an inflammatory process and a fibroproliferative repair process. The detection of pigments in specific types of ERM, like those associated with lamellar macular hole (LMH) or secondary to retinal detachment (RD), diabetes, and PVR, suggested that retinal pigment epithelium (RPE) cells may have a role in the development of these vitreoretinal disorders. The reduction of the ERM cellularity with the patient's age supports the hypothesis that ERM evolves in time up to a fibrous tissue formation.

1. Introduction

Epiretinal membrane (ERM) formation is a well-known disease entity that can be idiopathic or secondary [1]. Idiopathic ERM (iERM) occurrence, causing a macular pucker (MP), usually is an age-related process [2, 3]. Secondary ERM can be due to a variety of retinal disorders including proliferative diabetic retinopathy (PDR), central retinal vein occlusion (CRVO), uveitis, proliferative vitreoretinopathy (PVR), retinal detachment (RD) surgery, trauma, macular hole (MH), retinitis pigmentosa, myopia, Terson syndrome, Eales disease, and Coats disease [4–9]. ERM can be distinguished in three types based on their cell composition and closely associated with the underlying disease: conventional or tractional ERM (C ERM) commonly associated with MP; atypical ERM (A ERM) associated with full thickness macular hole (FTMH) and lamellar macular hole (LMH), also known by various names: "dense," "epiretinal proliferation," "degenerative ERM" [10–14]; and neovascular ERM associated with metabolic or vascular retinal diseases. Although the pathogenic mechanisms underlying the different vitreoretinal disorders have been widely studied, the types of cells involved in these processes are not yet fully understood. Studies on excised tissue obtained during surgical treatment of different

fibrocontractive retinal disorders have demonstrated that the number and types of cells found varies considerably. A wide variety of cell types such as glial cells (including microglia, Müller cells, and fibrous astrocytes), cells from the retinal pigment epithelium (RPE), blood-borne immune cells (macrophages, lymphocytes, and neutrophils), fibrocytes, and myofibrocytes were identified [15–19]. The aim of this study is to evaluate the microscopic characteristics of vitreoretinal membranes surgically excised for treating different types of fibrocontractive retinal disorders. In this study, the authors investigated the microscopic characteristics and cell composition of a range of surgically excised proliferative membranes and internal limiting membranes, in order to provide new data supporting or challenging the pathogenic theories proposed until now.

2. Materials and Methods

Intraocular membrane tissue specimens were collected during a consecutive series of vitreoretinal surgeries for the treatment of patients affected by different fibrocontractive retinal disorders. All interventions were performed by the same surgeon (R. F.) at the Department of Ophthalmology in Rovereto, Trento, Italy, between January 2016 and September 2017. Ethics Committee approved this study. At the time of surgery, each participant was informed about the benefits and potential risks of the treatment. Informed consent was obtained from all participants. Collected data included age (years), gender (male/female), eye (right/left), underlying pathology causing surgical treatment, and best corrected visual acuity (BCVA) measured in Snellen and converted to the logarithm of the minimum angle of resolution (logMAR). Specimens were catalogued according to the type of excised tissue according to surgeon indication: internal limiting membrane (ILM), ERM, ERM + ILM when both membranes were excised simultaneously, and PVR. In addition, ERM specimens were grouped according to the recently proposed tomographic criteria for the definition of ERM associated with LMH: conventional ERM (C ERM) and atypical ERM (A ERM) [12, 14]. C ERM was characterized by a highly reflective line adjacent and overlying the retinal nerve fibre layer, and A ERM was characterized by a thick membrane delimited by a highly reflective line and filled by the moderately reflective material [12, 14].

2.1. Preparation of Specimens. Excised tissues were deposited in between silicon foam foils, inserted in a histology cassette, labelled, and immediately fixed in 10% buffered formalin for a minimum of 24 hours before proceeding with the microscopic preparation and analysis. Fixed membranes were prepared for several different microscopic analyses with both optical microscopy (OM) and scanning electron microscopy (SEM). All samples were washed twice in distilled water and whole mounted on glass slides for a first analysis of the unstained sample by OM. A set of representative images were obtained under an optical microscope (DLIM, Leica, Germany) equipped with a high-resolution CCD colour camera (DFC420, Leica, Germany), with a magnification ranging from 40 to 630 times. Colour images of unstained samples were obtained under transmitted light and phase contrast to evaluate tissue morphology and presence of pigment. Samples were then unmounted and stained with haematoxylin (5 mins in Mayer's haematoxylin) before being mounted again and observed for the presence of nucleated cells. A new set of representative colour images was obtained under the same optical microscope at similar magnification.

2.1.1. Cellularity Score. OM imaging after staining with haematoxylin allowed to evaluate the presence or absence of cellular nuclei and their distribution (homogeneous or inhomogeneous) across the tissue sample. The amount of cell nuclei (cellularity) was scored semiquantitatively from 0 to 3 according to the following semiquantitative criteria: 0 (absence of nuclei), 1 (≤50 nucleated cells per mm^2), 2 (50–100 nucleated cells per mm^2), and 3 (≥100 nucleated cells per mm^2) (Figure 1). The cellularity scores were assigned after joined review and evaluation of the collected images by three investigators (F. P., E. B., and F. T.).

2.1.2. Pigmentation Score. The amount of intratissue pigment (pigmentation) was evaluated according to a semiquantitative score ranging from 0 to 3 according to the following definitions: 0 (absence of pigment), 1 (granulated pigment in <50% of the tissue sample), and 2 (granulated pigment present across the whole sample or yellow/light brown pigmented diffused areas in less than 50% of the sample) to 3 (brown pigmented areas diffused in the whole sample) (Figure 2). Similar to the cellularity, pigmentation scores were assigned after joined review and evaluation of the collected images by three investigators (F. P., E. B., and F. T.).

2.1.3. Morphological Study. A subset of seventeen samples also underwent ultrastructural characterization by scanning electron microscopy (SEM). SEM analysis was conducted by using both environmental (E-SEM) and conventional high-vacuum (HV-SEM) operative modes. The E-SEM mode allowed imaging of fully hydrated samples without the need for conductive coating, thus informing the native status of the sample. HV-SEM was applied to obtain high-resolution images of micromorphologies at the membrane surface. Differently from E-SEM, HV-SEM required complete dehydration and metallic coating for guaranteeing sample conductivity. HV-SEM preparation was obtained by dehydration in ascending hydroalcoholic solutions, drying in a laminar flow cabinet, mounting on a sample holder, and sputter-coating with gold. SEM imaging in both E-SEM and HV-SEM modes was performed with a XL30 ESEM FEG scanning electron microscope (FEI, Philips, The Netherlands). High-resolution micrographs were obtained with a magnification ranging from 500 to 2000 time in the E-SEM mode and up to 10000 times in the HV-SEM mode. Details of surface morphology and any eventual cell-like structure were imaged and stored.

2.1.4. Immunohistochemical Study. In a second different subset of seventeen samples, immunohistochemical staining

0 1 2 3

Cellularity score	0	1	2	3	Total number of samples
Membrane subgroup	Number (%)	Number (%)	Number (%)	Number (%)	
C ERM	0 (0.0)	2 (14.3)	7 (50.0)	5 (35.7)	14
A ERM	0 (0.0)	1 (33.3)	1 (33.3)	1 (33.3)	3
ILM	0 (0.0)	5 (41.7)	6 (50.0)	1 (8.3)	12
ERM + ILM	0 (0.0)	4 (26.6)	10 (66.7)	1 (6.7)	15
PVR	0 (0.0)	0 (0)	4 (57.1)	3 (42.9)	7

C ERM: conventional epiretinal membrane
A ERM: atypical epiretinal membrane
ILM: internal limiting membrane
ERM + ILM: epiretinal membrane + internal limiting membrane
PVR: proliferative vitreoretinopathy

Figure 1: Cellularity score. Representative images for each score criteria are reported on top of the image. Cellularity score results according to each membrane specimen subgroup are summarized in the table.

0 1 2 3

Pigmentation score	0	1	2	3	Total number of samples
Membrane subgroup	Number (%)	Number (%)	Number (%)	Number (%)	
C ERM	8 (61.5)	1 (7.7)	1 (7.7)	3 (23.1)	13
A ERM	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	2
ILM	11 (68.7)	3 (18.7)	2 (12.5)	0 (0.0)	16
ERM + ILM	16 (88.8)	1 (5.6)	1 (5.6)	0 (0.0)	18
PVR	0 (0.0)	0 (0.0)	0 (0.0)	7 (100.0)	7

C ERM: conventional epiretinal membrane
A ERM: atypical epiretinal membrane
ILM: internal limiting membrane
ERM + ILM: epiretinal membrane + internal limiting membrane
PVR: proliferative vitreoretinopathy

Figure 2: Pigmentation score. Representative images for each score criteria are reported on top of the image. Pigmentation score results according to each membrane specimen subgroup are summarized in the table.

was performed with antibody to alpha smooth muscle actin (alpha-SMA) to target intracellular actin filaments or CD68 for macrophages/microglia.

2.1.5. Statistical Analysis. SPSS Software Version 22.0 (IBM Corporation, New York, NY) for the statistical analysis was used. Descriptive statistics are absolute and relative

frequencies for qualitative variables (gender, eye, types of specimens, and pathology) and means, standard deviation, and median for quantitative variables (age and BCVA). The logistic regression model was used to evaluate the association between subgroup of specimens and cellularity score. The Shapiro–Wilk test was used for evaluating normal distribution of values. The ANOVA test and post hoc correction for multiple comparison (Bonferroni correction) were used for evaluating correlation between age vs. cellularity score and age vs. pigmentation score. Fisher's test was used to evaluate the association between pigmentation score and specimen subgroups.

3. Results

Sixty-nine specimens were collected from 64 eyes: 36 (56.25%) right and 28 (43.75%) left; of 64 consecutive patients, 28 (43.75%) were males and 36 (56.25%) were females. Patients mean age was 72.35 ± 7.06 (range from 58 to 88 years). Preoperative mean BCVA was 0.7 ± 0.2 (20/100 letters), from 0.2 to 1 logMAR. Data were analysed after grouping according to the following tissue types: ILM (20 specimens), ERM (22 specimens), ILM + ERM (20 specimens), and PVR (7 specimens). Tables 1 and 2 summarize demographic data of specimen subgroups and the surgically treated retinal diseases. The comparison among the subgroups of specimens did not highlight any statistical difference in age, gender, and eye of patients.

3.1. Cellularity. The cellularity score was evaluated on 51 out of the 69 collected specimens. C ERM and PVR subgroups were characterized by higher cellularity scores than ILMs. Microscopic study showed that 85.7% of specimens of the C ERM subgroup and 100% of the PVR subgroup were in the score 2-3. ERM + ILM and ILM subgroups were characterized by low-intermediate cellularity; specifically, 93.3% of ERM + ILM specimens and 91.7% of ILM specimens were characterized by a cellularity score 1-2 (Figure 1). The A ERM subgroup resulted homogenously distributed over the full range of cellularity scores. Logistic regression analysis showed a significant association between the type of specimen and cellularity; specifically, a specimen with cellularity score 3 has a 15 time higher probability of being ERM or PVR than ILM (odd ratio 15.0, 95% CI: 1.2–185.2). The relationship between the three cellularity score subgroups of ERM and patient's age was evaluated. The normality test highlighted normal distribution of patients' age for each cellularity score subgroup (score 1, $P = 0.99$; score 2, $P = 0.90$; and score 3, $P = 0.68$). Significant differences in patients' age between the three subgroups of the cellularity score ($P = 0.124$) was found: specifically, between subgroups of patients having their samples scored 1 and 2 ($P = 0.0127$) and 1 and 3 ($P = 0.0304$). No significant difference in patient's age was found between subgroups of patients having their membrane samples scored 2 and 3. In a summary, the analysis showed that the cellularity was related to the age; the younger the patient, the higher the cellularity score. Figure 3 shows a boxplot of patient's age grouped by the cellularity score assigned to their membranes.

3.1.1. Pigmentation. The pigmentation score was evaluated on 56 (79.7%) out of the 69 collected specimens (Figure 2). C ERM (8 specimens), C ERM + ILM (16 specimens), and ILM (11 specimens) associated with idiopathic MP were characterized by the absence (score 0) of pigmentation (Figures 4(a)–4(c)). The 2 specimens of A ERM associated with LMH were characterized by some degree (score 2) of pigmentation (Figures 4(d) and 4(e)). ERM (2 specimens), ERM + ILM (2 specimen), and ILM (5 specimens) associated with diabetic retinopathy were characterized by low-moderate (score 1 or 2) degree of pigmentation (Figures 4(d), 4(f)–4(h)). ERM secondary to RD repair under PDMS (1 case), ERM associated with RD and FTMH (1 case), and ERM associated with retinoschisis (1 case) were characterized by high degree of pigmentation (score 3) (Figures 4(i)–4(k)). PVR specimens were characterized by high degree of pigmentation (score 3) (Figures 4(l)–4(n)). We evaluated the association between pigmentation score and type of specimens, and a significant association between PVR specimen and pigmentation score 3 was found (Fisher's test $P < 0.0001$). The relationship between the three pigmentation score subgroups and patient's age was evaluated. Normality test highlighted normal age distribution for the four scores subgroups (score 0, $P = 0.12$; score 1, $P = 0.71$; score 2, $P = 0.13$; and score 3, $P = 0.22$). Significant difference on patients' age among the 4 subgroups of the pigmentation score ($P = 0.016$) was found. The younger the patient, the greater the pigmentation score (Figure 5). Specifically, a significant difference between subgroup score 0 and score 3 was found ($P = 0.045$).

3.1.2. Scanning Electron Microscopy: Morphological Findings. ILM specimens were characterized on two different surfaces: vitreous side and retinal side. The retinal side appeared to be characterized by folds and cells corresponding to nerve fibres and retinal vessels. The vitreous side appeared smoother and more regular at the E-SEM investigation (Figures 6(a) and 6(b)). High-resolution magnification in the HV-SEM mode allowed to highlight the morphological characteristics of the cells adherent to the surgically excised membranes. On the ILM specimens, rounded cells with a hole/indentation along the course of the collagen fibres and a micromorphology compatible with the endfeet of the Müller cells were found at the HV-SEM investigation (Figures 7(a) and 7(b)). On the ERM specimens and typically on the C ERM associated with LMH, rounded cells with short and long microvilli (possibly myofibroblast-like cells) were found (Figure 7(c)). On the PVR specimens and A ERM associated with LMH, SEM showed elongated cells with irregular villi, with a morphology compatible with that of the RPE cells at different transdifferentiation stages (Figures 7(d) and 7(e)). Globular arrangements of microgranules with irregularly shaped granules (Figure 7(f)) were also identified, possibly related to the presence of pigmented aggregates.

3.1.3. Immunohistochemical Study. Positive staining to the macrophages marker (CD68) was found in few specimens of ERM (Figures 8(a) and 8(b)). Positive staining to anti-alpha-

Table 1: Membrane specimen subgroup and patient's demographic data.

Specimen subgroup	Total number of collected specimens Number (%)	Patient age Years, mean ± SD (range)	Gender Male/femalenumber	Eye Right/left number
ILM	20 (28.9)	72.45 ± 5.78 (64–80)	9/11	11/9
ERM	22 (31.8)	73.22 ± 6.78 (58–88)	7/15	12/10
ERM + ILM	20 (28.9)	74.42 ± 7.01 (61–85)	10/10	12/8
PVR	7 (10.4)	63.57 ± 6 (53–70)	4/3	4/3

A ERM, atypical epiretinal membrane; C ERM, conventional epiretinal membrane; ILM, internal limiting membrane; PVR, proliferative vitreoretinopathy.

Table 2: Underlying eye pathology according to the membrane subgroup.

Pathology	ILM	ERM		ERM + ILM	PVR
		C ERM	A ERM		
	Number	Number	Number	Number	Number
Idiopathic MP	12	11	—	18	—
ERM secondary to CRVO	4	—	—	—	—
RD under PDMS	—	1	—	—	5
RD secondary to PVR	2	—	—	1	1
DR	1	6	—	—	—
RD secondary to FTMH	—	1	—	—	1
CNV	—	1	—	—	—
LMH	1	—	2	1 (A ERM + ILM)	—

A ERM, atypical epiretinal membrane; C ERM, conventional epiretinal membrane; ILM, internal limiting membrane; PVR, proliferative vitreoretinopathy; MP, macular pucker; CRVO, central retinal venous occlusion; RD, retinal detachment; PDMS, polydimethylsiloxane; DR, diabetic retinopathy; FTMH, full thickness macular hole; CNV, choroidal neovascularization; LMH, lamellar macular hole.

Figure 3: Cellularity score boxplot vs patient's age. P value is indicated for subgroups showing statistical difference.

SMA was found in specimens of iERM and in a specimen of C ERM associated with LMH in which myofibroblast-like cells were identified. On the contrary, low-positive staining or no staining to anti-α-SMA was found in a specimen of A ERM associated with LMH (Figures 8(c) and 8(d)).

4. Discussion

4.1. Internal Limiting Membrane. The origin of the adhesion forces between the retina and the vitreous body is not yet fully understood, and little is known about the role of the ILM in maintaining this adhesion. Some studies report the presence of collagen fibres that from the vitreous cortex fit into the ILM's structure [20–24]. Vitreous cortex-ILM adhesion is age-related, and it thickens in the course of life, affecting the ability of Müller cells to maintain vitreomacular adhesion [15, 16, 25]. It has been recognized that SEM imaging allows to identify the ILM and ERM structures [26]. In the current paper, the authors found that ILM specimens were characterized by some degree of cellularity. ILMs were expected to be acellular, constituted by fibronectin, type IV collagen, and laminin, but the presence of cell components was detected by both OM and SEM on the surgically excised samples collected in this study. High-magnification SEM observation allowed to morphologically evaluate these cell components that appeared as vesicular structures adherent to the retinal surface of the ILM. These observations are confirmed by the experiments on the donor eyes published by Sebag [20], who associated these cell components to the endfeet of Müller cells by using transmission electron microscopy. However, there are important limitations in understanding how and why the proliferative vitreoretinal membranes develop. Currently, limited knowledge of the cells that are really involved in these processes is available. Some authors have used immunohistochemical staining using the glial fibrillary acidic protein (GFAP), a specific marker of Müller cells, detecting a strong positivity and concluding that Müller cells can proliferate and activate, thus becoming the main cells responsible for the formation of these membranes [18, 27–30]. Conversely, other studies have shown that GFAP positive cells also respond to markers of hyalocytes and macrophages, thus raising doubts about colocalization issues and the possibility of a reliable identification of these cells based on the sole immunohistochemistry. According to the latest available evidence, the most reliable hypothesis is that the hyalocytes are able to differentiate into macrophages and can phagocyte the endfeet of the Müller cells acquiring their specific markers [5, 15, 27, 28]. SEM images collected in this study allowed to highlight that

Figure 4: Pigmentation score of different specimens analysed in the study. Membranes from a macular pucker with pigmentation score 0: conventional epiretinal membrane (a); conventional epiretinal membrane removed with the internal limiting membrane (ERM + ILM) (b); internal limiting membrane (ILM) (c). (d, e) Atypical epiretinal membrane (A ERM) associated with lamellar macular hole (LMH) with pigmentation score 1. Specimens of membranes from diabetic retinopathy (DR) with score 1-2: ERM from DR (f); ERM + ILM secondary to DR (g); ILM from ERM secondary to DR with pigmentation score 1 (h). Specimens with pigmentation score 3: ERM from RD with FTMH pigmentation score 3 (i); ERM from RD after PPV + PDMS with pigmentation score 3 (j); ERM associated with retinoschisis with pigmentation score 3 (k). (l–n) Proliferative vitreoretinopathy (PVR) specimens with pigmentation score 3.

Figure 5: Pigmentation score boxplot vs patient's age. P value is indicated for subgroups showing statistical difference.

Figure 6: Scanning electron microscopy (SEM) of the vitreous (a) and retinal (b) surface of the internal limiting membrane (ILM). E-SEM mode, original magnification 2000 times.

Figure 7: Morphological characteristics of adherent cells to the membranes surgically excised. (a, b) Rounded cells with a hole/indentation along the course of the collagen fibres, from the internal limiting membrane (ILM) specimen. (c) Rounded cells with short and long microvilli, from the epiretinal membrane (ERM) specimen. Elongated cells with regular (d) and irregular (e) villi from the proliferative vitreoretinopathy (PVR) specimen, corresponding to retinal pigmented epithelium (RPE) cells. (f) Globular arrangements of irregularly shaped granules and of microgranules with ovoid and needle shape. Scanning electron microscopy, HV-SEM mode, original magnifications ranging from 4000 to 10000 times.

Figure 8: Immunohistochemical staining for CD68 or anti-α-SMA. (a, b) CD68 staining of epiretinal membrane (ERM) specimens. Macrophages appear as brownish agglomerate. (c, d) Anti-α-SMA staining of epiretinal membranes (ERM) associated with lamellar macular hole (LMH). Conventional ERM (c) appears brown due to the positive stain compared to the atypical epiretinal membrane (A ERM) (d). OCT images are given in the insets.

the positivity of GFAP does not necessarily indicate the presence of Müller cells but could also be due to the presence of Müller cells endfeet alone, having no role in the development of the membrane. In addition to these considerations, the risk of iatrogenic damage of Müller cells due to the surgical removal of ILM should be considered as previously reported by other authors [25, 27]. ERM is a type of glial scar tissue produced in an attempt to protect the neuroretina from further damage by pathogenic factors present in the vitreous and injured RPE. ERM is composed of the extracellular matrix (collagen, laminin, tenascin, fibronectin, vitronectin, and thrombospondin) and other types of not fully identified cells. In this study, the cellularity of ERM specimens resulted to be inversely correlated with patient age. The higher the ERM cellularity, the lower the patient's age. This result could be influenced by the onset of the pathology, unknown to the authors, and it could express a transition from an initial cell proliferation phase to a phase of fibrotic evolution in the older age. The cells were not homogeneously distributed, but they appeared in clusters in different areas of the ERM specimens. In some cases, the authors identified the presence of macrophages into the cellular clusters. This finding could be an expression of an early stage of the evolution of ERM, an expression of active cell proliferation and cell repair, before the ERM evolution changes from early cellular composition to a late paucicellular and more fibrotic composition. Other studies confirmed that ERM was composed of glial cells and macrophages in the early stage, and then, over time, cellular component disappeared and ERM was eventually constituted by the extracellular matrix [31]. The pigmentation tissue score

Figure 9: Polymorphonuclear leukocytes in the proliferative diabetic retinopathy (PDR) specimens, characterized by the nucleus usually lobed into three segments (white arrows). Original magnification: 640x.

of ERM specimens in this study was variable. Tissue pigmentation was markedly higher in ERM specimens secondary to RD and in PVR. It was moderately present in A ERM with LMH and ERM associated with RDP. Pigmentation was completely absent in iERM. The pigmentation of ERM secondary to RD and PVR can be explained by the fact that RPE cells migrate through a retinal tear and reach the vitreoretinal interface [32–35]. The pigmentation of A ERM could be due to a migration of RPE cells through the intraretinal defect of the LMH. This hypothesis is supported by the study of Son et al. that observed positive pan-cytokeratin staining in the ERM associated with LMH [35]. Pan-cytokeratin is a monoclonal antibody of all human epithelia. RPE is the only

layer of the retina that presents positivity to pan-cytokeratin staining. In a specimen of A ERM, a RPE-like cell was found, characterized by irregular microvilli, and no myofibroblasts were detected by anti-alpha-SMA. The authors suppose that RPE cells could migrate toward the vitreoretinal interface and transform in fibroblasts. This can explain the pigmentation and the absence of tractional properties of A ERM. There are similar theories that explain the presence of pigment into the ERM: other cells could undergo transformation into RPE cells, or RPE cells could migrate through occult breaks into the inner retina or through the inner retina stimulated by a defect of the ILM [28–38]. The reason for the presence of pigmentation in the ERM secondary to RDP remains still unclear. The pathological changes occurring during RDP are not fully understood yet. Haematoxylin staining allowed to identify the polymorphonuclear leukocytes in ERM associated with PDR because of the specific multinucleated morphology (Figure 9). Elevated systemic neutrophil count is associated with the presence and severity of DR as well as diabetes. This result indicates that systemic subclinical inflammation is related with DR, and neutrophil-mediated inflammation may play an important role in the pathogenesis of DR [39]. Regarding the staining with the alpha-SMA antibody in the C ERM and A ERM, the positivity was more frequently demonstrated in C ERM than in A ERM. Alpha-SMA is an intracellular actin presumed to be essential for extracellular matrix contraction [15]. The content of alpha-SMA in ERM was demonstrated to be correlated with clinical contractility [40, 41]. Cells of glial origin were shown to lose their typical GFAP expression by undergoing myofibroblast-like transdifferentiation, thereby losing the intermediate filament GFAP with coincident gains of SMA immunoreactivity [39].

5. Conclusions

OM and SEM proved to be informative tools for studying cell morphology of retinal membranes and represents a valid support for a deeper understanding of the available immunohistochemical study results. Indeed, the mutation in the expression of markers due to the transdifferentiation of the cells involved in these processes and the colocalisation of different markers do not allow the sole immunohistochemistry to give reliable information on the origin and identity of the cells involved in vitreoretinal proliferative processes. In this study, the authors highlighted a reduction of the cellularity of ERM related to the patients' age supporting the evolution of the ERM from a cell proliferative phase to a fibrous transformation. The detection of myofibroblasts demonstrates their main role in the development of ERM. The detection of pigment and RPE cells in A ERM specimens associated with LMH and in the secondary ERM specimens supports the hypothesis of a pathogenic role of RPE cells. Further studies integrating morphological investigation with immunohistochemistry on larger numbers of samples should be developed to unravel the type and role of different cells into the setting and development of vitreoretinal pathologies associated with proliferative membranes.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Rino Frisina and Francesco Tessarolo contributed equally to the work.

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Clinical Study

The Role of Single-Layered Flap in Temporal Inverted Internal Limiting Membrane Flap Technique for Macular Holes: Pros and Cons

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Purpose. To assess the safety and effectiveness of the single-layered inverted internal limiting membrane (ILM) flap technique for treating chronic, large, or highly myopic macular holes (MHs). *Methods*. The medical records of 20 eyes of 20 consecutive Japanese patients with large MHs ($n = 6$) (minimal diameter, >400 μm), chronic MHs ($n = 2$) (symptom duration, >24 months), MHs in high myopia ($n = 11$) (axial length, >26 mm), and MHs in a patient unable to maintain prone positioning postoperatively ($n = 1$) were reviewed retrospectively. All patients underwent 25-gauge pars plana vitrectomy and the temporal inverted ILM flap technique. A semicircular ILM notch was made temporally two disc diameters from the MH using a 25-gauge knife, and the ILM was peeled temporally to create a semicircular ILM flap using a 25-gauge forceps. The single-layered ILM flap was inverted in a nasal direction to cover the MH. When an epiretinal membrane (ERM) was present, it was peeled before the ILM flap was inverted. *Results*. The MHs closed successfully in all (100%) eyes postoperatively. In the MHs associated with an ERM, after hole closure, gradual foveal deformation occurred in both the area from which the ILM was not peeled and the ILM flap inverted side. *Conclusions*. The single-layered inverted ILM flap technique, a simple surgery to treat MHs, provides scaffolding for retinal gliosis and may facilitate bridge formation between the walls of the MH under the flap. Considering the 100% success rate of MH closure, this technique seems to be effective and safe for treating chronic, large, or highly myopic MHs and MHs in patients unable to maintain postoperative prone positioning. In the MHs associated with ERMs, gradual foveal deformation was observed after ERM peeling. Further studies are needed to minimize surgical complications and understand the mechanism of this technique. This trial is registered with UMIN000035091.

1. Introduction

Internal limiting membrane (ILM) peeling has become a standard procedure in the surgical treatment of idiopathic macular holes (MHs) in recent years. The satisfactory results with single-procedure MH closure rates of 50% to 88% for large MHs exceeding 400 μm [1, 2], 40% to 83% for chronic MHs [3, 4], 63% to 90% for MHs with high myopia [5–7], and 60% to 100% without postoperative face-down positioning [8, 9] have been reported; however, surgical closure of these MHs remains challenging. Michalewska et al. first reported the inverted ILM flap technique as a new surgical strategy that was performed successfully to treat large MHs and MHs in highly myopic eyes for which a poor single-procedure MH closure rate was expected [10, 11]. The temporal inverted ILM flap technique, a modified form in which the ILM is peeled from the temporal side of the fovea only was performed to treat large MHs. This procedure recently was reported to decrease the risk of surgical trauma and dissociated optic nerve fiber layer appearance with the same anatomic and functional results compared with the original inverted ILM flap technique [12]. We reported a case of a successfully performed temporal inverted ILM flap technique combined with intraocular sulfur hexafluoride (SF_6) gas tamponade to treat a patient with a MH who could not maintain postoperative prone positioning [13]. Recently,

various modifications of the original inverted ILM flap technique have been reported, e.g., covering or filling the MH with the ILM flap and inverting from all sides or less. Because the same anatomic and functional results have been achieved compared with the ILM peeling technique [14], the indications for the inverted ILM flap technique have been widening. However, some complications related to the inverted ILM flap technique have been reported, including worse postoperative visual acuity (VA) than the preoperative level [15, 16], expansion of retinal pigment epithelial (RPE) atrophy [17], and prevention of MH closure and/or functional recovery of the outer retina by the inverted ILM flap [18]. The current study reports the effectiveness of the single-layered inverted ILM flap technique performed to treat chronic, large, or highly myopic MHs and MHs in patients unable to maintain postoperative prone positioning and foveal deformation that have not been reported previously.

2. Methods

The current study was part of the study protocol "Epidemiologic Study of Ocular Morphology and Function," that the Ethics Committee of Shimane University Hospital approved. The study adhered to the tenets of the Declaration of Helsinki. The ethics committee waived the requirement for informed consent regarding the use of patients' medical record data in accordance with the regulations of the Japanese Guidelines for Epidemiologic Study issued by the Japanese Government, and instead, the protocol was posted at the outpatient clinic to inform participants of the study.

We retrospectively reviewed the medical records of 20 consecutive Japanese patients with large MHs (minimal diameter, >400 μm), chronic MHs (symptomatic duration, >24 months), MHs in high myopia (axial length, >26 mm), and MHs in patients who could not maintain postoperative prone positioning after vitrectomy. These patients underwent the temporal inverted ILM flap technique with gas tamponade with SF_6 at Shimane University Hospital from March 2014 to February 2018. All patients underwent thorough ophthalmologic examinations that included measurement of the best-corrected VA (BCVA) using a Landolt decimal acuity chart, the results of which were converted to the logarithm of the minimal angle of resolution VA; axial length measured by AL-3000 ultrasound biometry (Tomey, Nagoya, Japan); indirect ophthalmoscopy; and three-dimensional optical coherence tomography (OCT)-2000 spectral-domain OCT (Topcon, Tokyo, Japan). The three-dimensional scan had a resolution of 512×128 and a scan length of 6.0×6.0 mm. The MH measurements included determination of the maximal diameter, defined as the longest distance of the MH base, and the minimal diameter, defined as the shortest distance between the MH edges. Patients with a history of retinal surgery, retinal detachment, diabetic retinopathy, retinal vascular occlusion, uveitis, and trauma were excluded.

2.1. Surgical Method. A 25-gauge pars plana vitrectomy combined with the temporal inverted ILM flap technique which have previously been described [13] was performed. Core vitrectomy and ILM staining with a 0.125% solution of indocyanine green were performed. If an epiretinal membrane (ERM) was present, it was peeled. Then, a 25-gauge MVR knife (MANI, Utsunomiya, Japan) was used to create a semicircular ILM notch two disc diameters from the MH in a temporal area, and the 25-gauge end grasping forceps (Alcon, Fort Worth, TX, USA) was used to peel ILM in the temporal macula to create a semicircular ILM flap and to invert the single-layered ILM flap in a nasal direction to fully cover the MH (Figures 1(a) and 1(b)). Next, a low-molecular-weight viscoelastic material (Viscoat, Alcon) was placed on the inverted flap to stabilize it (Figure 1(c)). After fluid-air exchange, 20% SF_6 gas was injected into the vitreous cavity. Phacoemulsification with intraocular lens implantation was performed simultaneously in all phakic patients because of the development of cataracts that hinder visual improvement after vitrectomy. The patients, except for a patient who could not maintain postoperative prone positioning, were advised to maintain a face-down position for 2 days postoperatively. Y. T. performed all surgeries. The surgical techniques are shown in Supplementary video (available here).

2.2. Statistical Analysis. Statistical analyses were performed using JMP version 11 software (JMP Statistical Discovery, Cary, NC, USA). The difference between the preoperative and postoperative BCVAs was compared using the Wilcoxon signed-rank test.

3. Results

Twenty eyes of 20 patients (12 women, 8 men; mean age, 66.8 ± 9.9 years; range, 48–82 years) were included in this study. Six patients had large MHs, two patients had chronic MHs, 11 patients had MHs with high myopia, and one patient could not maintain postoperative prone positioning. The characteristics of the 20 eyes are summarized in Table 1.

ERMs were present with the MHs in four (20%) eyes. Phacoemulsification with intraocular lens implantation was performed in all 14 phakic eyes. The postoperative follow-up time ranged from 6 to 36 months.

Regarding anatomic outcomes, the MH closure rate was 100% after the first surgery (Table 2). In two cases with chronic MHs, two cases with MHs in high myopia, and one case of a patient with a MH who could not maintain postoperative prone positioning, MH closure as a result of only the single-layered inverted ILM flap, referred to as "flap closure," was observed at two weeks after surgery (Figure 2(c)). A representative case of a 55-year-old woman with a MH in high myopia is shown in Figure 2.

During the first surgery, no complications, e.g., peripheral retinal tear and detachment, occurred in any case. Spectral-domain OCT showed postoperative restoration of the external limiting membrane (ELM) and ellipsoid zone (EZ) in 10 (50%) and 7 (35%) eyes at the final visit, respectively. The restoration of the EZ was always preceded by that of the ELM. In chronic MH cases, restoration of those

Figure 1: Schematic drawing of the temporal ILM flap technique. After a semicircular ILM notch (blue arrow) is created two disc diameters from the temporal edge of MH (red circle), the ILM is peeled and inverted in the nasal direction to fully cover the MH (blue dashed arrow) (a). An indocyanine green-stained temporal ILM flap created at the temporal macular is inverted in the nasal direction (arrow) to cover the MH (arrowhead) (b). A cross-sectional drawing of the temporal ILM flap technique. The temporal ILM flap (arrow) is inverted toward the nasal retina to cover the MH and is stabilized with a low-molecular-weight viscoelastic material (arrowhead) (c). Figure 1(a) is reproduced from Takai et al. [13] (under the Creative Commons Attribution License/public domain).

two structures did not occur (Table 3). In a 66-year-old man with a MH associated with an ERM in high myopia, gradual foveal deformation occurred, i.e., elevation and displacement toward the optic disc on the nasal side of the fovea after MH closure (Figure 3). The foveal deformation stopped after postoperative week 12, and the decimal BCVA was maintained at 1.0, which negated the need for additional surgery. Except for this case, no serial complications developed.

The functional improvements are summarized in Table 2. In general, a significant postoperative improvement in the BCVA was seen in eyes with large MHs and MHs in high myopia ($p < 0.05$, Wilcoxon signed-rank test). The BCVA also improved in eyes with chronic MHs and the eye of the patient who could not maintain postoperative prone positioning, although the difference did not reach significance because of the small sample size.

4. Discussion

ILM peeling is the main surgical approach for treating MH. However, for large MHs, chronic MHs, MHs in high myopia, and MHs in patients unable to maintain postoperative prone positioning, the literature has reported relatively low closure rates [1–6, 9]. Michalewska et al. first reported the effectiveness of the inverted ILM flap technique for treating large idiopathic MHs and myopic MHs [10, 11]. In a comparative study of the ILM peeling technique versus the inverted ILM flap technique for treating full-thickness large MHs, the MH closure rate and VA improvement rate after the inverted ILM flap technique were significantly higher than those following ILM peeling [14]. The current findings agreed with the effectiveness of the inverted ILM flap technique for treating chronic, large, or highly myopic MHs and MHs in patients unable to maintain postoperative prone positioning. In the original inverted ILM flap technique, after circumferential ILM peeling, the trimmed ILM flaps using remnant ILM left at the MH edge were inverted and placed over the surface of the MH from all sides. A difficulty in the original technique was that the ILM flap detached in 14% (7 of 50 eyes) of cases during fluid-air exchange [10]. Recently, using the perfluoro-*n*-octane or ophthalmic viscosurgical devices effectively prevented retroversion and detachment of the inverted ILM flap until the fluid-air exchange was completed [19, 20]. However, in the current temporal inverted ILM flap technique, one large (two-disc-diameter) single-layered ILM flap with a wider connection to the retina was inverted to cover the MH and did not detach spontaneously or easily flip back with injection of the viscoelastic material during fluid-air exchange. The higher reliability and simplicity of this procedure may have contributed to the good closure rates of MHs in the current study.

Table 1: Patient baseline clinical characteristics.

Factors	All cases (n = 20)
Mean age ± SD, years	66.8 ± 9.9
Range	48–82
Gender (male/female)	8/12
Mean BCVA ± SD, logMAR	0.73 ± 0.35
MH type no. (%)	
Large MH	6 (30%)
Chronic MH	2 (10%)
MH in high myopia	11 (55%)
MH in patient unable to maintain postoperative prone positioning	1 (5%)
Mean MH diameter (±SD)	
Large MH (n = 6)	
Minimal diameter, μm	480 ± 74
Maximal diameter, μm	858 ± 324
Chronic MH (n = 2)	
Minimal diameter, μm	845 ± 43
Maximal diameter, μm	1470 ± 309
MH in high myopia (n = 11)	
Minimal diameter, μm	278 ± 154
Maximal diameter, μm	897 ± 740
MH in patient unable to maintain postoperative prone positioning (n = 1)	
Minimal diameter, μm	405
Maximal diameter, μm	867
Lens status (phakic: IOL)	14 : 6

SD, standard deviation; IOL, intraocular lens, pseudophakia.

Table 2: Surgical outcomes.

Characteristic	Before surgery	Final visit	p^*
MH closure (%)			
Large MH (n = 6)		6 (100%)	
Chronic MH (n = 2)		2 (100%)	
MH in high myopia (n = 11)		11 (100%)	
MH in patient unable to maintain postoperative prone positioning (n = 1)		1 (100%)	
Mean BCVA ± SD, logMAR (improved ≥0.3 logMAR, %)			
Large MH	0.59 ± 0.27	0.26 ± 0.31 (83.3%)	0.0313
Chronic MH	0.91 ± 0.55	0.55 ± 0.21 (50%)	0.2500
MH in high myopia	0.77 ± 0.38	0.35 ± 0.37 (81.8%)	0.0005
MH in patient unable to maintain postoperative prone positioning	0.82	0.52 (100%)	0.5000

*Wilcoxon signed-rank test.

The mechanism of the original method of MH closure is that the filled ILM flap in the MH space might stimulate the proliferation of glial cells that fill MHs. This packing method resulted in the multilayered membrane observed in the OCT [10] images obtained postoperatively, and the small trimmed ILM flaps that migrated to the bottom of the MH were obstacles to natural MH closure and/or functional recovery of the outer retina [18]. However, in the temporal inverted ILM flap technique, one large single-layered ILM flap provides a more regular structure for glial cell proliferation and does not reach the bottom of the MH or become an obstacle to natural MH closure. In addition, several studies have shown that complete restoration of both the ELM and EZ is prevented when the glial cell proliferation affects all retinal layers. The restoration of those structures has been reported to predict good postoperative visual outcomes; thus, the manner in which MHs close, i.e., whether glial cell proliferation affects some or all retinal layers, may be an important factor that predicts the visual prognosis, because partial proliferation would not affect the restoration of the outer retinal band [21–23].

The exact mechanism of the MH closure using the temporal inverted ILM flap technique is not precisely understood. Serial OCT observations of a current case (Figure 2) showed the course of the early structural recovery of the macula after MH surgery with the temporal inverted ILM flap technique. In the current cases, MH closure started from the proliferation of the hyperreflective tissue in the MH space just beneath the covered ILM flap (Figure 2(d)), and retinal layer remodeling then was induced gradually (Figure 2(e)). With the current technique, any glial cells adhering to the outer side of ILM flap cannot migrate to the fully sealed MH space; thus, glial cells inside the MH wall were speculated to proliferate. However, adherent cells proliferate and migrate minimally without a basement membrane, e.g., lens epithelial cells cannot migrate into an open area after posterior capsulotomy; thus, the mechanism of the temporal inverted ILM flap technique may be that a scaffold is provided as a basement membrane for MH wall gliosis without providing a possible obstacle to the bottom of the MH by inverting a single-layered ILM flap. This mechanism may explain the results of a study by Kase et al. [24], which suggested that glial cells placed on the hole may produce intermediate filaments and provoke tissue remodeling within the MH, and Shiode et al. [25] proposed that the ILM functions as a scaffold for the proliferation and migration of Muller cells when the original inverted ILM flap technique is performed. In the ILM peeling technique, in which the retina is relaxed and glial cell proliferation is induced by complete peeling, the ILM which is the most rigid part of the retina is involved in the mechanism of the MH closure [26, 27]. Complete ILM peeling relaxes the retina more than incomplete ILM removal, which occurs during the temporal inverted ILM flap technique, but a higher rate of MH closure has been reported with the inverted ILM flap technique than with the ILM peeling technique for treating chronic, large, or highly myopic MHs. This may indicate that more glial cell proliferation occurs in association with the temporal inverted ILM flap technique.

The inverted ILM flap technique may have some limitations. The rates of ELM and EZ recovery were significantly lower in the original inverted group than in the ILM peeling group [14]. Another limitation was decreased VA. Deshpande and Narayanan [15] and Hirano et al. [16] reported worsening postoperative VA compared with preoperatively. Imai and Azumi [17] observed expansion of RPE atrophy. In the current study, postoperative restoration of the ELM and EZ occurred in 10 (50%) and seven (35%) eyes at the final

Figure 2: Preoperative and postoperative fundus and OCT images. A 55-year-old woman with a MH in high myopia (a). The preoperative minimal and maximal MH diameters are 604 μm and 2,296 μm, respectively (b). The axial length is 27.8 mm and the decimal BCVA is 0.04. At postoperative week 2, the MH remains opens under the covered ILM flap (flap closure) (arrow) (c). At postoperative week 4, the MH edges form a bridge under the ILM flap (arrow) (d). At postoperative week 6, the MH is closed leaving a partially defective ELM and EZ (arrow) (e, f). The decimal BCVA is 0.1.

Table 3: Structural restoration of the bands at final visit.

Line or band no. eyes (%)	Large MH (n = 6)	Chronic MH (n = 2)	MH in high myopia (n = 11)	MH in patient unable to maintain postoperative prone positioning (n = 1)
ELM	4 (67%)	0 (0%)	5 (45%)	1 (100%)
EZ	2 (33%)	0 (0%)	4 (36%)	1 (100%)

visit, respectively. These outcomes were similar to those of the ILM peeling technique. In addition, we did not observe VA worsening or expansion of RPE atrophy in the current cases, thus providing a single-layered flap covering the MH as a scaffold for MH wall gliosis without interposing tissue within the hole may provoke the partial proliferation caused

Figure 3: Preoperative and postoperative fundus and OCT images. A 66-year-old man with a MH associated with an ERM (arrow) in high myopia (a). The preoperative minimal and maximal MH diameters are 214 μm and 1,235 μm, respectively. An ERM (arrow) and cystoid retinal change (arrowheads) are seen (b). The axial length is 26.1 mm and the decimal BCVA is 0.4. At postoperative week 2, the MH is closed (c). The decimal BCVA has improved to 1.0. At postoperative week 4, retinal thickening on the inverted side of the ILM flap is seen (arrowhead) (d). At postoperative week 8, the retinal thickening has increased and the stump of shrunken inverted ILM flap was observed (arrow) (e, f). The foveal deformation stopped after postoperative week 12, and the decimal BCVA is maintained at 1.0.

by the manner in which the glial cells fill the hole from the retinal surface to the RPE side [22]. Achieving single-layered flap closure intraoperatively may be an important factor in the anatomic and VA improvement seen with the temporal inverted ILM flap technique. However, gradual foveal deformation after MH closure was observed in a case with high myopia associated with an ERM in the current study. ERMs contain glial cells, myofibroblasts, and hyalocytes seen histopathologically [28]. Regarding the ERM surgery, a meta-analysis reported that the rate of ERM recurrence after the initial surgery was higher in the group in which the ILM was not peeled compared with the group in which the ILM was peeled [29]. Residual ERM fragments on the ILM after ERM peeling were thought to proliferate and form the recurrent ERM [30]. The argument in favor of ILM peeling has been that the ILM may serve as a scaffold for cellular proliferation. In the current study, although the inverted ILM flap technique was performed after ERM peeling, cellular proliferation and constriction of the inverted ILM were observed only on the side in which the ILM was not peeled and where the ILM flap was inverted. This may support the theory that the ILM serves as a scaffold for ERM

recurrence. In the temporal inverted ILM flap technique, the ILM is functioned by providing a single-layered flap covering the MH to serve as a scaffold for MH wall gliosis. However, in the cases of MHs associated with ERMs, the ILMs may be risk factors for the gradual foveal deformation after MH closure resulting from cellular proliferation. Recently, because the same treatment outcome was reported between the inverted ILM flap technique and ILM peeling to treat small idiopathic MHs (<400 μm) and nonmyopic MHs (axial length, <26 mm), the indications for the inverted ILM flap technique are widening. However, we should note that postoperative retinal contraction might occur on the nasal side of the MH despite closure due to cell reproliferation on the unpeeled ILM when an ERM is present. This could ultimately affect both the anatomic and functional outcomes despite MH closure, inducing metamorphopsia or MH reopening. Further studies with longer follow-up are needed to test this hypothesis.

Because of the retrospective nature of the current study, the small number of cases, and the absence of a case-control design, the data require careful interpretation. We reported the efficacy of the single-layered inverted ILM flap technique for treating chronic, large, or highly myopic MHs and MHs in patients unable to maintain postoperative prone positioning and retinal contraction, which have not been reported. Further studies are needed to minimize the surgical complications and understand the mechanism of this technique.

5. Conclusions

The single-layered inverted ILM flap technique is a simple surgical strategy, provides a scaffold for retinal gliosis, and possibly facilitates bridge formation between the walls of the MH just beneath the ILM flap. Regarding the MH closure rate and better VA improvement, this technique should be an effective and safe method to treat chronic, large, or highly myopic MHs and MHs in patients unable to maintain postoperative prone positioning. In the MHs associated with ERMs, gradual foveal deformation developed on the side where the ILM was not peeled and the side where the ILM flap was inverted after MH closure. Further studies are needed to minimize surgical complications and understand the mechanism of this technique.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

No authors have conflicts of interest associated with this work.

Supplementary Materials

This surgical video of the temporal inverted flap technique shows removal of residual vitreous cortex, creation of a semicircular ILM notch two disc diameters from the MH in a temporal area using a 25-gauge MVR knife, inversion of the ILM flap in a nasal direction to fully cover the MH, placement of a low-molecular-weight viscoelastic material on the inverted flap for stabilization, and fluid-air exchange. (*Supplementary Materials*)

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Research Article

Inverted ILM Flap for the Treatment of Myopic Macular Holes: Healing Processes and Morphological Changes in Comparison with Complete ILM Removal

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Purpose. To investigate the microstructural changes after successful myopic macular hole (MMH) surgery, comparing inverted ILM flap and complete ILM removal techniques, and their association with visual function. *Methods*. Spectral-domain optical coherence tomography (SD-OCT) was used to evaluate both external limiting membrane (ELM) and ellipsoid zone (EZ) recovery in 40 eyes of 39 patients who underwent pars plana vitrectomy with either inverted internal limiting membrane flap technique ($n = 27$) or complete ILM removal ($n = 13$) to achieve MH closure. The association between ELM and EZ recovery and visual acuity was also investigated. The patients were followed up at 1 year. *Results*. ELM and EZ was recovered in 72% and 62% of cases, respectively, regardless of the surgical techniques 1 year after surgery. A strong positive association between the ELM and EZ recovery and the mean BCVA was found: regardless of the surgical technique, this was statistically significant at each time point ($p < 0.05$). None of the baseline variables were found to act as predictive factors for either ELM or EZ. *Conclusion*. The inverted ILM flap technique did not affect the MMH healing processes compared to complete ILM removal. Thus, the presence of the ILM plug did not interfere with the restoration of both ELM and EZ, which correlated with functional recovery.

1. Introduction

Myopic macular holes (MMHs) are one of the major causes of vision loss associated with high myopia and still represent a major cause of legal blindness worldwide [1–4]. The pathophysiological mechanism of MMHs is not completely clear. Nevertheless, several anatomical features of pathological myopia are involved, including anteroposterior, tangential traction, and retinal pigment epithelium (RPE) atrophy, as consequences of an abnormal posterior scleral wall growth leading to posterior staphyloma (PS) [5]. The surgical treatment for MMHs is still under debate. Several techniques have been attempted, including pars plana vitrectomy (PPV) with different tamponades, additional laser photocoagulation of the hole margin [6, 7], episcleral buckling of the macular area [8], and infolding the sclera [9]. Regardless, PPV associated with inner limiting membrane (ILM) peeling and gas tamponade represents the most widely chosen technique [10–16], although its results are not significantly better in comparison with the other approaches, and its MMH closure rate is inferior when compared with idiopathic MHs [17, 18]. Michalewska has reported encouraging results using the inverted internal limiting membrane (ILM) flap technique in large idiopathic MHs [19]. Subsequently, together with other authors, the same group confirmed similar positive results even for MMHs, either associated or unassociated with retinal detachment (RD) or macular schisis (MS) [20–22]. Chen and Yang compared this new technique to ILM removal for MMH-associated RDs, finding inverted ILM flap to improve anatomical and functional results [23]. More recently, our group demonstrated that inverted ILM flap was associated with better anatomical results in comparison to complete ILM removal, even in MMHs unassociated with RD [24],

although no statistically significant difference in visual recovery was found between the two surgical techniques in the case of MMH closure. Although the inverted ILM flap technique has shown a higher MMH closure rate in comparison to complete ILM removal, the mechanisms by which the holes close following this procedure are still unknown. Moreover, doubts have been raised that the flap might act as a plug of fibrotic scar tissue, filling the hole. This might limit the microstructural recovery of the ellipsoid zone and interfere with the restoration of visual acuity. This hypothesis appears to be contradicted by a recent study describing reconstructive anatomical changes in foveal microstructure in both idiopathic and myopic MHs treated with inverted ILM flap [25], although the authors did not provide a comparison group. On the other hand, Iwasaki et al. evaluated the postoperative outer retinal layer recovery in eyes undergoing vitrectomy for large MH (>400 microns), finding poorer anatomical and visual results associated with inverted ILM flap compared with ILM peeling [24, 25]. These observations are in contrast with other publications and suggest a standing lack of agreement on this topic.

The aim of this study is to investigate the microstructural changes after successful MMH repair, comparing the anatomical and functional results obtained with inverted ILM flap and complete ILM removal techniques, paying special attention to factors that might have a negative functional impact.

1.1. Patients and Methods. This is a retrospective study based on the review of 70 consecutive patients' medical records who were affected by MMHs and who underwent surgical treatment at Sacro Cuore-Don Calabria Hospital in Verona (Italy) between 2009 and 2015. High myopia was defined as axial length >26.5 mm or refractive error >6 diopters (D). Only eyes that obtained a successful MMH closure after one surgical intervention and a minimum of twelve months follow-up were considered for the study. Only flat/closed holes, based on the classification proposed by Tornambe et al. [26], were included. Elevated/open or flat/open was considered anatomic failures. Exclusion criteria were the presence of a patchy chorioretinal atrophy involving the fovea (diagnosis based on spectral-domain optical coherence tomography (SD-OCT), showing light backscattering and the absence of outer retinal layers around the MMH), previous retinal surgery, the presence of choroidal neovascularization (CNV), diabetic retinopathy, retinal vascular occlusion, or other ocular conditions that could influence best-corrected visual acuity (BCVA), with the exception of lens opacity, inadequate imaging due to lack of quality, or impossibility to define the status of the external retinal bands secondary to long axial length and/or posterior staphyloma. Fifteen patients (14 in the ILM peeling group and 1 in the ILM flap technique) were excluded due to the lack of anatomic closure of the hole.

Patients treated before April 2013 had undergone PPV and complete ILM removal and gas tamponade, while patients treated after April 2013 underwent PPV, inverted ILM flap, and gas tamponade.

All interventions and investigations adhered to the tenets of the Declaration of Helsinki. This study was approved by the Institutional Review Board Committee of Sacro Cuore-Don Calabria Hospital. At the baseline and at every follow-up visit, a complete ophthalmic examination was performed, including BCVA measurement and SD-OCT evaluation. Axial length was also measured at the baseline (IOLMaster, Carl Zeiss Meditec, Germany). BCVA was measured using the standard Snellen eye charts. When visual acuity was evaluated with finger counting and hand motion, the measurements were assigned the equivalent Snellen acuity, namely, 20/2,000 and 20/20,000. A combined confocal scanning laser ophthalmoscope and SD-OCT (Spectralis HRA-OCT, Heidelberg Engineering GmbH, Heidelberg, Germany) was used to confirm MMH status. The size was determined by measuring the minimum diameter in OCT images. Follow-up examinations were scheduled at 1, 3, 6, and 12 months after the operation, and all patients completed the 12 months of follow-up visits. The eye-tracking dual-beam technology (TruTrack™ Active Eye Tracking Software, Heidelberg Engineering, Heidelberg, Germany) mitigates eye movement artifacts and ensures point-to-point correlations between the OCT scan and fundus images. The software also provides an "automatic real-time" (ART) function to reduce noise and increase image quality. With ART activated, multiple frames (B-scans) of the same scanning location are performed during the scanning process, and only scans with elevated ART (range 90–100) were considered. To ensure maximum scan reproducibility, the first fovea centered scan (horizontal or vertical, according to the shape of the staphyloma) acquired at the preoperative visit was set as a reference scan. To further limit misalignment errors, two expert retinal experts (MM and AA) performed and analyzed all the OCT scans. The following outer retinal features were recorded at each time point: (1) ELM integrity, (2) EZ integrity, (3) EZ gap in microns when present, and (4) the presence of MS.

1.2. Surgical Technique

1.2.1. Complete ILM Removal. A complete vitrectomy was performed. A 23G system was used instead of smaller gauges because a longer and stiffer tip can provide better safety in highly myopic eyes. Great attention was paid to removing any remnants of the vitreous cortex after staining with triamcinolone acetonide. If present, any epiretinal membrane was peeled. Following this, the ILM was stained with a mixture of brilliant blue G and trypan blue (Membrane Dual; Dorc, The Netherlands) for about 30 seconds, and a circle approximately within the vascular arcades and centered on the macular hole was peeled off. At the end of the surgery, the eye was filled with an isovolemic mixture of sulfur hexafluoride (SF_6). The patients were advised to maintain a face-down position for approximately eight hours a day for at least three days.

1.2.2. ILM Inverted Flap Technique. The surgical procedure followed the same steps, except for the ILM removal around

the MMH. The ILM peeling started about 1,000 microns from the edge of the hole and was temporarily interrupted at about 500 microns from the center. Then, most of the detached ILM was removed with the cutter. Before the air-fluid exchange, the peeling was completed up to the edge of the hole and the flap was gently positioned to cover the MMH. At the time of fluid-air exchange, low intraocular pressure and passive aspiration were used to avoid turbulence that could have caused a flap displacement. In addition, during this maneuver, the backflush needle was placed on the nasal side of the disc to generate a centripetal laminar flow to move the temporal side of the flap toward the optic disc, resulting in proper MMH roofing.

1.3. Statistical Analysis. Results are expressed as mean and standard deviation (SD) if the variables are continuous and as a percentage if the variables are categorical. The Shapiro–Wilk test was employed to test normality for the continuous variables. The two-sample paired t-test or the Wilcoxon matched-pairs signed-ranks test was used to compare the mean of continuous variables at the baseline versus the mean at subsequent follow-up. Similarly, in the subgroups, the two-sample t-test or the Wilcoxon rank-sum test was used to compare the mean of continuous variables for two independent groups. The linear correlation between continuous variables were assessed by the Pearson correlation coefficient (r). To analyze the EZ gap progression during the follow-up period, a trend test with corrections for ties was used. A stepwise logistic regression analysis at 12 months follow-up was performed to clarify whether MH diameter, MS, surgical technique, age, gender, or preoperative BCVA could have played a role in the prediction of external retina anatomical recovery. A p value < 0.05 was considered statistically significant. Analyses were performed using STATA version 15 (StataCorp, College Station, TX, USA).

2. Results

A total of 40 eyes from 39 patients met the inclusion criteria and were enrolled in the study. Twenty-seven eyes were operated on with the inverted ILM flap technique (inverted flap group), while 13 were operated on using the ILM peeling technique (peeling group). The demographic characteristics of both the peeling group and the inverted flap group are shown in Table 1.

The preoperative BCVA was slightly lower in the inverted flap group than in the peeling group at the baseline, while it was slightly higher in the same group at the end of the follow-up. Nevertheless, the difference was not statistically significant at any time point. No statistically significant differences were found between the two groups in preoperative MMH minimum diameter, axial length, and age.

Table 2 shows the number of eyes with a complete recovery of ELM and EZ at 1, 2, 6, and 12 months after surgery in both the peeling and inverted flap groups. The difference between the two groups was not statistically significant at any time point. Regardless of the surgical technique, ELM foveal defects decreased progressively up to 6 months, at which point the ELM recovered in 72% of the examined subjects. No further improvements were observed in either group at 12 months. On the other hand, EZ recovery progressed steadily throughout the whole follow-up period, reaching completion in 62% of the investigated subjects (Figure 1).

We also investigated the association between functional and morphological parameters, finding a strong positive association between the ELM and EZ recovery and the mean BCVA. Regardless of the surgical technique, this was statistically significant at each time point ($p < 0.05$) (Figure 2).

The subfoveal EZ gap was also measured at each time point. A statistically significant decreasing trend was found when the whole sample was studied (p value < 0.0001) and also when the analysis stratified the two surgical techniques (peeling group p value $= 0.014$; inverted flap group p value $= 0.005$).

The role of the preoperative variables included in Table 1 in predicting ELM and EZ restoration was investigated. According to the stepwise logistic regression analysis at 12 months, none of the preoperative variables were significantly predictive factors of either ELM and EZ recovery or EZ gap reduction.

Figure 3 reports two cases belonging to the inverted ILM flap group and peeling group, respectively. The baseline characteristics of the two eyes were similar in terms of myopia grade and MMH diameter. During the follow-up, ELM recovered before EZ in both eyes. In the inverted ILM flap group, a progressive reabsorption of the hyperreflective material corresponding to the ILM flap was also noticed. One year after surgery, ELM and EZ recovery was completed and the two cases appeared to be extremely similar.

3. Discussion

The present study performed a comparison of anatomical and functional results obtained with inverted ILM flap and complete ILM removal techniques for MMH treatment. The results showed no significant differences in either the microstructural changes occurring after successful MMH repair with the two techniques or in postoperative BCVA.

The MMH closure rate has varied widely amongst authors [27, 28], and a correlation between axial length and MMH closure has never been demonstrated [20, 23]. The majority of OCT-based studies have confirmed the clinical suspicion that the closure rate of myopic MHs was much lower than in idiopathic cases and ranged from 60 to 90% [17, 18]. This discrepancy is likely to be related to the limited elasticity of the retina, which should be stretched to cover the staphyloma [1]. Therefore, an elevated/open or flat/open MH shape has been frequently reported after surgery for MMH after vitrectomy and ILM peeling [29–32].

Michalewska first demonstrated the effectiveness of the inverted ILM flap technique, both in large idiopathic MHs (>400 microns) [19] and in MMHs [21]. The inverted ILM flap technique was shown to be effective in improving both visual acuity and the MH closure rate. Other authors

Table 1: Baseline demographics factors for patients affected by myopic macular hole (MMH).

	Inverted ILM flap (n = 27)	ILM peeling (n = 13)	p value	Total (n = 40)
Gender (M : F)	7 : 20	3 : 10	—	10 : 30
Age (years), mean (SD)	57.8 (10.0)	62.9 (13.3)	0.1179	59.5 (11.3)
Eye (right-left)	14 : 13	6 : 7	—	20 : 20
BCVA baseline decimal, mean (SD)	0.24 (0.11)	0.28 (0.13)	0.1644	0.25 (0.12)
Axial length (mm), mean (SD)	29.3 (2.9)	31.0 (3.0)	0.1340	29.7 (3.0)
MMH minimum diameter in μm, mean (SD)	440 (191)	368 μm (179)	0.1258	416 (188)
Lens				
Aphakic	1 (4%)	0 (0%)		1 (2.5%)
Pseudophakic before Vx	11 (41%)	9 (69%)		20 (50%)
Phacoemulsification during Vx	9 (33%)	3 (23%)		12 (30%)
Phacoemulsification after Vx	1 (4%)	1 (8%)		2 (5%)
Cataract	5 (18%)	0 (0%)		5 (12.5%)

Table 2: Eyes demonstrating complete restoration of external limiting membrane (ELM) and ellipsoid zone (EZ) integrity at different time points.

	1 month	3 months	6 months	1 year
Whole sample (n = 40)				
ELM, n (%)	16 (40)	23 (59)	28 (72)	28 (72)
EZ, n (%)	6 (15)	14 (36)	21 (54)	24 (62)
Inverted flap (n = 27)				
ELM, n (%)	11 (41)	16 (62)	18 (69)	18 (69)
EZ, n (%)	3 (11)	10 (38)	15 (58)	16 (62)
ILM peeling (n = 13)				
ELM, n (%)	5 (39)	7 (54)	10 (77)	10 (77)
EZ, n (%)	3 (23)	4 (31)	6 (46)	8 (62)
ELM p values (inverted vs peeling)	0.4519	0.3147	0.2996	0.2996
EZ p values (inverted vs peeling)	0.1591	0.3326	0.2378	0.5000

Figure 1: External limiting membrane (ELM) (a) and ellipsoid zone (EZ) (b) recovery rate during the follow-up in both inverted flap and peeling group. No statistically significant differences were found between the two surgical techniques at any time points.

Figure 2: Association between best-corrected visual acuity (BCVA) and external limiting membrane (ELM) and ellipsoid zone (EZ) recovery during the follow-up in the whole sample. Regardless of the surgical technique, a statistically significant positive association between BCVA and ELM/EZ restoration was found at each time point. In Table 2, the number of cases with ELM and EZ recovery is shown for each time point. Asterisks indicate a statistically significant difference between the two contiguous points ($p < 0.05$). ELM– EZ– = neither ELM nor EZ recovery; ELM+ EZ– = ELM recovery; ELM+ EZ+ = ELM and EZ recovery.

presented similar results in MMHs [10, 22], even when associated with RD [10]. More recently, an inverted ILM flap and complete ILM removal were compared for the treatment of MMHs associated or unassociated with RD. The inverted ILM flap was confirmed as associated with better anatomic results [23, 24]. Nevertheless, its exact mechanism of action is not completely clear and some ophthalmologists are skeptical about this technique as they assume that the presence of an ILM plug inside the hole could affect the functional outcome. In other words, the inverted ILM flap technique might improve the closure rate of MMHs, yet jeopardize improvement in visual acuity.

In this study, we found no statistically significant difference in postoperative BCVA between the eyes treated with complete ILM peeling and those that received an ILM flap. The absence of a significant functional difference between the two groups suggests that the presence of the ILM plug did not affect visual recovery in our series. However, very little has been published thus far about an inverted ILM flap possibly interfering with the MH healing process. Very recently, Iwasaki proposed evidence in opposition to our data, with a retrospective study on 24 eyes undergoing either ILM peeling ($n = 10$) or inverted ILM flap ($n = 14$) for large MH (<400 microns). The authors reported both a significantly lower recovery rate and ELM recovery time in the inverted ILM flap group compared to the ILM peeling group [33]. However, there is potential bias in this study. First, the number of cases in the 2 groups is rather low (10 and 14) and the authors do not indicate the technique selection criteria. Second, the mean hole diameter in the ILM flap group was more than 100 microns higher than in the ILM peeling group and likely did not reach full statistical significance ($p = 0.053$) only because of the low numbers of eyes included in the study. Third, a minimum follow-up of 6 months is quite short to exhaustively assess the recovery of the outer retina layers. Moreover, the sample is quite heterogeneous as it includes two highly myopic cases and an eye with inactive diabetic retinopathy. Nevertheless, these opposing hypotheses confirm that the mechanism of the inverted ILM flap needs further investigation, even if there is enough evidence that it promotes MH closure, especially in the case of large diameter and myopic eyes.

The dynamic and progressive repair of the outer retinal layer after vitrectomy and ILM peeling for idiopathic MH was described in detail by Bottoni et al. [34]. ELM restoration was reported as complete within 1–3 months, while EZ restoration could take up to 12 months to occur. The authors observed that the recovery of ELM, EZ, and the outer nuclear layer (ONL) took place months after the MH closure and were associated with visual acuity improvement. Our series has demonstrated a similar behavior, as shown in Figure 2. A statistically significant association between ELM/EZ integrity and BCVA was observed at each time point. The positive relationship between ELM integrity and BCVA has already been demonstrated in other diseases, like macular degeneration [35, 36] and diabetic macular edema [37, 38].

Interestingly, we found that the timing and restoration rate of the ELM and EZ did not differ significantly in the inverted flap group compared to the ILM peeling group (Figure 1). This represents a remarkable observation as it indicates that the ILM plug does not interfere with the physiological healing process described after ILM peeling [34].

As shown in Figure 3, the OCT scans revealed the presence of hyperreflective material in close contact with RPE 1 month after surgery. This is likely related to the ILM flap present inside the hole. During the follow-up, a displacement of this material toward the inner retinal layers occurred, and at the same time, the ELM became detectable. This observation may support the ILM flap's role as a scaffold for retinal layer repair after surgery for both idiopathic and myopic MHs [19, 39, 40]. Moreover, we hypothesized that the ILM, creating a separation between the vitreous cavity and the intraretinal environment, can promote the restoration of a favorable homeostatic condition for hole closure [41].

Hayashi and Kuriyama [25] described the microstructural changes after vitrectomy and ILM flap technique in patients that suffered from MMHs with or without RD, but unfortunately, they did not provide a control group with complete ILM peeling. Despite the same surgical technique, they found better outer retinal layer restoration in eyes without RD, probably because the outer retina detachment results in photoreceptor damage that cannot be recovered even after MMH closure. In addition, it is likely that a RD induced by a MMH occurs more frequently when extended chorioretinal atrophy and a deep staphyloma are present. Therefore, microstructural recovery and functional improvement are less likely in light of the underlying pathology.

Figure 3: Follow-up of 2 cases of myopic macular holes (MMHs), namely, operated on using inverted internal limiting membrane (ILM) flap technique (a–e) and with complete ILM removal (f–j). Regardless of the surgical technique, ELM and EZ recovered progressively, even if ELM recovered first. In the inverted ILM flap case, a progressive reabsorption of the ILM plug was also noticed. (a, f) Preoperative. (b, g) 1 month after surgery. (c, h) 3 months after surgery. (d, i) 6 months after surgery. (e, j) 12 months after surgery.

Our statistical analysis did not indicate any predictive factor for the microstructural outcomes of surgery. The MMH preoperative diameter, axial length, and surgical technique did not influence MMH closure processes secondary to surgery. Nevertheless, we only analyzed eyes that reached a flat, closed appearance on OCT. It should be reiterated that, in previously reported data, the ILM flap technique was found to have a statistically significant higher rate of MMH closure than the ILM peeling technique [24]. We can therefore conclude that, based on our experience, the ILM flap technique is preferable as it improves the anatomic outcome and has no negative implication for functional results.

A free flap of ILM transplantation has been proposed for large MHs after failed surgeries with ILM removal [42]. This is our choice for both idiopathic and myopic refractory MHs that had already undergone ILM peeling around the hole. Recently, autologous neurosensory retinal free flap transplantation has been suggested for repairing refractory MMHs [43]. The authors speculated the retinal free flap may improve both BCVA and retinal sensitivity after surgery. We think that it is unlikely that a retinal free flap could conduct a signal to the optic nerve as creating the flap interrupts the inner retinal circulation. Thus, the retinal free flap is likely to act as a tissue to effectively separate the subretinal space from the vitreous cavity, promoting spontaneous MH healing processes. The possibility that the transplanted retinal flap may represent a source of stem cells that can migrate into the native retina and promote outer retinal layer repair is speculative and needs further investigation. A retinal free flap should probably be considered only when residual ILM cannot be found to cover the MMH. For this reason, Wong and Steel [44] suggest not overextending the ILM peeling to preserve ILM for creating a free flap if the MMH failed to close.

In conclusion, in our series of successfully closed MMHs, we found that the inverted ILM flap technique did not affect the MMH healing processes compared to complete ILM removal. Thus, the presence of the ILM plug did not interfere with the restoration of both ELM and EZ, which correlated with functional recovery. A significant limitation of this study is the lack of randomization due to its retrospective nature. However, previous studies demonstrated that the inverted ILM flap technique resulted in a higher closure rate of MMHs in comparison to complete ILM removal [24]; therefore, we believe that it should be considered as the technique of choice for the treatment of MMHs. Nevertheless, this technique's exact mechanism of action should be fully clarified to understand its real potential.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Review Article

Idiopathic Macular Hole: A Comprehensive Review of Its Pathogenesis and of Advanced Studies on Metamorphopsia

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Vitreous anteroposterior traction is an important factor that affects macular hole (MH) formation at the early stage, and vitreous tangential traction can lead to further hole expansion after hole formation. Recent studies have highlighted the significance of Müller cells for the pathogenesis of MH. Since the advent of MH treatment, success rates for MH closure have significantly improved, as has postoperative visual acuity. However, metamorphopsia, an initial and common symptom of MH, still exists. Metamorphopsia is significantly related to the deterioration of visual quality of life and can be used as an independent index to evaluate visual function before and after surgery. In MH patients, metamorphopsia has different manifestations representing different clinical implications. M-CHARTS, as a new means of inspection, can quantify the degrees of metamorphopsia, and with the development of optical coherence tomography (OCT), layer-by-layer scanning of the retinal structure has become possible. These methods enable detailed analysis of the connections between the degree of metamorphopsia and relevant OCT parameters. Preoperative OCT parameters can be used to evaluate the prognosis of the postoperative visual function of MH patients and are therefore of great significance in guiding the treatment of MH patients.

1. Introduction

Idiopathic macular hole (IMH), as a kind of common macular diseases, involves tissue defects including the retinal internal limiting membrane (ILM) and even the photoreceptor (PR) layer [1], and it is known that vitreous traction on local retina, posterior vitreous detachment (PVD) around the macular fovea, and continuous adhesion are major etiological factors in most IMH cases [1–4]. IMH typically affects elderly patients, and approximately two-thirds of patients are females [5]. The main clinical manifestations of IMH include decreased vision, metamorphopsia, and central dark spots, which can occur suddenly or gradually. The incidence of MH among the common population has been reported to range from 0.2% to 0.8% [4, 6]. To understand the pathogenesis of macular hole in relation to metamorphopsia, we must first clarify the pathogenesis of macular hole, that is, the whole process from the impending macular hole to the complete formation of the macular hole. Secondly, it is necessary to explore the related research of metamorphopsia. In this way, the study metamorphopsia of macular holes can be fully understood.

2. Several Hypotheses on the Development of MH

2.1. Vitreous Macular Traction in the Pathogenesis of IMH. Among the hypotheses concerning the pathogenesis of IMH, the most extensively accepted one is the exertion of direct A-P (anterior-posterior) traction by the posterior vitreous cortex on the macular fovea [1–3, 7, 8]. In healthy human eyes, the vitreous humor of the posterior vitreous cortex slowly passes through the optic disc, which realizes the separation of the posterior vitreous cortex and the posterior pole. In contrast, in human eyes at the risk of IMH formation, abnormal vitreous macular adhesions produce dynamic traction, and the contraction of collagen fibers in the longitudinal direction causes progressive anterior traction until avulsion of the Müller cap occurs [9–11].

According to recent research on the early stage of IMH formation, the strength of A-P traction was higher when the area of perifoveal vitreous detachment was smaller. However, tangential traction could not have an effect until the IMH had formed. Tangential traction is formed when the residual vitreous remains on the fovea after the PVD contracts [12], during which Müller cells proliferate and invade the ILM. When the proliferating glial cells on the ILM shrinks, the hole is enlarged [13–17].

Studies on the visual distortion of macular holes emphasize the role of the photoreceptor cell layer, which is the origin of the initial stage of the signal transduction pathway. The above exposition on the pathogenesis of the macular hole is from only the macroscopic level. Although this perspective emphasizes the role of the vitreous traction in the fovea, it does not allow for studies of occurrence and development of the macular hole at the cellular and molecular levels. To elucidate the cause of MH visual distortion at the cellular level, further study of the pathogenesis of macular holes is needed. Therefore, with the latest research on Müller cells in the macular, we will have a clearer understanding of the whole process of macular hole development.

2.2. Role of Müller Cells in the Pathogenesis of IMH

2.2.1. Unique Function of Müller Cells. Müller cells are also called radial glial cells. The cell bodies of Müller cells are located in the inner nuclear layer (INL), and many cellular processes in Müller cells span the whole thickness of the neurosensory retina. Müller cells form the inner retinal surfaces at the ILM level, and all types of cell bodies and the retinal neuronal processes are ensheathed in these cells. In contrast, Müller cells proliferate and form the external limiting membrane (ELM) at the PR layer level. The ELM is connected to the ILM at the fovea center due to thickening of the Müller cell layer, creating a cone-shaped appearance. This forms the Müller cap, which is a reservoir of xanthophylls, and it enables Müller cells to protect to the retina [18, 19]. Moreover, multiple functional interactions exist between neurons and Müller cells, including interactions involving glutamate recycling, substance exchange in ganglion cells, and extracellular ion homeostasis, etc. Müller cells possess an abundance of neurotransmitter receptors and voltage-gated channels and are involved in mediate neuronal cell protection [15, 16, 20–22].

2.2.2. Spatial Distribution of Müller Cells in the Fovea of the Macula

(1) Spatial Distribution of Müller Cells in the Macular Fovea. Fovea formation involves two major events, i. e., the centrifugal migration of inner retinal cells and the centripetal movement of peripheral PRs. As a result, the fovea lacks the inner retinal layer, and the cones exist in the fovea alone. Gass proposed that Müller cell cones (MCCs), which are structures formed by Müller cells that take the shape of inverted cones, occupy almost of the one-third space of the internal foveola, and the MCCs act as glue in the foveola that bind all cone cells together. Retinal PR cells might perform centrifugal contraction without such a "plug". The retinal structure of the central foveola, which is considered the weakest part of the fovea, might be more easily affected by anterior vitreofoveal traction [18, 23, 24].

Müller cells in the fovea can be divided into the following 3 types: MCC cells [18], atypical Müller cells (ATMs) [25], and Z-shaped Müller cells [26]. MCC cells are located at the center of the foveola, while ATMs are found in the remaining parts of the foveola, a considerable distance away from the MCCs and approximately 400 mm away from the center of the foveola. The Z-shaped Müller cells are located in the parafoveolar area [18, 24–27].

2.2.3. Involvement of Müller Cells in MH Formation. When considering the special arrangement of Müller cells in the macular fovea and the degree and extent of A-P vitreomacular traction, there are two different types of full-thickness defects of the fovea: the dehiscent type and the tearing type.

The dehiscent type is characterized by cleavage towards the internal margin of the Henle fiber layer and the formation of foveolar pseudocysts, which was accompanied by the centrifugal tangent displacement of the photoreceptor cell layer, and vitreous traction is exerted on the foveolar floor. The smallest loss of the foveolar tissue would be realized if the ATMs and MCCs are pulled, which is especially true in the external layer that includes the PRs. If the intensity or extent of vitreofoveal traction and adhesion is great, then the Z-shaped Müller cells with eccentricity to the central area of the foveolar floor (the clivus) would be affected by this traction force. In the tearing type, the clivus witnesses the separation if the Z-shaped Müller cells is involved, being accompanied with extensive loss of the outer retinal tissue during full-thickness tearing [13, 14, 27–31]. In 1995, Gass modified the previous classification and proposed that the dehiscent-type defect, instead of the tearing type defects, was the origin of most of the MH cases [32].

3. Metamorphopsia

3.1. Definition and Significance of Metamorphopsia. Metamorphopsia in patients is the perception deviation of the horizontal or vertical line, and it sometimes may appear before the clinical manifestation of macular disease [33–38]. Patients may sometimes consider metamorphopsia as an unstable condition of vision instead of precise deformations of objects, and they focus better with slightly unconscious eye movements. Specific types of metamorphopsia include macropsia and micropsia. Micropsia, in which the human eye perceives an object to be smaller than it actually is, is more common. In macropsia, an object is perceived to be larger than it actually is. Recent studies have reported the nonlinear interactions between the shape and size of visual distortion and recognition of letters. In addition, Wittich et al. confirmed that there is no correlation between metamorphopsia and preoperative visual acuity [39–41]. This finding indicates that it may be difficult to distinguish the

change in distortion from the change in acuity. Amsler emphasized that it was important to detect a visual disorder early, although it could not be found in the fundus examination or the standard quantitative test (visual acuity examination, for example) of visual functions.

Visual distortion is the result of the structure change in the retina that causes the retinal layer to suffer displacement, which in turn causes distortion in space. As a common clinical manifestation of different macular diseases, visual distortion can serve as a sensitive biomarker to detect the occurrence, development, and alleviation of macular diseases. Some of the most common clinical manifestations of macular degeneration involving metamorphopsia include retinal detachment, macular serous detachment, vitreoretinal interface disease, CSC (central serous chorioretinopathy), diabetic macular edema and nondiabetic macular edema, and AMD (age-related macular degeneration).

Normal vision and a normal fundus may be present in functional disorders, but macular degeneration may occur. Therefore, in clinical practice, symptoms regarding visual function in patients are often underestimated. Visual distortion also significantly reduces the ability of patients to read and discriminate, and metamorphopsia negatively affects the quality of life of patients [42–45].

3.2. Pathogenesis of Metamorphopsia. The development of metamorphopsia involves both the cortical mechanism and the retinal mechanism, despite the previous perception that metamorphopsia was just caused by structural changes to the retina, with outer retinal displacement causing inappropriate optical signal transmission. With the advent of spectral OCT, the detailed re-evaluation of the retina could be performed. As a result, detailed reports of the relationship between metamorphopsia and OCT parameters have emerged, and these reports partially confirmed the previous hypothesis that viewed the change in the PR layers as the major reason for metamorphopsia. Nevertheless, some recent theories emphasize a correlation between the inner retina and cortical processing and metamorphopsia. The cerebral cortex is mainly affected by visual crowding effects and perceptual "filling-in" [24, 30, 33, 46–56].

3.3. Method of Measuring Metamorphopsia. To evaluate metamorphopsia, many functional examinations can be conducted, such as the Amsler grid and the mobile handheld home surveillance devices [57]. The Amsler grid [34, 37, 38, 58] was the first functional test to be evaluated for visual distortion. This test enables simple and fast qualitative assessment of changes in the visual function in the field of view of central 10°, which might appear prior to certain macular diseases or together with the development of these diseases. However, the standard Amsler grid, as a suprathreshold trial stimulus, cannot be used to detect early metamorphopsia because of its poor sensitivity; thus various trials have been inspired by the Amsler grid for the application of the quantification and early detection of metamorphopsia. Most of these tests, however, still need full clinical validation. For example, M-CHARTS, differential perimetry, SDH (shape discrimination hyperacuity), and PHP (preferential hyperacuity perimeter) tests have been applied to metamorphopsia assessment [59–62].

3.3.1. Amsler Grid. The Amsler grid is a black piece of cardboard of 10 square centimeters that is divided into small squares of 5 mm with white lines. A white point in the center is used as the fixed point. Black lines on a white background are also useful. When the grid is placed 28–30 cm in front of the patient's eyes, the whole grid is equivalent to 20°, and each small square is equivalent to 1°. This square was therefore designed by Amsler to test for diseases in the range of 10°. The blind spot is located at the nasal boundary approximately 5° outside the grid. Although the Amsler grid has been extensively applied to visual distortion, quantifying the severity of metamorphopsia is still difficult [34, 37, 38, 58].

3.3.2. M-CHARTS. In 1999, Matsumoto et al. [63] proposed quantifying the seriousness of visual distortion using M-CHARTS (Inami Co., Tokyo, Japan). The basic principle of the method is that when the dotted line substitutes for the straight line and the coarse intervals substitute the dot intervals, line distortion is reduced. Furthermore, when the dot intervals are enhanced, line distortion continues to be reduced until the line becomes nearly straight. M-CHARTS includes nineteen dotted lines, and the visual angle of dot intervals ranges from 0.2 degree to 2.0 degrees. Moreover, M-CHARTS is divided into two types: the type 1 single-line M-CHARTS (for general use) and the type 2 double-line M-CHARTS; the type 2 is composed of 2 lines that have an intervening fixation point for the purpose of MH patients. In this test, the patient is first asked to gaze at the target at the center and then vertical straight lines (0°) are shown. If the straight line is perceived as straight by the patient, then the metamorphopsia score of the patient is 0, and the test is complete. In contrast, if the patient sees the straight line as a curve or other irregular shapes, then he/she will be shown many interrupted lines composed of different dots, from fine dots to coarse dots. If the dotted line is recognized as straight by the patient, then the metamorphopsia score of the patient will be determined to be the visual angle used to separate the dots. Next, the same test is conducted using the horizontal lines after rotating the M-CHARTS at 90°. These tests are performed three times, with the mean value applied to data analysis. The advantages of M-CHARTS are its low cost, its portability, and its ease of use. However, it also has disadvantages of not being applicable to patients with serious central dark spots or low vision due to its design purpose of detecting and quantifying subtle deformations and is thus very demanding of visual quality. Nowomiejska et al. made a comparative analysis of the Amsler grid and M-CHARTS in evaluating bevacizumab for the treatment of neovascular AMD in metamorphopsia patients using OCT, and they concluded that the sensitivity of M-CHARTS might be better than that of the Amsler grid [50].

3.4. Different Manifestations of Visual Distortion. The Amsler grid can be used to detect a large number of

metamorphopsia in different forms. A straight line can break into a small/large wavy line or an angular deformity. In micropsia, the horizontal lines and the vertical lines appear to bend towards the center, while in macropsia, the lines bend from the center. In addition, researchers found correlations between macular diseases and metamorphopsia of varied types. For example, there are associations between small angular defects and myopic maculopathy, between AMD and wavy lines, between retinal detachment and diffuse visual distortions, and between postoperative retinal reattachment and diffuse irregularity of the grid (e.g., depicting by a tremulous hand) [34, 46, 59, 64–66].

4. MH and Metamorphopsia

4.1. Classification of Metamorphopsia in IMH Patients. In a retrospective study by Saito et al. [67] that included 54 eyes from 51 MH patients, two types of visual distortion were found using the Amsler grid test: the first type was pincushion distortion, with lines curved towards the center, and the second type was unpatterned metamorphopsia without a specific form. A total of 33 cases (61%) of pincushion distortion and 21 cases (39%) of unpatterned metamorphopsia were identified, and an association was found between the stage and duration of MH and the type of metamorphopsia. Approximately 70% of patients with early MH (duration ≤6 months) have pincushion distortion. In a comprehensive study of MH by Gass, it was found that vitreous tangential traction on the retina could enlarge the MH, and the enlargement of the MH is not accompanied by tissue loss [32]. In early MH, displacement of the PR layer caused by retinal shrinkage leads the vertical line to stimulate the displaced PR cells, thus forming the perception of a line curved towards the center, and this is pincushion distortion [68]. The retinal PR layer is most displaced in the central part of the fovea, and the peripheral part is gradually reduced. Patients with a short duration of MH maintain good PR function and have less perceptual filling-in in the brain. The perceptual filling-in effect occurs when a patient observes the Amsler grid, and an area that originally corresponded to the retinal defect is seen as distorted but continuous. One of the general examples of the perceptual filling-in effect is the filling-in of a nonphotosensitive area (physiological blind spot) of the retina which has a partial image in the surrounding area.

Compared with structural changes in the retina, the subjective visual perception of the patient is much more complicated. Patients with long-term MH exhibit unpatterned metamorphopsia. Because the MH is usually surrounded by a fluid cuff that leads to functional retinal damage, patients with long disease courses are more likely than those with short disease courses to lose retinal function around the hole. In addition, patients with long-term MH are more likely than those with short-term MH to lose retinal function surrounding the macular region. If the foveal cells become nonfunctioning during a long-standing case, the patient will have developed a true foveal scotoma. Schuchard noted that the scotoma is usually perceptual filling-in, and such filling-in is often reported by patients as distortion resembling unpatterned metamorphopsia depicted in this paper. Distortion in this case is considered to be the result of the mechanism of the cerebral cortex rather than simple retinal projection [67].

4.2. Study on the Mechanism between Metamorphopsia and IMH. Krøyer et al. [69, 70] claimed that the reasons for metamorphopsia were the eversion of PRs (caused by eversion of internal edges of holes) and tangential displacement of the PRs. They speculated that two types of PR layer displacements play a role in the metamorphopsia of MH: tangential displacement and eversion of the outer retina. In pincushion distortion, tangential displacement of PRs and eversion of PRs may explain why the patients perceive the flatter curve farther away from the fovea and the steepest curve nearest to the fovea center, respectively. Eversion of the outer retina is a critical factor for induced metamorphopsia and displacement of the PR layer. According to this theory, surgery may be sufficient to close the hole by eliminating retinal eversion, but metamorphopsia can persist, even after the inner layer of the hole is closed. However, the PR layer retains residual tangential displacement even after the inner layer of the MH has been closed. After successful repair of the MH, residual metamorphopsia unrelated to eccentricity indicates that PR cells are not completely repositioned. As Michalewska et al. described, even after the MH is closed, subretinal cysts still occur in many patients before the PR layer is completely repositioned [71], which explains why metamorphopsia persists after the MH is successfully repaired surgically (in which eversion of the MH edge has been eliminated and closure of the MH has been achieved; however, there is still tangential displacement). Burke concluded that both the cortical visual filling-in effect and PR layer displacement are important factors that can explain the degree of metamorphopsia in MH [72, 73].

4.3. Clinical Studies on Metamorphopsia in IMH. Arimura et al. [62] performed a linear regression analysis of the metamorphopsia score (M-score) measured using M-CHARTS and the MH shape (hole size and fluid cuff length). The finding is that there was an important correlation between the M-score and the fluid cuff (superficial retinal detachment), but there was no relationship between the M-score and MH diameter. To be specific, the significant correlation between the fluid cuff and M-score exists when the MH was smaller than 0.5 mm, but if the MH was bigger than 0.5 mm, such a significant correlation would not be present. No significant correlation was found between the M-score and the visual acuity [39]. Sugiura et al. [74] used type I M-CHARTS in a prospective continuous interventional study of 51 eyes and found that the preoperative and postoperative vertical M-scores of the MH patients were significantly higher than the horizontal M-scores. They also found a correlation between the average postoperative M-scores and the length of the ELM defect and the preoperative basal diameter of the MH and the preoperative area of intraretinal cysts in the fluid cuff. The largest influence factor of severity of metamorphopsia is

attributed to the preoperative area of intraretinal cysts [39, 41, 57, 75, 76].

In addition, the degree of metamorphopsia obtained using M-CHARTS is correlated with the foveal shape after surgical MH closure, particularly asymmetric extension of the foveal tissue. The reason for this might be the induction of asymmetric tangential traction by asymmetric extension of the foveal tissue to prevent displacement of the PRs during recovery. It is true that asymmetric elongation generally appears in the INL and other nuclear layers instead of the PR layer, but PR displacement can be incurred by the traction of a certain retinal layer, which causes further visual distortion [77]. Another possible explanation is that the correct signal transduction is blocked by asymmetric extension of the retinal layer. In MH, many patients have intraretinal cysts, which may distort retinal microstructures such as Müller cells, amacrine cells, bipolar cells, and horizontal cells. Such morphological changes may cause abnormal synaptic function and reduce the sensitivity of PR cells, causing metamorphopsia. Associations exist between the horizontal M-score and vertical retinal changes, and between the vertical M-score and horizontal retinal changes [65, 72, 78].

Kim et al. [79] reported that tissues stretched longer towards the thicker regions of the retina. It has been speculated that the power of traction in the nasal direction is stronger when MH occurs, causing the horizontal retinal changes to be greater than the vertical retinal changes, which might explain why preoperative horizontal M-scores are smaller than preoperative vertical M-scores. After MH surgery, the fovea asymmetrically extends towards the nasal retina; thus, we speculate that the greater nasal extension provides a higher postoperative vertical metamorphopsia score.

Krasnicki et al. [80] reported improvements in metamorphopsia and BCVA (best-corrected visual acuity) after MH surgery. Considering the EZ (ellipsoid zone) defect and recovery of the ELM, a relatively long period of time was needed for improvement in BCVA to be observed. In contrast, metamorphopsia improved more quickly because postoperative morphology improved after the surgery and then entered a stable stage [71, 75].

Kinoshita et al. [72] reported improvement in horizontal metamorphopsia at 12 months after MH surgery, but vertical metamorphopsia gained stable improvement at 6 months. Okamoto et al. [65] revealed a significant poorer performance of horizontal metamorphopsia at 3–6 months after surgery compared with that at baseline. However, vertical metamorphopsia showed a significant improvement from baseline at 3 months after surgery but did not show a significant improvement at 6 months. Therefore, improvement in postoperative vertical metamorphopsia may not be as notable as improvement in postoperative horizontal metamorphopsia. It is possible that the directionality of retinal plasticity is limited by the existence of the optic disc and the direction of retinal nerve fibers.

5. Conclusion

Visual function affects a patient's visual quality of life and is not limited to postoperative visual acuity; postoperative improvement in metamorphopsia is also important. Through an in-depth study of the pathogenesis of MH and metamorphopsia, we conclude that metamorphopsia in MH is the result of tangential centrifugal displacement of the PR cell layer. As the disease progresses, the cerebral cortex participates in the development of metamorphopsia through the perceptual filling-in effect, which is in contrast to the simple abnormal retinal projection hypothesis. Quantitative statistical analysis of metamorphopsia can help determine the prognosis for postoperative visual function in patients, which is of great significance for guiding clinical treatment.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this article.

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Research Article

Comparison of Anatomical and Visual Outcomes between Idiopathic and Myopic Macular Holes Using the Internal Limiting Membrane or Inverted Internal Limiting Membrane Flap Technique

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Purpose. To compare the results of vitrectomy with those of internal limiting membrane (ILM) peeling or inverted ILM flap for treating myopic or idiopathic macular hole. *Methods*. Thirty-nine eyes of 39 patients undergoing vitrectomy with ILM peeling for macular hole (25 idiopathic and 14 myopic) and 27 eyes of 27 patients undergoing vitrectomy with inverted ILM flap (15 idiopathic and 12 myopic) were included. Outcome measures were macular hole closure by optical coherence tomography and visual acuity at 6 months. *Results*. Closure was achieved in 25 (100%) idiopathic and 12 (86%) myopic macular holes in the ILM peeling group and in 14 (93%) idiopathic and 11 (91.77%) macular holes in the inverted ILM flap group. There were no statistically significant differences in restoration of the external limiting membrane and ellipsoid zone between the groups. Median best-corrected visual acuity (logarithm of minimal angle of resolution) at the end of follow-up was 0.22 (20/32 Snellen) in idiopathic and 0.4 (20/50) in myopic ($P = 0.042$) patients in the ILM peeling group and 0.4 (20/50) in idiopathic and 0.4 (20/50) in myopic ($P = 0.652$) patients in the inverted ILM flap group. *Conclusion*. Both techniques were associated with high closure rates in myopic and idiopathic macular holes, with somewhat better visual outcomes in idiopathic cases. The small sample size may have provided insufficient power to support the superiority of one technique over the other in the two groups.

1. Introduction

The pathogenesis of macular hole (MH) is not fully understood and is considered to be multifactorial. It is believed to involve inwards traction from abnormal premacular vitreous cortex adhesion, thickening the internal limiting membrane (ILM) or epiretinal membrane, and in myopic MH, external traction from a posterior staphyloma [1, 2]. Surgery, a well-established treatment for MHs, has the aim of identifying and treating these vitreoretinal traction forces, which can be tangential, anteroposterior, or both.

Optical coherence tomography (OCT) has become a pivotal technique for the diagnosis and follow-up of idiopathic and myopic MHs, including the course of MH closure [3, 4]. The most common procedure for treating idiopathic MH is pars plana vitrectomy (PPV), posterior vitreous detachment, internal limiting membrane (ILM) peeling, filling of the vitreous cavity using a gas bubble, and postoperative face-down positioning [5]. In myopic MH, however, there is no widely accepted technique.

The inverted ILM flap technique, first described by Michalewska et al. [6], is a potentially useful surgical technique

for treating large, full-thickness idiopathic MH and myopic MH. Although the anatomic closure rates are high with this procedure, there is no consensus as to whether the functional outcome is more favorable with the inverted ILM technique than with complete ILM peeling.

The purpose of this study was to evaluate the anatomic and functional outcomes in patients with idiopathic MH or myopic MH using the inverted ILM flap technique versus complete ILM peeling.

2. Methods

2.1. Study Design and Participants. This is a retrospective, nonrandomized, comparative study of consecutive patients with MH treated by a single vitreoretinal surgeon (J. G.-A.) using small-gauge PPV (23- or 25-gauge) at the Ocular Microsurgery Institute (IMO, Instituto de Microcirugía Ocular) in Barcelona, Spain, between January 2013 and January 2018. The study was approved by the IMO ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent for participation was obtained from all patients.

All patients underwent a complete ophthalmologic examination and spectral domain optical coherence tomography (SD-OCT) using the Cirrus HD-OCT 4000 or 5000 system (Carl Zeiss Meditec, Inc., Dublin, CA, USA) before surgery and at 1 week, 1 month, and 6 months after surgery. Minimum and maximum hole diameters were measured using OCT.

Patients were divided into subgroups according to the ILM removal technique (peeling vs. inverted flap) and axial length (AL) < 26 mm (idiopathic MH) or ≥26 mm (myopic MH). We included all eyes with a full-thickness MH without retinal detachment (RD) and follow-up of at least 6 months. The exclusion criteria were as follows: (1) traumatic MH or history of eye trauma, (2) macular edema of any cause, (3) recurrent MH, (4) presence of glaucoma or any other chronic ocular disease, and (5) presence of a systemic disease such as diabetes mellitus.

2.2. Surgical Procedure. Vitrectomies were performed under retrobulbar anesthesia. All patients underwent standard 3-port 23- or 25-gauge PPV with posterior vitreous detachment using a soft silicone-tipped cannula or active suction with the vitrectomy probe. Any epiretinal membrane present was peeled. The ILM was stained with a mixture of brilliant blue G and trypan blue (MembraneBlue-Dual; Dorc, Zuidland, the Netherlands) for 1 minute, which was then aspirated with a silicone-tipped cannula.

In the complete ILM peeling group, the ILM was peeled off in a circular manner for about two disk diameters around the MH using a forceps (Storz Single-Use Vitreoretinal Asymmetric Peeling Forceps, Aliso Viejo, CA) and then removed. The inverted ILM flap technique was performed according to the original description by Michalewska et al. [6] with some modifications. During ILM peeling around the MH, the ILM flap was not entirely removed from the retina; instead, a remnant was left attached to the MH periphery. To place the flap, a small amount of perfluorocarbon liquid was introduced over the macula. The remnant ILM flap was inverted with a silicone cannula and then pushed into the MH to fill it. The perfluorocarbon facilitated manipulation of the inverted flap and the other surgical maneuvers. In phakic patients, if lens opacification prevented visualization of the fundus, standard phacoemulsification with intraocular lens implantation was performed before vitrectomy. To avoid movement of the flap, the initial fluid-air exchange was performed peripherally to eliminate all fluid before removing the central perfluoro-*n*-octane (HPF8; Alchimia srl, Padova, Italy). Remnant fluid on the disk was then eliminated. After fluid-air exchange, we reconfirmed that the ILM flap remained in place. As the ILM flap was stained with brilliant blue G, it could be visualized through the air filling the vitreous cavity. Hence, gas tamponade (10% C3F8) was applied, and patients were instructed to maintain a prone position for approximately 5 days after surgery.

The complete postoperative ophthalmologic examinations included best-corrected visual acuity (BCVA), intraocular pressure, slit-lamp evaluation, fundus assessment, and SD-OCT. A high-resolution five lines scan was used to visualize the details of the fovea. MH closure was defined by SD-OCT as complete disappearance of the hole and absence of a neurosensory defect over the fovea. During each postoperative visit, the presence of photoreceptor (i.e., ellipsoid zone (EZ)) defects and external limiting membrane (ELM) was estimated. Recovered foveal microstructure layers were evaluated by standard 3 mm macular horizontal and vertical cross-sectional images with OTC. Restoration of ELM/ellipsoid layers was defined as continuous reflection lines. Flat-open and elevated-open myopic MHs were considered surgical failures.

2.3. Statistical Analyses. The BCVA was recorded as a decimal value and was converted to the logarithm of minimal angle of resolution (logMAR) and Snellen fraction for the statistical analysis. Fisher's exact test was used to compare categorical data. Student's *t*-test was used to compare normally distributed continuous data, and the nonparametric Mann–Whitney *U* test was applied when data were not normally distributed. Categorical data are expressed as the frequency and percentage and continuous data as the median and interquartile range (IQR) (25%–75%) when data were not normally distributed. Statistical significance for 2-sided tests was set at $P < 0.05$. Statistical analyses were performed using SPSS 15.0 (SPSS, Inc., Chicago, IL).

3. Results

Over the period of the study, 39 patients (18 men and 21 women) (39 eyes) underwent vitrectomy using the ILM peeling technique and 27 patients (15 men and 12 women) (28 eyes) were treated with vitrectomy using the inverted ILM flap procedure. The median (SD) age of the patients was 64.14 (±10.86) years, and the distribution of the study variables was similar in the two groups (Table 1). At baseline,

Table 1: Preoperative characteristics of patients with MMH without RD undergoing ILM peeling or inverted ILM flap technique.

Variables	ILM peeling technique			Inverted ILM flap technique		
	AL < 26 mm ($n = 25$)	AL ≥ 26 mm ($n = 14$)	P	AL < 26 mm ($n = 15$)	AL ≥ 26 mm ($n = 12$)	P
Sex						
Men (n (%))	12 (48)	6 (43)	0.51	6 (40)	6 (50)	0.270
Women (n (%))	13 (52)	8 (57)		9 (60)	6 (50)	
Age (years, median (IQR))	66 (60.7–74.5)	63 (59.2–72.2)	0.458	65 (58.5–71.5)	59.5 (56–67)	0.428
Eye						
Right (n (%))	9 (36)	7 (50)	0.50	3 (20)	3 (25)	1.00
Left (n (%))	16 (64)	7 (50)		12 (80)	9 (75)	
AL (mm, median (IQR))	23.69 (23.40–23.83)	30.09 (27.21–31.63)	0.001	23.29 (22.86–23.41)	28.7 (25.8–30)	0.001
AL >30 (%)		7 (50)			3 (25)	
Refractive error (diopters, median (IQR))	−1 (−2 to 0.25)	−13.19 (−18 to −8.62)	<0.001	−1.25 (−2 to −0.12)	−9.5 (−13.8 to −7.3)	0.001
Posterior staphyloma (%)	0	11 (79)		0	5 (42)	
Lens status						
Phakic	3 (12)	0	0.540	1 (7)	5 (42)	0.060
Phakic intraocular lens	22 (88)	14 (100)		14 (93)	7 (58)	
BCVA (logMAR, median (IQR))	0.4 (0.7–0.3)	0.6 (1–0.4)	0.119	0.8 (1.3–0.6)	0.45 (0.8–0.4)	0.001
BCVA (Snellen chart, median (IQR))	20/50 (20/100–20/40)	20/80 (20/200–20/50)		20/125 (20/400–20/80)	20/56 (20/126–20/50)	
Macular hole						
Minimum diameter (μm, median (IQR))	267 (125–324)	414 (294–559)	0.218	496 (362–633)	307 (170–453)	0.020
Chronic MH (n (%))	7 (28)	1 (7)	0.218	4 (27)	5 (45)	0.448

AL, axial length; BCVA, best-corrected visual acuity; ILM, internal limiting membrane; MH, macular hole.

there were no significant differences between idiopathic and myopic patients in the ILM peeling cohort ($P = 0.458$) or in the ILM flap cohort ($P = 0.428$) regarding MH diameter. Among myopic MH patients, 7 eyes in the ILM peeling group and 3 in the inverted flap group had an axial length >30 mm.

In patients treated with ILM peeling, average preoperative BCVA was 0.4 (IQR 0.7–0.3) logMAR (20/50 Snellen) in idiopathic MH and 0.6 (IQR 1–0.4) logMAR (20/80 Snellen) in myopic MH ($P = 0.119$), whereas in the inverted ILM flap group, BCVA was 0.8 (1.3–0.6) logMAR (20/125 Snellen) in idiopathic and 0.45 (0.8–0.4) logMAR (20/56 Snellen) in myopic MH ($P \leq 0.001$).

There were no statistical differences regarding the minimum diameter (μm) of the MHs. Phacoemulsification in combination with PPV was performed in 8 eyes (21%) in the peeling group and in 3 (25%) in the inverted flap group.

Functional and anatomic results are shown in Table 2. In the peeling group, mean postoperative BCVA was 0.22 (IQR 0.3–0.1) logMAR (20/32 Snellen) in idiopathic MH and 0.4 (IQR 0.7–0.22) logMAR (20/50 Snellen) in myopic MH ($P = 0.042$). In patients undergoing the inverted flap technique, BCVA was 0.4 (0.7–0.3) logMAR (20/50 Snellen) in idiopathic and 0.4 (0.85–0.3) logMAR (20/50 Snellen) in myopic MH ($P = 0.652$).

In the group of <26 mm axial length, there was a statistical difference in the results of BCVA between ILM peeling vs. inverted flap group ($P < 0.01$). In the group of >26 mm axial length, there was not a statistical difference between ILM peeling vs. inverted flap ($P = 0.98$).

Following vitrectomy with ILM peeling, MH closure was achieved in 100% (25 eyes) with AL < 26 mm and in 86% (12 eyes) with AL ≥ 26 mm ($P = 0.012$). In patients undergoing vitrectomy with inverted ILM flap, 93% (14 eyes) with AL < 26 mm and 91.7% (11 eyes) with AL ≥ 26 mm ($P = 1$) achieved MH closure (Figures 1 and 2). On SD-OCT at 6 months of follow-up in patients with closed MH, the external limiting membrane (ELM)/ellipsoid layers were restored in 19 of 25 eyes (AL < 26 mm) and in 5 of 12 eyes (AL ≥ 26 mm) in the ILM peeling group ($P = 0.168$) and in 5 of 14 eyes (AL < 26 mm) and in 5 of 11 eyes (AL ≥ 26 mm) in the inverted ILM flap group ($P = 0.697$). There were no statistically significant differences between any of the groups regarding restoration of the ELM and ellipsoid zone.

4. Discussion

The results of this study showed a similar closure rate with the use of the inverted ILM flap technique between eyes with AL < 26 mm (idiopathic MH) and AL ≥ 26 (myopic MH), although idiopathic MHs in the ILM peeling group had a somewhat higher closure rate ($P = 0.012$).

The minor diameter of macular hole at the baseline in the ILM peeling group than in the inverted ILM flap group in the idiopathic macular hole (265 μm respect of 465 μm) can be the reason for the higher closure rate in the first group compared with the second one. It could also be explained, in our retrospective study, as ILM peeling technique was the preferred technique for the surgeon (G-A), in cases of macular hole <400 μm.

Table 2: Anatomical and functional results in patients undergoing ILM peeling or inverted ILM flap technique in relationship with the axial length: AL < 26 mm or AL ≥ 26 mm.

Variables	ILM peeling technique			Inverted ILM flap technique		
	AL < 26 mm ($n = 25$)	AL ≥ 26 mm ($n = 14$)	P	AL < 26 mm ($n = 15$)	AL ≥ 26 mm ($n = 12$)	P
Macular hole						
Open	0	2 (14)	0.012	1 (7)	1 (8.3)	1.000
Closed at 6 months	25 (100)	12 (86)		14 (93)	11 (91.7)	
Chronic MH						
Closed	7/7 (100)	0/1	—	3/4 (75)	4/5 (80)	1.000
Restoration of ELM/ellipsoid zone at 6 months	19/25 (76)	5/12 (42)	0.168	5/14 (36)	5/11 (45)	0.697
BCVA (logMAR), median (IQR)						
At 6 months	0.22 (0.3–0.1)	0.4 (0.7–0.22)	0.042	0.4 (0.7–0.3)	0.4 (0.85–0.3)	0.652
BCVA (Snellen chart), median (IQR)						
At 6 months	20/32 (20/40–20/25)	20/50 (20/100–20/32)	0.138	20/50 (20/100–20/40)	20/50 (20/141–20/39)	0.652
Increased BCVA						
At 6 months	19 (76)	10 (71)	0.142	13 (87)	6 (50)	0.031
Increased or stable BCVA						
At 6 months	25 (100)	12 (86)	0.123	15 (100)	9 (75)	0.075

AL, axial length; BCVA, best-corrected visual acuity; ELM, external limiting membrane; ILM, internal limiting membrane; MH, macular hole.

Figure 1: 46-year-old woman with an axial length of 30.98 mm and a BCVA of 20/400, with inner and external retinoschisis and myopic macular hole. (a) Fundus photograph showing the chorioretinal atrophy and the macular hole. (b, c) Structural OCT showing the inner and external retinoschisis and the macular hole with subretinal fluid. Vitrectomy followed by inverted flap ILM technique was performed. (d) Postoperative retinography showing closure of the hole. (e) Structural OCT whit macular hole closure, disappearance of retinoschisis, but bad restoration of external retinal layers.

Figure 2: 56-year-old man with an axial length of 38 mm and a BCVA of 20/400, with inner retinoschisis and a myopic macular hole. (a) Fundus retinography showing the posterior staphyloma involving macula and optic disc and the chorioretinal atrophy. (b, c) Structural horizontal and vertical OCT showing the inner retinoschisis and the macular hole of 650 microns. (d) Fundus retinography after vitrectomy and inverted flap technique. (e, f) Structural vertical and horizontal scan showing the closure of the macular hole, the resolution of the retinoschisis, and the restoration of all retinal layers.

Vitrectomy for MH, first described by Kelly and Wendel [7], has been the gold standard technique for this condition, although the success rates are much lower in large-diameter MH and in myopic eyes. ILM peeling and gas tamponade is a well-established surgical option for myopic MH without RD, and for cases without [8, 9] or with associated retinoschisis [10]. Closure rates after vitrectomy and ILM peeling are usually high in most studies. In the present series, closure rates were 100% (idiopathic) and 86% (myopic), values that are similar to the rates reported by others. In 24 highly myopic eyes with full-thickness MH without RD, García-Arumí et al. [3] reported successful anatomic MH closure at 6 months postoperatively in 87.5% of patients undergoing 1 surgery and in 100% with 2 surgeries. Other authors have reported closure rates of 83% to 100% [11]. With regard to the BCVA, the percentage of patients with a vision improvement after ILM peeling ranges from 41% to 83% [11, 12, 13, 14]. In the present study, BCVA increased in 76% of idiopathic MH and 71% of myopic MH cases (ILM peeling group), with no statistical differences.

In the original study of the inverted flap technique by Michalewska et al. [6], MH closure was achieved in 88% of patients undergoing standard 3-port PPV and in 98% of patients treated with the inverted ILM flap technique, in both large idiopathic MHs (>400 mm) and in myopic MHs. The authors hypothesized that this approach may induce glial cell proliferation, resulting in MH filling with proliferating cells that enhance closure as well as new positioning of photoreceptors in direct proximity to the fovea [6]. Other authors have also reported successful surgical repair of myopic MH using the inverted ILM flap [15, 16].

The present study, including patients with idiopathic MH and myopic MH, found that vitrectomy associated with standard ILM peeling was more effective in idiopathic than in myopic cases, whereas in the inverted flap group, there were no differences. In our patients undergoing ILM peeling, the closure rate was 100% in idiopathic MH and 86% in myopic MH, similar to the values reported in previous studies [17–19]. In the inverted ILM flap group, the closure rates of 93% in idiopathic and 91.7% in myopic MH were similar to those reported by Michalewska et al. [8, 15] in myopic MH. In the ILM peeling group, a BCVA improvement at the end of follow-up was observed in 76% of patients with AL < 26 mm//idiopathic and 71% of patients with AL ≥ 26 mm//myopic MH. In the inverted flap group, a BCVA improvement at the end of follow-up was documented in 87% of patients with AL < 26 mm//idiopathic and 50% of patients with AL ≥ 26 mm//myopic MH.

Restoration lines (ellipsoid zone and ELM) were evaluated by OCT. The better visual outcome in the idiopathic MH peeling group could be related to a higher percentage of recovery of both these layers at 6 months as compared to patients with myopic MH (76% vs. 42%). In the inverted flap group, the less favorable visual outcome may be related to the lower restoration rates in both idiopathic MH (36%) and myopic MH (20%). These findings suggest that the peeling technique may result in a greater BCVA improvement because of more complete restoration of the ELM and ellipsoid zones. It has been shown that ELM integrity is critical for achieving a normal IS/OS postoperatively [14, 20]. Wakabayashi et al. [20] have reported that evidence of ELM integrity on SD-OCT at 3 months is the most significant structural feature for predicting the 1-year postoperative BCVA in surgically closed MH.

The limitations of this study include a retrospective design, small sample size, and absence of randomization for the type of treatment. A larger sample size would likely have improved the statistical power of the study and more properly supported the conclusions. The degree of myopic chorioretinal atrophy is known to limit good visual outcome [21, 22], but this factor was not evaluated due to the difficulty of establishing a definite diagnosis. Nor was the relationship between restoration lines and visual acuity investigated. Finally, a follow-up substantially greater than 6 months would be needed to compare the long-term effects of the two techniques on improvement of visual acuity.

In summary, this study provides further evidence of high MH closure rates associated with use of either the ILM peeling technique or the inverted ILM flap technique in the management of patients with idiopathic or myopic MH. The results for visual outcome and restoration of the external layers were better with ILM peeling than with the inverted ILM flap procedure, but these findings should be interpreted with caution because of the relatively small sample and retrospective nature of the study. In this respect, conclusions regarding the superiority of one technique over the other cannot be established.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Clinical Study

Vertical and Horizontal M-Charts and Microperimetry for Assessment of the Visual Function in Patients after Vitrectomy with ILM Peeling due to Stage 4 Macular Hole

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Purpose. To examine the relationship between the morphological and functional results in eyes after pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling due to stage 4 full-thickness macular hole (FTMH). *Methods*. The study included 22 eyes that underwent successful PPV due to FTMH. Both vertical metamorphopsia (VM) and horizontal metamorphopsia (HM) were determined using type 2 M-charts, as well as best-corrected visual acuity (BCVA), microperimetry, and optical coherence tomography (OCT) were performed before PPV and 1 and 6 months postoperatively. *Results*. A significant improvement of BCVA and metamorphopsia scores measured by M-charts in particular periods before surgery, 1 and 6 months after PPV, was observed. The VM scores were consistently higher than the HM scores at all assessment times. There was a correlation found between VM and BCVA and microperimetry parameters before surgery. The macular sensitivity (MS) as well as macular integrity index increased from 1 month to 6 months after PPV and were correlated with postoperative visual acuity (VA). There was a correlation found between the hole diameter and MS and P2 parameter 6 months after PPV. There was a correlation found between mean duration of symptoms of FTMH and VA and VM score. *Conclusions*. VM scores seem to correlate better than HM scores with preoperative BCVA, microperimetry parameters, and duration of symptoms of the FTMH. VM scores are higher after PPV than HM scores in patients with stage 4 of the FTMH. This trial is registered with NCT03701542.

1. Introduction

The full-thickness macular hole (FTMH) is a defect in all layers of the neurosensorial retina including the anatomical area of the fovea with preserved intact retinal pigment epithelium [1]. FTMH affects mostly elderly people, more commonly females than males, and the female-to-male ratio is determined to be 3.3 to 1 [2]. The pars plana vitrectomy (PPV) is the most effective procedure for the treatment of FTMH, with reported closure rates of first intervention exceeding 90% [3]. The main surgical indication for vitrectomy in FTMH is stages 2, 3, and 4 [4]. The classical surgical procedure consists of the central vitreous excision, the internal limiting membrane (ILM) staining and peeling, intraocular tamponade using air or expandable gases, and postoperative patient positioning. A lot of factors have been investigated as potential predictors of final visual acuity (VA) following surgical repair of FTMH. Better surgical and functional results are associated with earlier stage of FTMH, better preoperative

VA, shorter duration of symptoms, and younger patient age [5].

In clinical practice to evaluate visual function, the VA alone is usually used; however, it does not always provide a complete visual identity. The Amsler test is very simple, cheap, and consists of evenly (every 5 mm) spaced horizontal and vertical lines. The Amsler test is widely used to evaluate metamorphopsia, but it does not provide quantification of the severity of metamorphopsia [6]. M-charts (Inami, Japan) developed in 1999 by Matsumoto et al. enable evaluation of the degree of metamorphopsia quantitatively in patients with macular disease [7].

To evaluate the visual function in macular diseases, microperimetry MAIA can also be used, as it measures retinal sensitivity of the macular region, and the results can be displayed over a fundus image [8]. The microperimetry is a useful tool for objective evaluation of macular function, progression of the disease, and effectiveness of therapy [9].

The purpose of this study was to analyse metamorphopsia using the Amsler test and M-charts, as well as evaluation of macular sensitivity (MS) by using microperimetry, correlation with macular hole diameter, after successful repair of FTMH.

2. Methods

It was a prospective study of 22 consecutive patients who underwent successful surgery for FTMH at the Department of General Ophthalmology in Lublin, Poland. The study was performed in accordance with the Declaration of Helsinki. The approval of Ethics Committee of the Medical University of Lublin, Poland, has been given (KE-0254/269/2018). The study has been registered at ClinicalTrials.gov under the number NCT03701542. Written informed consent was obtained from all patients.

Inclusion criterion was the presentation of FTMH. Exclusion criteria were as follows: preexisting ocular diseases that could influence the outcome of the surgery, history of ocular trauma, and ocular surgery except for cataract surgery. There were 19 females and 3 males included in the study with average age of 66.73 ± 5.87 years. The surgeries were performed under local anesthesia by 2 vitreoretinal surgeons (KN and RR) using the Constellation system (Alcon, Fort Worth, Texas, US). The surgical technique characterized a standard 3-port 23, 25, or 27 gauge PPV, internal limiting membrane (ILM) peeling, fluid-air exchange, and gas tamponade (20% sulfur hexafluoride-SF6 gas). The ILM was stained in all eyes with a vital dye Brilliant Blue G (Geuder, Heidelberg, Germany). ILM was peeled off with forceps in an area of ≥2 disc diameters around the FTMH. All eyes were pseudophakic; cataract surgery was performed by phacoemulsification and implantation of foldable intraocular lens before FTMH surgery. Patients were instructed to remain in a prone position for about one week after the surgery.

Collected preoperative data were as follows: subjective duration of symptoms and diameter of the FTMH. All patients underwent best-corrected visual acuity (BCVA) and best near visual acuity (BNVA) measurements, Amsler test, M-charts, microperimetry (MAIA CenterVue, Italy), optical coherence tomography (OCT) examination OCT-2000 (Topcon Corporation, Tokyo, Japan), slit-lamp examination, and dilated funduscopy. The patients were examined before vitrectomy, 1 and 6 months after surgery.

BCVA was measured using Snellen decimal charts and converted into logMAR values. BNVA was measured using Snellen charts. The BNVA and M-charts test were performed with the best near correction, in the same lighting conditions and from the distance of 30 cm.

The type 2 M-charts consist of a double 19 dotted line with increasing dot intervals from 0.2° to 2.0° of visual angle. The test is carried out in the vertical and horizontal directions separately. The M-charts result was considered positive if the metamorphopsia score was more than 0 [6].

OCT, first introduced in 1995, became the gold standard in assessment of macular structure. OCT images were used preoperatively for the confirmation of the diagnosis and for measuring of the hole diameter and postoperatively for confirming the closure of the macular hole. Macular hole diameter was measured in micrometers as the minimum distance between the margins of FTMH. The FTMH stage was classified according to the Gass classification [10]. There was only stage 4 FTMH included. FTMH closure after surgery was determined with both a slit-lamp examination and OCT.

Microperimetry MAIA examination was performed in a dark room to analyse the retinal sensitivity and fixation stability (macular integrity index, $P1$ and $P2$ parameters). The background luminance was 4 asb, stimulus intensity range was 0–36 dB, stimulus size was Goldmann III, stimulus duration was 200 ms, and testing protocol was 4-2 threshold strategy.

Statistical analysis was performed using STATISTICA 13.0 software (StatSoft, Poland). All values were presented as the means and medians ± standard deviation, and for nonmeasurable parameters, cardinality and percentage are used. The Shapiro–Wilk test analysed measurable parameters. The Friedman ANOVA test was used to compare the preoperative and postoperative results. The R Spearman correlation was used to evaluate the relationship between the variables. $p < 0.05$ was considered to be of statistical significance.

3. Results

3.1. Visual Acuity. The mean BCVA before FTMH surgery was 1.04 ± 0.40 logMAR. The mean postoperative BCVA of all patients after 1 month was 0.64 ± 0.27 logMAR and after 6 months was 0.47 ± 0.22 logMAR (Figure 1). Statistical analysis showed a significant improvement in the BCVA after the surgery, and there were also significant differences in BCVA assessment in particular periods before surgery, at 1 and at 6 months after PPV ($p < 0.00001$).

The mean diameter of FTMH before vitrectomy was $609.45 \pm 150.45\,\mu$m. The mean duration of symptoms was 12.11 ± 5.90 months.

There was no correlation between BCVA before surgery and patients' age ($p = 0.28$), diameter of the FTMH ($p = 1.98$), and duration of symptoms ($p = 0.61$).

Figure 1: Medians, 25 and 75% quartiles, and maximum and minimum values of the visual acuity (logMAR) before pars plana vitrectomy (PPV) and after 1 and six months of the follow-up.

Figure 2: Medians, 25 and 75% quartiles, and maximum and minimum values of metamorphopsia scores both in vertical direction (VM) and horizontal direction (HM).

Statistical analysis showed a significant relationship 1 month after vitrectomy between BCVA and duration of symptoms ($R = 0.46$), which was still significant after 6 months ($R = 0.47$). After 6 months, there was also a correlation between BCVA and diameter of the FTMH ($R = 0.46$).

The mean BNVA before surgery was 1.83 ± 0.68. The mean BNVA of all groups was 1.16 ± 0.47 on 1 month and 0.91 ± 0.49 on 6 months. Statistical analysis showed significant differences in BNVA before and after successful surgery ($p < 0.00001$). Preoperatively, the mean BNVA was significantly correlated with diameter of the FTMH ($R = 0.49$). It means that the higher the diameter of the FTMH, the higher the BNVA value.

There was a correlation found between BCVA before surgery and 1 and 6 months after vitrectomy. It means that better the BCVA before surgery, better the BCVA results after surgery.

3.2. Metamorphopsia Scores. The mean vertical metamorphopsia (MVM) score of all patients was 1.11 ± 0.32 before surgery, improved to 0.85 ± 0.57 on 1 month and 0.86 ± 0.56 on 6 months (Figure 2). Statistical analysis showed significant differences in the VM score in particular periods before surgery, 1 and 6 months after PPV ($p = 0.002$).

The mean horizontal metamorphopsia (MHM) score of all patients was 1.03 ± 0.38 before surgery, 0.64 ± 0.42 on 1 month and 0.65 ± 0.42 on 6 months. Statistical analysis showed significant differences in the HM score in particular periods before surgery, 1 and 6 months after PPV ($p = 0.00002$).

The MVM scores were consistently higher than the MHM scores at all assessment times. Statistical analysis showed significant correlation between VM and HM scores, before surgery ($R = 0.69$), 1 month ($R = 0.72$), and 6 months ($R = 0.83$) after PPV.

There was a significant correlation between VM scores and microperimetry parameters before surgery, and no correlation was found between HM scores and microperimetry parameters (Table 1). No such correlation was found in regard to HM and VM scores 1 and 6 months after surgery.

Statistical analysis showed significant correlation between VM score and BCVA before vitrectomy ($R = 0.52$), but no such a correlation was found for the HM score. The higher the preoperative logMAR value, the higher the VM score. Statistical analysis did not show significant correlation between M-score (VM and HM scores) and BCVA after surgery ($p > 0.05$), as well as with preoperative diameter of FTMH at any assessment time ($p > 0.05$).

There was a correlation found between mean duration of symptoms of FTMH and VA and VM score.

3.3. Microperimetry. Mean macular sensitivity (MS) of all patients before surgery was 21.18 ± 2.92 dB, 22.80 ± 4.37 dB after 1 month, and 24.22 ± 5.03 dB after 6 months after PPV. Statistical analysis showed significant improvement in the MS before surgery, 1 and 6 months after PPV ($p < 0.00001$) (Figure 3).

The macular integrity index was 95.12 ± 20.96 before surgery, 91.10 ± 15.77 on 1 month, and 80.80 ± 25.74 on 6 months after PPV. Statistical analysis showed significant improvement in the macular integrity index before surgery, 1 and 6 months after PPV ($p = 0.0009$).

Mean fixation stability $P1$ and $P2$ values of all patients were $P1 = 60.09 \pm 24.06$ and $P2 = 88.73 \pm 11.94$ before

Table 1: Correlation between horizontal (HM) and vertical (VM) M-charts and microperimetry parameters.

Parameters	VM		HM	
	R	p	R	p
Average threshold (dB)	−0.47	0.03*	−0.39	0.08
$P1$	−0.51	0.02*	−0.38	0.08
$P2$	−0.48	0.02*	−0.35	0.11
Macular integrity	−0.02	0.92	0.03	0.90

*$p < 0.05$ indicates that significant correlations were found between two parameters.

Figure 3: Medians, 25 and 75% quartiles, and maximum and minimum values of the following parameters in microperimetry: average threshold (in decibels), $P1$ and $P2$ fixation stability (%), and macular integrity (in decibels, dB).

surgery, $P1 = 63.32 \pm 27.05$ and $P2 = 86.05 \pm 19.71$ on 1 month, and $P1 = 65.73 \pm 18.56$ and $P2 = 92.00 \pm 6.12$ on 6 months after PPV. There were no significant differences in these parameters after statistical analysis.

Statistical analysis did not show significant correlation between microperimetry and preoperative BCVA ($p > 0.05$), while after surgery, there was a correlation between BCVA and MS ($R = -0.64$) on 1 month and on 6 months ($R = 0.56$) and between BCVA and macular integrity ($R = 0.70$) on 1 month and ($R = -0.48$) on 6 months.

There was a correlation found between FTMH diameter and MS and $P2$ parameter 6 months after PPV.

4. Discussion

The current study was performed to assess the functional characteristics and surgical outcomes using M-charts and microperimetry in a group of patients with FTMH.

We observed a significant improvement of BCVA and reduction of metamorphopsia after successful FTMH surgery, which was similar to the previous studies.

Kim et al. investigated the time to visual recovery after FTMH surgery. They observed significant differences in BCVA at 1 and 3 months after PPV, and BCVA stabilized after 6 months [11]. We also observed continuous improvement in VA from 1 month after PPV to 6 months after the operation. Shinoda et al. reported visual recovery at 3 months after MH surgery in a 25-gauge vitrectomy group and at 9 months after surgery in a 20-gauge vitrectomy group [12]. Mini-invasive surgery provides the shorter operation time, less trauma to the ocular surface, reduced amount of irrigation fluid, and is the reason for shorter recovery time. Directly after PPV, 77.27% of our patients had better VA results. At final follow-up period, we got the result of 100% VA improvement. It is a satisfactory outcome because Leisser et al. had BCVA improved in 83% of the cases and Amram et al. reported that 86% of eyes had improved BCVA at the final follow-up period of 1 year [13, 14]. Although percentage of patients with BCVA improvement is very important, it is necessary to estimate the level of final correction. The significant improvement of BCVA (greater than 50%) after 6 months we obtained in 50.00% of patients. The medium BCVA improvement (≥18%) was in 45.45% eyes, and 4.55% of patients had poor BCVA result (<18%). We also found the correlation between preoperative BCVA and 6 months after surgery. Better postoperative VA was correlated with better preoperative VA ($R = 0.46$), which was similar to the previous study [15].

Wendel et al. suggested better improvement in VA of patients undergoing FTMH repair with less than 6 months' duration of visual symptoms [16]. Delay from preoperative assessment to surgery can be a significant predictor of outcomes at final follow-up. In our study, duration of visual symptoms was 12.11 ± 5.90 months. Reasons for delay to surgery include patient or/and staff scheduling difficulties, lack of patient-perceived urgency, healthcare system, and other social factors.

We established lower postoperative BCVA due to larger diameter of FTMH. It is consistent with the study of Kim et al. that final visual acuity was poor in patients with a larger basal hole diameter [11].

Metamorphopsia is a common symptom affecting quality of vision due to the displacement of the photoreceptors and outer segments from their original position [17].

In our study, the Amsler test was abnormal preoperatively in 100% of patients, but it does not give the information about the severity of metamorphopsia. Ninety percent of our patients after successful surgery reported distortion of image using the Amsler test; however, the evaluation of their intensity is also difficult to assess.

In our study, the MVM score of all patients before surgery was 1.11 ± 0.32 and the MHM score was 1.03 ± 0.38. We observed a significant improvement of these parameters after surgical repair of macula. The MVM score 6 months after surgery was 0.86 ± 0.56, and the MHM score was 0.65 ± 0.42. Furthermore, the VM scores were consistently higher than the corresponding HM scores, and there was a

trend—the higher the VM, the higher the HM scores at all assessment times. It is a similar result to the previous study [6, 17, 18].

In our study, the major finding was that VM scores seem to correlate better with preoperative BCVA, microperimetry parameters, and duration of symptoms of FTMH. VM scores are also higher after PPV than HM scores in patients with stage 4 FTMH. Most of the authors [7, 19, 20] present only general score of M-charts. Wada et al. analyse both HM and VM scores [6].

The higher VM score was reported and speculated that the nasal outer segments had a tendency to be thicker than other sides in FTMH, since the greater stretching of tissues toward the thicker retinal regions. The larger horizontal retinal changes may be due to the higher VM score [17].

Arimura et al. believed that the VM score was correlated with the horizontal retinal contraction and the HM score was correlated with the vertical retinal contraction [18].

Liang et al. also found that the VM score was significantly higher than the HM score, they concluded the reason behind the asymmetrically elongation, and the higher VM score remains to be further studied. Liang et al. also reported the relationship between M-score and macular parameters. They found that the postoperative mean M-score was significantly positively correlated with the mean minimal diameter of FTMH, but there was no correlation between preoperative M-score and the mean minimal diameter. Furthermore, they proposed that the mean minimal diameter of FTMH may be a prognostic factor for postoperative metamorphopsia, which may help one to predict postoperative metamorphopsia before surgery [17]. Our results contrast with this study, because we did not find any correlation between M-scores and minimal diameter of FTMH. Also, the other researchers showed no significant correlations between the VM and HM scores and any of the preoperative OCT parameters at any assessment time [6, 19]. It may reflect a difference in the average minimum diameter of the FTMH in different study populations. In addition, in our study, there was a significant correlation between preoperative VM score and BCVA. We agree with the other researchers that preoperative metamorphopsia measured by M-charts may have more complicated affected factors besides macular parameters and evaluating M-scores, especially VM score in addition to BCVA can be an independent treatment outcome [6, 17].

To assess the functional success of the surgery, we used microperimetry measuring retinal sensitivity and the fixation behavior while fundus is directly examined. It is rapid, safe, noninvasive, and useful tool for evaluation of macular function [9]. We observed preoperatively a significant loss of sensitivity of macular area affected by a disease, and the mean sensitivity (dB) was 21.18 ± 2.92. Six months after surgery, the mean sensitivity was better (24.22 ± 5.03). The macular integrity index is a numerical value that describes the likelihood that a patient's responses are normal, suspect, or abnormal when compared to age-adjusted normative data. It does not represent the severity of the disease process. There is no direct relationship between the average threshold value (dB) and the macular integrity index. Preoperatively, in our group, the mean macular integrity index was 95.12 ± 20.96 and 6 months after surgery was 80.80 ± 25.74. The lower value of the macular integrity index means the better respond and postoperative improvement of this parameter. We found the correlation between the postoperative mean MS and the preoperative size of FTMH. The larger diameter of FTMH provides the lower value of MS. The higher MS and lower macular integrity index are correlated with better postoperative BCVA. Our results and connections between MS and diameter of FTMH or MS and quality of postoperative BCVA are similar to the result previously shown by Bonnabel et al. [15]. It needs to be highlighted that, we did not find any significant correlation between MS and preoperative BCVA ($p > 0.05$), so microperimetry can be an additional, useful tool in predicting the postoperative prognosis and objective evaluation of changes in visual outcome. Additionally, we found correlation between microperimetry and M-score before PPV. Parameters such as average threshold value, $P1$, and $P2$, were correlated with the VM score. There were no similar connections with the HM score ($p > 0.05$). The lower VM score provides the better MS, $P1$, and $P2$ results.

Preoperative, intraoperative, and postoperative factors have been investigated as potential predictors of final VA following surgical repair of FTMH. Among preoperative factors, two well established are symptom duration and preoperative VA. The other factors are patient age and OCT parameters such as stage of FTMH, minimum diameter or/and base diameter of the FTMH, central subfield retinal thickness, height of the FTMH and diameter of internal/external segments layer IS/OS, and external limiting membrane (ELM) defects [5, 21, 22]. However, these parameters are anatomical, imaging-based features, and to estimate the result of FTMH surgery, functional tests are required too.

In summary, this study evaluated prospectively metamorphopsia using M-charts and Amsler test, and MS result in microperimetry MAIA among patients after successful vitrectomy due to FTMH. Both microperimetry and M-charts test, especially VM-score, provide more comprehensive information of the visual function of FTMH patients before and after surgery and can be useful, additional predictor factors of succeed vitrectomy and postoperative results.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Clinical Study

Morphology of Peeled Internal Limiting Membrane in Macular Hole Surgery

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Purpose. The aim of this work was to describe the ultrastructure and behavior of peeled internal limiting membrane (ILM) in macular hole (MH) surgery. *Methods*. Seven patients with MH were included, and vitrectomy with ILM peeling was performed in all patients. The ILM inverted flap technique was used. Two other flaps of ILM of the same patient were collected and studied using light and transmission electron microscopy (TEM). ILM cell type, distribution, and morphology were analyzed, and the proliferation or fusion potential of the ILM interface was evaluated. *Results*. ILM vitreous sides in apposition showed signs of proliferative fibrotic activity, producing a basal membrane that merges ILM sides. *Conclusions*. Epiretinal cells in ILM show proliferative capacity, with formation of microfibrils between adjacent sides of the ILM, which may explain adherence of ILM flaps to the hole border, contributing to closure of the hole in MH surgery. This trail is registered with NCT03799575.

1. Introduction

Full thickness macular hole (MH) is an anatomic opening in the fovea, the central area of the retina, and affects mostly women after the 5th decade. As the fovea is responsible for central vision, the loss of vision caused by a MH is very severe. MH was considered untreatable until Kelly and Wendel reported closing a macular hole after pars plana vitrectomy, which removed all anteroposterior (AP) traction [1].

Besides the importance of AP vitreoretinal traction in MH formation, tangential traction seems to have a significant role in progression and recurrence of MHs [2]. Activated glial cells, especially Muller cells and astrocytes, may proliferate and migrate from the retinal side to the vitreous side and form epiretinal cells causing tangential traction [3]. Also, hyalocytes from the vitreous cavity may induce cellular proliferation at the internal limiting membrane (ILM) [4]. These hyalocytes are found on the vitreous cortex, in close contact with the ILM at the posterior retina, and may have macrophagic-like activity [2].

ILM peeling is widely accepted as a safe surgical technique, showing a high success rate in MH closure [5]. The recent inverted flap technique introduced by Michalewska and Nawrocki for large macular holes allows for an even higher closure rate [6]. Instead of removing one piece of ILM, with this technique, the ILM is peeled until the hole border and one larger piece is left free and inverted over the hole and kept secure with intraocular gas, allowing for a large macular hole to close (Figure 1). The inverted flap to cover a large macular hole may be a temporal or superior flap of partially peeled ILM [7].

Herein, we describe novel findings concerning the morphological features of peeled ILM during IMH surgery that may help to explain the mechanisms of hole closure after MH surgery.

2. Patients and Methods

2.1. Surgical Procedure. Seven patients with MH larger than 400 μm, according to OCT-based classification [8] were

Figure 1: Schematic representation of the position of peeled ILM in macular hole surgery. Inverted flap with vitreous side adherent to vitreous side of ILM of the other border, not inverted.

submitted to a standard surgical procedure. The surgery was performed by the same surgeon (MF) and consisted of a 23-gauge, three-port pars plana vitrectomy and ILM peeling. Balanced salt solution (BSS; Alcon, Fort Worth, TX) was used as an irrigation solution. Posterior vitreous detachment was completed when needed and assisted with triamcinolone acetonide. A single-use macular contact lens (Grieshaber®, Alcon, TX) was used in ILM peeling. Brilliant Blue® Dual (Geuder, Germany) assisted ILM identification, which was then engaged with an end-grip intraocular forceps. ILM was peeled in a rosette way around the macula and trimmed until the border of the hole, but one large flap was left, large enough to invert over the macular hole. Two other samples of ILM, per patient, were also collected, elsewhere in the macular area, and harvested for laboratory analysis.

The tenets of the Declaration of Helsinki were followed. All patients provided written informed consent to the surgical and study procedures. Approval was obtained from the Ethics Committee of Hospital Santa Maria.

2.2. Laboratory Analysis. Of the two samples of ILM per patient that were harvested, one was immediately fixed and submitted to optic microscopy (OM) and transmission electron microscopy (TEM) analysis and the other sample was incubated in enriched medium 199 (Gibco) for 20 minutes at room temperature, after which it was also fixed and submitted to OM and TEM analysis. Analysis of all samples followed the protocol available at https://doi.org/10.17504/protocols.io.qjiduke.

2.3. Image Acquisition. Six electron micrographs were acquired for each fragment, using a Hitachi H-7000 electron microscope equipped with a megaview III digital camera. Fields of interest were randomly selected, and 15,000x magnification images were acquired.

2.4. Quantitative Analysis. Collagen areas were measured using the iTEM software (Olympus©) measurement tool. For each micrograph, collagen areas were manually assessed in relation to the total amount of sample present, and average values for each patient and fragment were calculated. A collagen fraction (%) for each fragment was also calculated (values in μm^2).

3. Results

3.1. Macular Hole Closure. The macular hole was closed and vision improved in all seven patients. In postoperative OCT, each macular hole was covered with ILM and bridging of external limiting membrane (Figure 2).

3.2. Histology and Immunohistochemistry. ILM samples were stained with anti-GFAP antibody (antiglial fibrillary acidic protein), and the majority of cells found were positive for anti-GFAP. GFAP is the hallmark protein in astrocytes [9], a main type of glial cells in the central nervous system (Figure 3).

3.3. Light Microscopic Features. Microscopy analysis of semithin sections of both samples showed a continuous folded and wrinkled ILM strand. The vitreous side of the ILM was smooth and continuous while the retinal side was characterized by irregular undulations (Figure 4).

3.4. Transmission Electron Microscopy. The morphological features of both the vitreous and the retinal sides of the ILM were evaluated in terms of cell distribution. The retinal side had scarce cells, while the vitreous side had some epiretinal cells.

The same structures on both sides of the ILM were identified: the fragment that was immediately fixed was wrinkled with both the vitreous and retinal sides showing no evidence of merging activity nor fibrotic material between the two sides of the juxtaposed ILM (Figure 5).

On the contrary, in the ILM sample that was kept in enriched medium for 20 minutes, the two vitreous sides of the folded piece of ILM came in contact and proliferative fibrotic material was present in the areas where adhesion occurred. In terms of morphology and structure, these fibers resemble collagen microfibrils/fibers (Figures 6 and 7).

Table 1 describes the percentage area of collagen in each observed sample, fixed immediately upon collection and after 20 min incubation with enriched medium.

4. Discussion

ILM peeling has been the standard procedure in MH surgery allowing closure rates of nearly 100% [10]. However, large macular holes, over 400 μm diameter, have an increased risk of failure, and 44% do not close at first surgery, with 19% having been reported to stay flat and open [6]. Macular hole surgery has improved the rate of closure after the introduction of the inverted flap technique, especially in long-standing and large macular holes and in holes seen in high myopia [11]. Also, in cases of refractory macular holes, the autologous transplantation of ILM allowed for an improved anatomical outcome of these macular holes [12].

In these difficult macular holes, after releasing all anteroposterior and tangential tractions, the surgical technique of sealing the macular hole with inverted ILM consists in closing the hole with ILM peeled to the hole border, inverted over, and then attached to the borders of

Figure 2: Preoperative (left) and postoperative (right) OCT of every patient. (a) Patient A. (b) Patient B. (c) Patient C. (d) Patient D. (e) Patient E. (f) Patient F. (g) Patient G.

Figure 3: Internal limiting membrane (blue). Glial cells protein A coupled to 15 nm gold particle (gold), marked with black arrows and magnified.

Figure 4: Optic light microscopy of ILM. V: vitreous side; R: retinal side. *Vitreous side contact; **retinal side contact.

Figure 5: Juxtaposed sides of ILM with no apparent interaction between the vitreous side (V) and the retinal side (R). Bar: 2 μm.

Figure 6: Representative electron micrographs of ILM of patient A, showing both vitreous sides (V) of the same membrane merged, and, in the center, the existence of fibers. Bar: 500 nm.

the hole, instead of completely peeling all ILMs around the hole. In case of autologous transplant, there is no more ILM near the hole to peel. A piece of ILM is peeled elsewhere in the retina of the same eye and is carefully placed on top of the hole, with the help of perfluorocarbon liquid, secured with air and gas. The peeled ILM, transplanted or inverted, contains Muller cells fragments that can induce gliosis on the retina and on the surface of the ILM. The macular hole closes, eventually due to the merging of the ILM with structures at the hole borders, and we speculate that the creation of this closed space may activate growth factors that induce cell realignment. In an

(a) (b) (c)

Figure 7: Transmission electron microscopy details of two internal limiting membrane (ILM) fragments from patients A, B, and C, with and without enriched medium. (a1–c1) Fragments of ILM from each patient which were immediately fixed. (a2–c2) A second ILM fragment of the same patient after 20-minute incubation in the enriched medium. Percentage area of collagen.

Table 1: Area of collagen in percentage (%) on samples fixed upon collection and after 20 min incubation with enriched medium.

	Collagen area fraction (%)	
	Fixed upon collection	Fixed after medium enrichment
Patient A	0.00	19.50
Patient B	0.00	6.68
Patient C	0.00	50.23
Patient D	5.77	17.78
Patient E	0.00	17.78
Patient F	0.00	0.00
Patient G	2.87	7.46

Values in $\%\mu m^2$.

experimental animal model, Shiode et al. tried to identify the components of the ILM that were important for the proliferation of Muller cells and collagen and fibronectin were found to enhance their migration [13]. Yokota et al. described newly synthesized collagen fibers in an ultrastructure study of peeled ILM after vitrectomy for myopic traction maculopathy [14]. Schumann et al. reported newly formed collagen at the vitreous side of the ILM removed from failed macular hole surgery [15]. In our study, we found a merging tendency of ILM pieces when kept in enriched media, in six of seven patients, accompanied by collagen fibers and fibrosis, as observed by TEM analysis. Considering our results and the results reported by Schumann at al. associated with the novel inverted flap, we speculate that this fibrosis may actually happen in the ILM vitreous side of our patients' eyes, allowing for hole closure, either because the vitreous side of the ILM has epiretinal cells or because of the presence of collagen fibers from the vitreous cavity.

In a clinical situation, surgery with vitrectomy and ILM peeling relieves anteroposterior and tangential mechanical forces. Gas tamponade creates prolonged contact of ILM tissue fragment with each other or with the underlying retinal tissue, which seems to be fundamental for hole closure. In our study, we found that when the two vitreous sides of ILM were in contact, epiretinal cells present in the ILM vitreous side form microfibrils that may contribute to the sealing process of MH surgery.

The limitations of this study include the small number of studied cases, with the possible consequence of randomness in the obtained findings. The identification of specific immunohistochemical markers for better cell characterization will also be a future added value. Also, the type of collagen, old and newly synthesized, has not been characterized.

Data Availability

All data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Mun Faria contributed to conceptualization and investigation. David Sousa was involved in methodology, review, and editing. Bruna Almeida contributed resources. Andreia Pinto was responsible for investigation. Nuno Ferreira was involved in validation, review, and editing.

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Review Article

Pathogenesis and Management of Macular Hole: Review of Current Advances

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Macular hole has been believed to be a disorder of vitreomacular interface, which forms as a result of abnormal vitreous traction from incomplete vitreous detachment. However, our recent studies demonstrated that dynamic forces, caused by mobile posterior cortical vitreous with fluid currents, exist already at early stages of macular hole development. Therefore, in eyes with flexible vitreous, the contributions of tractional forces due to vitreous shrinkage are unlikely. These facts indicate that in the development of idiopathic macular holes, there is a greater contribution of dynamic forces than has been previously reported. This review also evaluates the recent findings in the assessment of the idiopathic macular holes and the recent therapeutic strategies for optimal management. Inner limiting membrane is considered to improve anatomical closure rate; however, it is still questionable if peeling is necessary in holes less than 250 μm. There are plenty of publications indicating that in the management of small and medium size hole (less than 400 μm), use of long-lasting gas and face-down position is not always required; however, it may be necessary for the treatment of large holes. Ocriplasmin and expansile gas had been reported to be successful for management of small- and medium-sized holes and vitreomacular attachment.

1. Introduction

Macular hole is a retinal defect located in the centre of the fovea, causing significant vision impairment [1]. Knapp in 1869 was the first who reported a macular hole with traumatic origin [2]. The term "hole in the macula" was used by Ogilvie in 1900 [3].

There are two types of macular holes which can be observed: idiopathic macular holes (IMH) [1], which is caused by vitreous traction on the foveal centre anteroposterior and tangential directions, and traumatic macular hole (TMH) usually caused by mechanic blunt injury of the eye [4]. However, in the recent literature, the term idiopathic is not used anymore, as the vitreous traction is the known reason for MH development [5].

Development of MH with retinal detachment is a specific complication of high myopia with posterior staphyloma (although in some patients with a staphyloma retinal detachment can develop without a hole) [6].

MHs can resolve, persist stable, or progress to full-thickness macular holes. According to Gass, in case if complete posterior vitreous detachment develops, the fovea can return to normal, or if Müller cell cone is stripped from the retinal surface, a lamellar hole may develop [1].

In the general population, the prevalence of MHs was reported to be around 3.3 per 1,000 people [7]. Until 1991, MH was considered to be an untreatable condition, but for the past decade, surgical techniques for closing the hole and improving the central vision are carried out as a routine practice. Vitrectomy surgery with the use of long-acting gas and postoperative positioning face-down for 1 week was the only available treatment; however, nowadays, there are a number of options to choose from. This review discusses the recent finding on the management of

IMHand classification and surgical options for optimal treatment.

2. Classification, Evaluation, and Pathogenesis

In the MH formation, an important role is on the vitreous traction [8]. Gass classification is based on stepwise development of macular holes according to how the vitreous exerts traction on the fovea (Table 1). In 2013, the international vitreomacular traction study (IVTS) proposed anatomic classification based on OCT findings [9], in which MHs are divided into primary or secondary by cause and also by the presence or absence of vitreous attachment. Additionally, based on the horizontally measured linear width at the narrowest point of the hole, they had been classified into small (≤250 μm), medium (>250 μm and ≤400 μm), and large (>400 μm) [9]. However, in a recent publication, according to Soon et al., there is a little difference between 350 μm and 450 μm MH, and in sense of planning surgery, 400 μm is not very practical [10]. According to their study, 650 μm is a much better marker to divide medium and large macular holes, based on their results with 90% success in standard full-thickness macular hole (FTMH) vitrectomy involving internal limiting membrane (ILM) peel and gas tamponade on medium MH between 250 and 650 μm [10]. They noted in their study that standard surgery for large MH (>650 μm) is less successful, and such techniques as ILM flaps and retinal expansion technique for macular hole apposition (RETMA) should be considered for this matter [10]. Also, in a study of Yu et al., they conclude that stage 3 MHs, instead of smaller diameters and shorter duration of symptoms, have similar clinical and morphological features with stage 4 MHs according to Gass' classification (1995), where MHs smaller than 400 μm are excluded from stage 3 compared to 1988 classification [11].

Recent publication of results of European Eye Epidemiology (E3) consortium to standardize epidemiological studies proposed a spectral-domain optical coherence tomography- (SD-OCT-) based classification for macular diseases, where MHs are subclassified as small (<250 μm), medium (>250 to ≤400 μm), and large macular hole (>400 μm) [13]. A detailed classification with the acronym WISPERR, which includes 6 domains, width of vitreoretinal attachment, vitreoretinal interface changes, shape, pigment epithelial changes, elevation of the lowest point of vitreous attachment, and intraretinal changes separated into inner and outer retinal changes of focal vitreomacular attachment (VMA) and traction, has been suggested [14]. Chun et al. suggested to modify classification of MH based on OCT findings [12] into 2 types of MHs based on the level of preoperative tissue defects (the differences between them depended on peculiar characteristics of Müller cells in the fovea); additionally, this classification system determines closure patterns and visual outcomes after surgery [12]. MH subdivided according to the tissue defects into A type: dehiscent type, macular holes with few outer foveal tissue defects from central dehiscence (the A type is the photoreceptor retraction-dominant, in which foveal pseudocysts and intrafoveal splitting occur) and B type: tearing type, macular holes occur from substantial outer tissue loss as a result of full-thickness tearing (tractional force affects Müller cells eccentric to the centre of the foveolar floor, when traction is large and vitreofoveal adhesion in intensive). Stage 2 MHs are subdivided into 2-A and 2-B holes, where stage 1-A holes progress to stage 2-A holes, and stage 1-B holes progress to stage 2-B holes. In both cases, the anterior traction of the incompletely detached posterior hyaloid is a major factor contributing to the progression of holes from A to B type [12]. Preoperative examination should include measurements of visual acuity, metamorphopsia record by Amsler chart, slit-lamp biomicroscopy, and OCT evaluation. OCT helps not only visualize the vitreomacular traction but also to plan the surgical manoeuvres. It is very important to pay attention on the size of the holes since the size is crucial for visual prognosis and anatomical closure [12].

Some holes, especially without vitreomacular attachment (VMA), may close spontaneously. Spontaneous resolution of such holes was reported in a range from 2.7% to 8.6% of cases [15–17]. Some patients can be observed with so-called macular microholes, holes within 50–100 μm without VMA [18]. But usually holes progress and 34.4%–79% [19, 20] had progression in hole size from 2 to 6 years follow up. Takahashi et al. reported that a second full-thickness MH was developed in 5 of 16 fellow eyes (31%) with a foveolar detachment and in 5 of 9 fellow eyes with a foveolar detachment and inner foveal splits [21].

SD-OCT provides precise measurements of MH dimensions, and contemporary equipment allows to obtain images with the resolution between 10 μm and 25 μm [22]. OCT images are very helpful for examining relationships between the retina and vitreous as well as associated structures adjacent to and outside of the macula.

Measurements of base diameter (BD) and minimum linear diameter (MLD), hole form factor, macular hole index, and tractional hole index are described for MH evaluation [23, 24].

In 2012, Mori et al. published the results of wide-angle montaged images of SD-OCT in patients with macular hole. They described two patterns of posterior vitreous configuration, "smooth or wavy" vitreous surfaces. Posterior vitreous cortex had a smooth curvature at the onset of separation, and with progressive separation, posterior vitreous folds increased. This finding indicates redundancy progression of posterior cortical vitreous through the process of MH formation. This "wavy" interface implies vitreous mobility. The mass and movement of the vitreous represents the potential force to act on the retina. In addition, granular hyperreflection was observed in 50% to 60% of eyes with stage 1 or 2 holes in the peripheral vitreous and in 33% of eyes with stage 3 or 4 holes, and also they described areas of peripheral double-layered retinoschisis in the peripheral retina adherent to posterior vitreous cortex [25].

There has been a controversy in the origin of vitreous traction in the pathogenesis of MH formation. Guyer and Green [26] and Johnson [27] suggested that dynamic tractional forces that are generated by posterior cortical vitreous movement during the rotations of the eye may play an important role in the development of MH. Mori et al. also

Table 1: Classifications of macular holes.

Gass stages	Description	OCT	IVTS group classification	E3-SD-OCT-based classification	Chun et al. classification [12]	
					Type A: dehiscence and centrifugal retraction	Type B: tearing or full thickness fovea
Stage 0	VMA in the fellow eye of a patient with a known/previous MH without any change in foveal architecture		VMA			
Stage 1A	Impending macular hole with outer retinal elevation from RPE at foveal centre		VMT without MH: can occur with outer or inner retinal changes or both		(i) Impending hole (ii) Occult hole	Occult hole
1B						
Stage 2	≤400 μm MH with VMA		Small- or medium-sized MH with VMT	(i) Small (<250 μm) (ii) Medium (>250 to ≤400 μm)	Opercula that are still attached to the hole edge	Opercula that are still attached to the hole edge
Stage 3	>400 μm MH without VMA		Large MH without VMT	Large macular hole (>400 μm)	Small holes (i.e., <400 μm) and longer lengths from the tip of the ELM to the GCL	>400 μm
Stage 4	MH with complete posterior vitreous detachment		Small, medium, or large MH without VMT			

IVTS, International Vitreomacular Traction Study Group classification; E3-SD-OCT, European Eye Epidemiology (E3) consortium spectral-domain optical coherence tomography-based classification; VMA, vitreomacular adhesion; RPE, retinal pigment epithelium; MH, macular hole; VMT, vitreomacular traction; ELM, external limiting membrane; GCL, ganglion cell layer.

described the mobility of posterior cortical vitreous, using the OCT tracking system. They scanned baseline and after the vertical and horizontal saccades of the same area of the fundus using eye tracking system. The tracking system of OCT enables image registration of the same area allowing longitudinal imaging. These merged images demonstrated the posterior vitreous duplication, indicating its mobility. It was reported that the incidence of cortical vitreous duplication in eyes with idiopathic MH was 92%, increasing with progressing stage of the MH [28]. Therefore, they proposed that role of dynamic forces to the development of idiopathic MH is greater than that has been thought previously.

Additionally, need to mention, even though IVTS group provided in 2013 definitions of lamellar MH and macular pseudohole based on B-scan OCT image findings [9], recent advances in OCT allowed to include such findings as lamellar hole-associated epiretinal proliferation [29]. In recent study, Romano et al. evaluated the macular pigment optical density (MPOD) by the one-wavelength fundus reflectance method, and they found statistically significant differences in MPOD between healthy eyes and eyes with vitreoretinal interface syndromes (iERM or MH) in case of MH, and they observed the lack of macular pigment in an area corresponding to the hole surface, which occurred as a result of opening of the fovea and a centrifugal displacement of the macular pigment [30].

3. Treatment

The most important prediction for successful MH surgery is preoperative visual acuity (VA). The better the preoperative VA is, the higher the rates of visual gain and anatomical closure [31, 32]. Short duration of symptoms is also a crucial factor for better visual outcomes and anatomical closure of MH [33]. Stage 1 MH can be spontaneously resolved in some

occasions; however, they need to be under close observation [15]. Stage 2 and higher are usually indications for surgical correction, for better surgical results (anatomical and functional) [11, 15].

3.1. Vitrectomy. Vitrectomy for closure of MH is reported to have high success (85%–100%) [34]. Jackson et al. reported a multicentre database study of 1,045 patients, where 48.6% achieved visual success at 12 weeks postoperatively; it was increased to 58.3% at 52 weeks [35]. Herneiss et al. reported results after 1 year following pars plana vitrectomy (PPV), where macular hole closure was achieved in 57 of 59 patients (97%), and significant improvements in general vision and quality of life were reported [36].

3.2. Internal Limiting Membrane (ILM) Peeling. Eckardt et al. in 1997 [37] was the first to describe ILM peeling, and it was reported to give good results and increase the rate of closure for MH. Several randomized control trials confirmed the efficacy of ILM peeling in MH surgery. According to Lois et al. [38], at 1 month postoperatively in patients undergoing ILM peeling, closure was achieved in 84% compared with 48% who did not have ILM peeling ($P < 0.001$).

Nowadays, ILM peeling becomes a routine technique for MH surgery for most surgeons. For staining the ILM, such adjuvants as indocyanine green [39], triamcinolone acetonide [40], and brilliant blue G (BBG) [41] are used. Variations of ILM peel such as inverted ILM peeling and ILM-free flap are in a use for surgeons. In large MH, Michalewska et al. reported a surgical technique called inverted ILM peeling to overcome surgical failures [42]. Kuriyama et al. reported that this technique demonstrated an outstanding result in cases of MH associated with pathologic myopia [43]. According to recent randomized control trials (RCT), inverted ILM flap technique demonstrated higher anatomical success rate with a better functional outcome; however, statistically significant difference was not achieved [44]. Soon et al. reported application of ILM peeling for the management of large MH [10], and they claim 90% success with standard MH vitrectomy involving ILM peel and gas tamponade in medium MH between 250 and 650 μm. Free flap ILM is used in patients with persistent MH hole after previous surgery, where a free patch of peripheral peeled ILM is placed over or in the MH [45].

As an alternative to ILM peeling ILM, abrasion had been proposed, in order to thin the ILM and loosen its adhesion to the underlying retina while still stimulating glial cell activation [46]. However, ILM peel can have negative consequences on a function (paracentral scotomas and reduced central retinal sensitivity) and retinal structure (changes in the retinal morphology such as retinal displacement); some techniques of ILM peeling and variety of dyes used may add some other risks (such as submacular RPE atrophy of glial cells response on closure, dye toxicity, etc.) [47].

3.3. Gas Type and Tamponade. Fluid-air exchange with subsequent gas exchange was usually carried out, after vitrectomy and ILM peeling [48]. Gas tamponade is helping in hole closure by preventing trans-hole fluid leakage from the vitreous cavity, pumping the retinal pigment epithelium in order to remove the subretinal fluid, decreased retinal oedema by reducing transretinal uveal-scleral outflow, also generating interfacial surface tension force between the retina and the gas bubble in order to pull the hole edges [49], helping glial cell to migrate for the gap closure by creating the surface [50, 51].

Different isovolumetric gas concentrations used by surgeons and total duration of gas filling usually range from 2 to 11 weeks (2–2.5 for SF6, 4–6 for C2F6, and 8–11 for C3F8) [8].

Closure rate of 90% with SF6 and 91% with C3F8 was reported in a retrospective cohort study with face-down positioning postoperatively [52]. In a prospective randomized control trial published by Briand et al., 59 patients were randomized to either SF6 or C3F8 with differing posture regimes. In those patients, closure was achieved in 93.3% and 92.9% and best-corrected visual acuity improved by 17.7 letters and 16.9 letters, respectively [53].

3.4. Posturing. Maintaining the face-down positioning with gas tamponade was reported to be useful in the MH closure; however, it is not comfortable for patients and can be associated with complications, such as back pain or ulnar nerve palsies [54]. However, optimal duration of posturing is still questionable. Recent publications indicate that long-lasting posturing is not necessary for MH closure after vitrectomy with ILM peeling and a long-acting gas tamponade [55–57].

OCT in the early postoperative period is reported to be a useful tool to determine whether MH is closed even in gas-filled eyes. Swept-source optical coherence tomography (SS-OCT) is known to have longer wavelength than spectral domain OCT and has the ability of a higher penetration through the opaque media, thus resulting in high-quality, high-resolution images in gas-filled eyes [58, 59]. The SS-OCT was reported to be able to determine the MH status in gas-filled eyes as early as 2 hours after surgery [60]. Sano et al. reported that use of the SS-OCT protocol can significantly decrease the duration of the face-down positioning after MH surgery, thus preventing from unnecessary posturing in eyes with a closed MH [61]. Chow and Chaudhary published their findings of an OCT-based positioning for MH surgery with daily SD-OCT imaging in 35 eyes until the MH was confirmed to be closed when face-down positioning was stopped [62]. Using OCT control for monitoring MH closure is helpful for improvement of surgical outcome and minimizing discomfort for the patients.

3.5. Ocriplasmin. Ocriplasmin is a truncated form of human plasmin with proteolytic activity for vitreoretinal interface components including fibronectin and laminin; it was approved for the treatment of symptomatic VMA, including association of VMA with MH of <400 [8, 15]. A single intravitreal injection of ocriplasmin (125 μg) demonstrated a better resolution of macular adhesion (26.5 vs. 10.1% in the

placebo group) as well as an increased rate of nonsurgical macular hole closure (40.6 vs. 10.6% in the placebo group) in a multicentre, randomized, double-blind, phase III trials [63]. Ocriplasmin applied as intravitreal injection and by activation of endogenous matrix metalloproteinase-2 resulting in precipitation of VR separation, in case of early formation of MH, can result in hole closure [64]. Ocriplasmin was reported to be safe according to phase III trials; however, some adverse effects such as floaters, photopsia, and transiently blurred vision can be observed, and those effects occur due to vitreolytic effect [65].

3.6. 27-Gauge Vitrectomy. 27 G surgery is a technique using instruments with a diameter of instrument ~0.35 mm. However, visual outcome and closure results were reported to be comparable for narrow-gauge surgery vs 20 G [66]. Sakaguchi et al. reported that epiretinal membrane removal surgery without vitrectomy can be performed with the 27-gauge system [67].

4. Conclusion

Current treatment options for MH management discussed in this review allow to achieve high rate of macular closure and improve visual recovery. Use of repeated OCT is useful for confirmation that correct tactic had been chosen particular for expansile gas or ocriplasmin usage. For the patients with small or medium holes, significantly better results are expected by application of ocriplasmin, however, with lower closure rate that surgery. Holes without VMA vitrectomy is usually the only possible treatment with the choice to perform ILM peeling and uses a short-term or long-term gas or prone posture.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Comparative Study between Pars Plana Vitrectomy with Internal Limiting Membrane Peel and Pars Plana Vitrectomy with Internal Limiting Membrane Flap Technique for Management of Traumatic Full Thickness Macular Holes

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Purpose. To compare the efficacy of PPV and ILM peel versus PPV and IFT in patients with traumatic FTMH. *Methods*. Retrospective interventional comparative case series including two groups of patients with traumatic FTMH. Patients were divided into group I (ILM peel) and group II (IFT). The main outcome measure was closure of the macular hole and restoration of the foveal microstructure. The independent-samples *T*-test and ANOVA test were used to study the mean between 2 groups and calculate the *P* value, whereas the bivariate correlation procedure studied the interaction between the variables tested. *Results*. Group I included 28 patients. Mean preoperative MLD was 757 μm. Mean preoperative BCVA was approximately 20/320. Group II included 12 patients. Mean preoperative MLD was 529.5 μm. Mean preoperative BCVA was 20/320. Group I had a macular hole closure rate of 75% versus 92% in group II $P = 0.05$. Mean BCVA improvement was 2.5 lines in group I versus 5 lines in group II $P = 0.02$. Disrupted ELM and IS/OS was the most salient finding in both groups. *Conclusion*. IFT has a significantly superior anatomic and functional outcome compared to ILM peel in traumatic FTMH.

1. Introduction

The key success of pars plana vitrectomy (PPV) and gas tamponade for FTMH introduced by Kelly and Wendel [1, 2] was attributed to counteracting the anteroposterior vitreous traction at the perifoveal area. On the contrary, the fluid-gas exchange flattened the subretinal fluid cuff surrounding the hole, and the gas bubble then prevented fluid currents from interfering with the healing process [3–7]. The introduction of internal limiting membrane (ILM) maculorhexis was a significant rider to the original technique that greatly spurred the success rates of surgery, although with better response in smaller size holes compared to larger size holes > 400 μm in diameter [8–10]. Peeling off the ILM from the vicinity of a FTMH had dual benefit. Firstly, it eliminated the tangential forces created by glial cells migrating through ILM microrips. Secondly, it induced shearing of the Müller cells' foot plates thereby triggering glial cells proliferation along the interface created by the gas bubble, eventually inducing closure of the hole [11]. While

this scenario applied to primary FTMH that were caused by anomalous vitreofoveolar traction, similar success was not achieved in FTMH secondary to trauma [12, 13]. The pathogenic mechanisms entailed in traumatic FTMH formation included direct injury from blunt trauma inducing the classic trampoline effect or from open globe injury, and indirect injury from a propagating shock wave of chorioretinitis sclopetaria or pressure necrosis of the foveal area by subfoveal hemorrhage [14–17]. These mechanisms steered the pathological cascade to a common endpoint, which is hole formation due to tissue loss. This meant posing a significant pathological element that could not be rectified by the aforementioned surgical maneuvers and that hindered anatomical closure and retinal layers' structural recovery. Accordingly, traumatic FTMH acquired notoriety of frequent initial failure, late reopening, and worse final visual outcome compared to the primary variant [18, 19]. The aim of the current study is to compare the efficacy of PPV and ILM peel versus PPV and ILM flap technique (IFT) in terms of anatomic and functional outcomes in patients with traumatic FTMH.

2. Patients and Methods

This was a retrospective interventional comparative case series that analyzed data of 40 consecutive patients with traumatic FTMH, who were treated in a private ophthalmic center, Magrabi Eye Hospital, Tanta, Egypt, over the past 5 years. Prior to 2017, our surgical protocol for treating traumatic holes consisted of PPV and ILM peel. As from 2017, all patients underwent PPV and IFT. Preoperative data included age, gender, eye involved, type of trauma, and duration of the disease. Best-corrected visual acuity (BCVA) was measured using the Snellen notation and converted to logarithm of minimum angle of resolution (logMAR) for statistical analysis. Diagnosis of FTMH was based on biomicroscopic examination and optical coherence tomography (OCT) imaging (Cirrus HD-OCT 4000 (Carl Zeiss Meditech, Inc., Dublin, California, USA)) or Heidelberg Spectralis Spectral-Domain OCT (SD-OCT (Heidelberg Engineering, Inc., Heidelberg, Germany)), using high-definition 5-line raster scans and 3-dimensional 512×128 macular cube scans passing through the fovea. Biomicroscopically, an FTMH was defined as a central round retinal defect with a rim of elevated retina. Weiss's ring and/or prefoveolar opacity may be present or absent. The size of the central retinal defect was calibrated against the diameter of one of the large tributaries of the central retinal vein close to the optic disc margin [3]. On OCT imaging, an FTMH was defined as an anatomic defect in the fovea involving all neural layers from the ILM to the retinal pigment epithelium (RPE) detected on at least one OCT B-scan. The size of the hole was assessed using the minimum linear diameter (MLD), which was measured using software built-in calipers feature. The MLD was determined by drawing a horizontal line parallel to the RPE between the narrowest hole points in the midretina, i.e., at the shortest distance across the full thickness defect [20]. The study recruited exclusively patients with naïve FTMH with unequivocal history of blunt ocular trauma. Exclusion criteria included recurrent or persistent macular holes following previous surgery, associated retinal detachment or proliferative vitreoretinopathy, significant corneal opacity that would hinder ILM surgery, associated consecutive optic atrophy due to traumatic optic neuropathy, or a follow-up duration less than 3 months. Recruited patients were classified into two treatment arms. Group I included patients who underwent PPV with ILM peel, whereas group II included patients who underwent PPV with IFT. The main outcome measure was closure of the macular hole and restoration of foveal microstructure. Secondary outcome measures were correlation between preoperative MLD, baseline BCVA, duration of the hole prior to surgical intervention, and the anatomical outcome (type of closure and status of foveal microstructure) and the functional outcome (postoperative BCVA), in addition to development of complications. Selection of patients for enrollment in the study and all surgical procedures entailed were undertaken by single vitreoretinal surgeon (HG). The current study was approved by the Institutional Review Board of Magrabi Eye Hospital in Egypt. The study adhered strictly to the tenets of the Declaration of Helsinki (2013 revision). All individuals enrolled in the study received thorough explanation of the surgical procedures entailed, the expected outcomes and possible complications. Afterwards, they were asked to sign an informed consent before undertaking surgery. The consent included a statement that authorized the authors to publish patients' data for research purposes in an anonymous manner that does not allow identification of the patient.

2.1. Surgical Technique. Recruited patients who presented with concomitant significant cataract that could hinder adequate visualization during PPV and ILM manipulation underwent PPV combined with standard phacoemulsification with foldable intraocular lens implantation within the capsular bag. Surgical technique in all cases consisted of 23-gauge 3-port PPV, followed by triamcinolone acetonide- (TA-) assisted induction of posterior vitreous detachment (PVD) that was accomplished by applying aspiration over the optic nerve head (ONH) using the vitreous cutter. Once induced, PVD was carried up to the equator. We routinely used TA for ILM peel. After PVD induction, 0.2 ml TA suspension was sprayed onto the macular area. The supernatant suspension is aspirated from the vitreous cavity while allowing large-sized TA particles to settle down over the ILM. Peeling was started by directly pinching the ILM at a point of natural weakness over the inferior temporal arcade using a 23-gauge Eckardt end-gripping forceps (D.O.R.C. Dutch Ophthalmic Research Center (International) B.V., Netherlands). Once a flap is created, it is slightly elevated over the retinal surface then ripped tangentially in a rhexis fashion for at least 2 disc diameters (DD) from the hole. ILM peeling maneuver was performed centripetal to the fovea to avoid enlargement of the hole. During ILM removal, the peeled ILM flap with overlying TA particles was easily identified from the unpeeled ILM. Additional clues for ILM identification included its peculiar glistening reflex, which provided clear contrast with the dull-white appearance of the denuded retina in the peeled area,

and/or petechial surface hemorrhages in the peeled area. In cases with inadequate visualization of the ILM, we resorted to ILM-blue stain (D.O.R.C. Dutch Ophthalmic Research Center (International) B.V., Netherlands).

In group I, the ILM was completely removed off the macular hole, whereas in group II, the ILM peel was stopped at the edges of the macular hole forming an island of ILM floating into the vitreous cavity with a 360° attachment to the hole. Redundant peripheral edges of the flap were trimmed by the vitreous cutter using shaving mode with minimal suction. No attempts were made to fold over, dip, or tuck the flap inside the hole to avoid traumatizing the RPE. The retinal periphery was then inspected by scleral depression to check for iatrogenic holes, followed by fluid-air exchange. After removal of the 3 cannulas air/C2F6, hexafluoroethane gas exchange was performed using two 30-gauge needles, one for injection of 14% C2F6 and the other for simultaneous air venting (Supplemental digital content, video 1 demonstrates the IFT using TA). Postoperatively, patients were asked to adopt a drinking-bird positioning protocol, in which the patient had to maintain a face-down posture every other 15 minutes for 50% of his/her waking time for 1 week or until 50% of the gas was absorbed as judged by biomicroscopic examination.

2.2. Postoperative Follow-Up. During the postoperative period, patients were examined at 1 day, 1 week, 1 month, and 3 months thereafter. Postoperative data included BCVA, intraocular pressure (IOP) measurement, assessment of macular hole closure biomicroscopically and on OCT examination, and development of postoperative complications.

2.2.1. Macular Hole Closure. On biomicroscopy, macular hole closure was defined as complete apposition of the hole margins and restoration of the foveal light reflex. Patients were then classified according to the closure type and restoration of foveal microstructure on OCT imaging as follows.

(1) Closure Type. U-type configuration was defined as closed macular hole with normal foveal contour; V-type configuration was defined as closed macular hole with steep foveal contour, whereas W-type configuration was considered an open flat macular hole with persistent neurosensory retinal defect [21].

(2) Foveal Microstructure. Category 1 included eyes with restored external limiting membrane (ELM) and inner segment/outer segment (IS/OS) junction; category 2 included eyes with restored ELM and disrupted IS/OS junction, whereas category 3 included eyes with disrupted both ELM and IS/OS junction. Category 4 included eyes with persistent open hole after surgery.

2.3. Statistical Analysis

2.3.1. Independent-Samples T-Test. The independent-samples T-test procedure compares means for two groups of cases. Ideally, for this test, the subjects should be randomly assigned to two groups, so that any difference in response is due to the treatment and not due to other factors. For each variable, sample size, mean, standard deviation, and standard error of the mean were calculated. For the difference in means, mean and standard error were calculated. The significance of the measured T-test value was considered as follows: not significant (NS) when $P > 0.05$, significant (S) when $P \leq 0.05$ (*), highly significant (HS) when $P < 0.01$(**), and very highly significant (V.H.S.) when $P < 0.001$(***), where P is the probability (reflect of null hypothesis).

2.3.2. Analysis of Variance (ANOVA): (F-Test). ANOVA is a procedure used for testing the differences among the means of two or more treatments. It was noted that if means of subgroups are greatly different, the variance of the combined groups is much larger than the variance of the separate groups. The ANOVA format for the analysis of differences in means is based on this fact.

2.3.3. Correlation Matrix. The bivariate correlation procedure computes Pearson's correlation coefficient that measures how variables are related. Two variables can be perfectly related, but if the relationship is not linear, Pearson's correlation coefficient is not an appropriate statistic. The results of r value were checked on r table to find out the significant level.

3. Results

3.1. Baseline Patients' Characteristics. The study included 40 eyes of 40 patients divided in 2 groups. Group I included 28 patients (23 males and 5 females), with a mean age of 21.4 years (range: 5–54 years; SD 13). Mean preoperative MLD was 757 μm (range: 412 μm–1200 μm; SD 221). Mean preoperative BCVA was 1.25 logMAR (Snellen equivalent approximately 20/320) (range: 1.5–0.7 logMAR; SD 0.3). Mean duration prior to surgical intervention was 9 months (range: 0.06–120 months; SD 23.5). Mean duration of follow-up after surgery was 37 months (range: 3–171 months; SD 45). Group II included 12 male patients, with a mean age of 18 years (range: 7–30 years; SD 7). Mean preoperative MLD was 529.5 μm (range: 225 μm-808 μm; SD 148). Mean preoperative BCVA was 1.2 logMAR (Snellen equivalent approximately 20/320) (range: 1.5–0.6 logMAR; SD 0.3). Mean duration prior to surgical intervention was 5 months (range: 0.3–12 months; SD 4.5). Mean duration of follow-up after surgery was 6.3 months (range: 3–12 months; SD 3.3). Statistical analysis revealed no significant difference between both groups in terms of preoperative BCVA and duration prior to surgical intervention, ($P = 0.5$), although both groups differed significantly in terms of preoperative MLD and duration of follow-up after surgery, ($P = 0.003$ and 0.025, respectively). Baseline patients' characteristics of each group are summarized in Table 1.

3.2. Postoperative Anatomical Outcome

3.2.1. Closure Type. Postoperatively, V-type configuration was the main closure type detected in group I, as it occurred

Table 1: Baseline patients' characteristics.

Baseline characteristics	Group I $N = 28$	Group II $N = 12$
Age (years)		
Mean	21.4	18
<20	16 (57%)	7 (58%)
20–40	9 (32%)	5 (42%)
>40	3 (11%)	—
Gender		
Male	23 (82%)	12 (100%)
Female	5 (18%)	—
BCVA logMAR (Snellen)		
Mean	1.25 (~20/320)	1.2 (20/320)
>1 (<20/200)	19 (68%)	8 (67%)
1–0.7 (20/100–20/200)	9 (32%)	2 (17%)
<0.7 (>20/100)	—	2 (17%)
MLD (μm)		
Mean	757	529.5
<400	—	1 (8.3%)
400–600	9 (32%)	8 (67%)
601–800	5 (18%)	2 (17%)
>800	14 (50%)	1 (8.3%)
Disease duration (months)		
Mean	9	5
<1	12 (43%)	2 (17%)
1–6	10 (36%)	6 (50%)
>6–12	2 (7%)	4 (33.3%)
>12	4 (14%)	—
Follow-up (months)		
Mean	37	6.3
3–6	11 (39%)	7 (58%)
>6–12	5 (18%)	5 (42%)
>12	12 (43%)	—

BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution; μm, micron; MLD, minimum linear diameter.

in 15 eyes (53.5%), W-type configuration occurred in 7 eyes (25%), whereas U-type configuration was detected in 6 eyes (21.4%). In group II, U-type configuration was detected in 6 eyes (50%), V-type configuration was detected in 5 eyes (42%), and W-type configuration was detected in 1 eye (8.3%) (Figures 1–3).

3.2.2. Foveal Microstructure. In group I, 3 eyes (11%) had restored ELM and IS/OS, 5 eyes (18%) had restored ELM and disrupted IS/OS, 13 eyes (46.4%) had disrupted ELM and IS/OS, and 7 eyes (25%) had persistent open holes. In group II, failure of restoration of both layers was detected in 10 eyes (83.3%). Restoration of ELM and IS/OS and persistent open hole were detected in 1 eye (8.3%) each. Therefore, disrupted ELM and IS/OS was the most salient finding in both groups.

3.3. Postoperative Functional Outcome. At the end of follow-up, mean BCVA in group I was 1 logMAR (Snellen equivalent 20/200) (range: 1.5–0.2 logMAR; SD 0.4). Mean improvement was 2.5 lines. Three patients (11%) had final BCVA 0.3 logMAR or better (Snellen equivalent ≥ 20/40). On the contrary, mean BCVA in group II was 0.7 logMAR (Snellen equivalent 20/100) (range: 1.3–0.4 logMAR; SD 0.2). Mean improvement was 5 lines. No patient in group II achieved final BCVA 0.3 logMAR or better.

3.4. Complications. Cataract formation or progression of incipient cataract that required cataract surgery during the course of follow-up occurred in 12 eyes (43%) in group I and in 3 eyes (25%) in group II. Postoperative anatomical and functional outcomes of each group are summarized in Table 2.

3.5. Statistical Correlation of Studied Parameters

3.5.1. Surgical Technique: PPV with ILM Peel versus PPV with IFT. Statistical analysis revealed significant correlation between IFT, better postoperative BCVA, and more favorable closure type of macular hole compared to ILM peel, p 0.02 and p 0.05, respectively. Failure of restoration of foveal microstructure was the most common outcome of both techniques (64.4% vs. 83.3% in ILM peel and IFT, respectively) (Table 3).

3.5.2. Correlation between Preoperative Parameters and Anatomical Outcome (Type of Macular Hole Closure and Foveal Microstructure). Statistical analysis in group I and group II, in terms of correlation between preoperative MLD and disease duration prior to surgical intervention versus type of macular hole closure and the degree of restoration of foveal microstructure whether absent, partial, or complete, revealed no statistical significance between these variables.

3.5.3. Correlation between Preoperative Parameters and Final BCVA. Statistical analysis revealed that preoperative BCVA and preoperative MLD were statistically significant parameters influencing the postoperative BCVA in group I patients only, p 0.03 and p 0.004, respectively. Conversely, duration of disease prior to surgical intervention was not a significant factor influencing postoperative BCVA in both groups (Tables 4 and 5).

4. Discussion

In the present study, we report our experience in using PPV and ILM peel versus PPV and IFT for management of traumatic FTMH. Analysis of the anatomical and functional outcomes in group I revealed macular hole closure rate of 75%, of which 21.4% was U-type. BCVA improved by a mean of 2.5 lines. Three patients (11%) had final BCVA 0.3 logMAR or better (Snellen ≥ 20/40). In group II, the macular hole closure rate was 92%, of which 50% was U-type. BCVA improved by a mean of 5 lines. In comparison, Kuhn et al. [22] reported 17 eyes with traumatic macular hole that were treated with PPV and ILM peel. The authors had macular hole closure rate of 100% and improvement of BCVA ≥2 lines in 94% of eyes. It is worthy of note that all eyes in that series had either stage 2 or stage 3 holes at presentation, in comparison to the present study in

Figure 1: (a) Color photo of the left eye of a 16-year-old male patient. The patient sustained blunt trauma to the left eye with a brick approximately 12 months earlier. His BCVA was 0.05 Snellen. The posterior pole showed a large FTMH approximately 2/3 DD (white arrow). Note the area of diffuse RPE mottling with RPE pigment clumps in the superior vicinity of the hole denoting the chronic course (white arrowheads). (b) High-definition 5-line raster OCT image of the same eye showed large FTMH with MLD 808 μm. Note the cystic thickening at the edges of the hole. (c) Color photo of the same eye approximately 6 weeks after PPV and IFT, showing successful hole closure (white arrow). His final BCVA was 0.2 Snellen. (d) High-definition 5-line raster OCT image postoperatively showing U-type closure. The ELM and IS/OS were not restored. Note the curled edge of the ILM flap (white arrow).

Figure 2: (a) High-definition 5-line raster OCT image of the right eye of a 14-year-old male. The patient was hit by a tennis ball at 1.5 months. The resultant FTMH had MLD 725 μm. His BCVA was 0.05 Snellen. Note the cystic thickening at the edges of the hole. (b) High-definition 5-line raster OCT image of the same eye 2 months after PPV and IFT showing V-type closure. The ELM and IS/OS were not restored. The free ILM flap crumbled into the macular hole (white arrowheads). His final BCVA was 0.4 Snellen.

which the MLD was 757 μm and 529.5 μm in groups I and II, respectively. Johnson et al. [14] studied retrospectively 25 eyes with traumatic macular holes and reported macular hole closure rate of 96% and mean improvement of BCVA $\geq$ 2 lines in 84% of cases. Twenty-one patients (84%) had stage 2 or 3 holes. ILM was peeled in only 3 cases, and autologous serum was used in 48% of cases. Weichel and Colyer [15] reported macular hole closure rate of 67%. The authors included eyes with both closed and open globe injuries. ILM peel was not done in any case. They did not comment on the size of the macular hole at presentation. A case series by Ou et al. [17] included 5 patients with

(a)

(b)

Figure 3: (a) Radial scan OCT image of the left eye of a 16-year-old male. The patient was hit by a closed fist at 15 days. The MLD of the FTMH was 359 μm. His BCVA was 0.1 Snellen. Note the cystic thickening at the edges of the hole with typical pregnant drawbridge appearance. (b) Radial scan OCT of the same eye approximately 2.5 months after PPV and IFT showing U-type closure. Note the residual subfoveal neurosensory detachment, fully restored ELM, and partially restored IS/OS layer. The ILM flap was seen folded on itself into the macular hole (white arrowhead). His final BCVA was 0.4 Snellen.

Table 2: Postoperative anatomical and functional outcomes.

Postoperative outcome	Group I $N = 28$	Group II $N = 12$
Closure type		
U-type	6 (21.4%)	6 (50%)
V-type	15 (53.5%)	5 (42%)
W-type	7 (25%)	1 (8.3%)
Foveal microstructure		
Fully restored	3 (11%)	1 (8.3%)
Partially restored	5 (18%)	—
Not restored	13 (46.4%)	10 (83.3%)
Persistent open hole	7 (25%)	1 (8.3%)
BCVA logMAR (Snellen)		
Mean	1 (20/200)	0.7 (20/100)
>1 (<20/200)	9 (32%)	1 (8.3%)
1–0.4 (20/50–20/200)	15 (53.5%)	11 (92%)
<0.4 (>20/50)	4 (14%)	—
Cataract formation	12 (43%)	3 (25%)

BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution.

traumatic macular hole secondary to retinal hemorrhages in shaken baby syndrome. The authors performed PPV and ILM peel for 4 patients and reported macular hole closure rate of 75%. The mean macular hole diameter was 700 μm. A more recent retrospective comparative case series by Ghoraba et al. [23] compared the use of C3F8 and silicone oil in 2 groups of patients who underwent PPV and ILM peel for traumatic macular holes. The authors reported primary closure rate of 81.8% and final closure rate of 90.9% after reoperation, although no information was provided on the preoperative macular hole diameter. The authors mentioned that the overall mean improvement of BCVA was 3 and 4 lines in the silicone oil and C3F8 groups, respectively. There was no information on subgroup stratification in terms of lines of vision gained, lost, or unchanged and how did that correlate with foveal microstructure (Table 6).

To our knowledge, the present study is the first report comparing the outcome of ILM peel technique and IFT in traumatic macular holes. The paucity of literature on outcomes of comparison of both techniques in this particular

Table 3: Correlation between surgical techniques (PPV with ILM peel versus PPV with IFT).

Groups	Postoperative BCVA		Foveal microstructure		Closure type	
	Mean	SE	Mean	SE	Mean	SE
Without IFT	0.96	0.07	2.85	0.17	2.03	0.13
With IFT	0.7	0.07	2.9	0.19	1.58	0.19
T value	0.19		0.2		1.91	
P value	0.02		0.84		0.05	

BCVA, best-corrected visual acuity; IFT, ILM flap technique; ILM, internal limiting membrane; PPV, pars plana vitrectomy; SE, standard error of the mean.

Table 4: Group I: statistical correlation between preoperative parameters and postoperative anatomic and functional outcomes.

		Postoperative BCVA (logMAR)	Closure type	Foveal microstructure
Preoperative BCVA (logMAR)	Pearson correlation	0.39*	0.12	0.07
	Sig. (2-tailed)	0.039	0.53	0.71
	N	28	28	28
Preoperative MLD (μm)	Pearson correlation	0.52**	0.26	0.28
	Sig. (2-tailed)	0.004	0.17	0.14
	N	28	28	28
Disease duration (months)	Pearson correlation	0.12	−0.11	−0.05
	Sig. (2-tailed)	0.53	0.54	0.78
	N	28	28	28

BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution; μm, micron; MLD, minimum linear diameter. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

Table 5: Group II: statistical correlation between preoperative parameters and postoperative anatomic and functional outcomes.

		Postoperative BCVA (logMAR)	Closure type	Foveal microstructure
Preoperative BCVA (logMAR)	Pearson correlation	0.27	−0.17	0.23
	Significance (2-tailed)	0.38	0.57	0.45
	N	12	12	12
Preoperative MLD (μm)	Pearson correlation	−0.14	0.19	0.48
	Significance (2-tailed)	0.96	0.54	0.11
	N	12	12	12
Disease duration (months)	Pearson correlation	0.09	−0.03	0.07
	Significance (2-tailed)	0.77	0.91	0.81
	N	12	12	12

BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution; μm, micron; MLD, minimum linear diameter; *N*, number.

category of macular holes is a significant deterrent to purposeful validation of our findings in the current study. Moreover, most of the published data on traumatic macular holes were derived from retrospective studies and case reports. Nevertheless, we could compare our results to other studies that compared both techniques in other categories of macular holes that are categorized as recalcitrant macular holes such as large holes and myopic macular holes. Table 7 summarizes the outcome of different studies that compared PPV and ILM peel versus inverted ILM flap technique in treating different recalcitrant macular holes in comparison with the outcome of the present study.

In summary, the results of the present study demonstrated that IFT is significantly superior to ILM peel in terms of more anatomical macular hole closure and final BCVA. It is worthy of note that, in the IFT group in the present study, we adopted Casini et al. [28] modification of the classic inverted ILM flap technique described by Michalewska et al. [24] in the sense that we did not attempt to invert the ILM flap and fold it inside the hole to avoid damaging the RPE at the bed of the hole. The rationale of our modified approach is that shearing of the foot plates of the Müller cells during ILM peel and residual attachment of the ILM flap to the hole edges would suffice to incite glial cell proliferation and that eventually fills up the macular hole and promotes its closure [11, 24, 31].

Limitations of the current study included its retrospective design that dictated inhomogeneity of the compiled data under the ILM peel group and the IFT group, in terms of number of eyes recruited, macular hole MLD, and duration of follow-up. For instance, 50% of patients in group I had baseline MLD >800 μm versus 8.3% in group II. Given that our statistical analysis revealed significant correlation between preoperative MLD and final BCVA in group I, this could mean that group I patients had worse visual outcome due to initial much larger MLD. However, we could argue that statistical analysis revealed no significant correlation

Table 6: Review of studies on PPV and ILM peel for traumatic macular hole.

Author	No. of eyes	Surgical technique	Anatomical closure, no. (%)	Functional outcome (mean final BCVA)
Kuhn et al. [22]	17	PPV-ILM peel SF6	17 (100)	6 lines
Johnson et al. [14]	25	PPV-ILM peel (3 cases) C3F8 Autologous serum (12 cases)	24 (96)	≥2 lines in 84% of cases
Ou et al. [17]	4	PPV ILM peel (4 cases) SO, air, C3F8, no tamponade (1 case)	3 (75)	Poor visual outcome
Ghoraba et al. [23]	22	PPV-ILM peel-SO (9 cases) PPV-ILM peel C3F8 (14 cases)	81.8% primary closure, 90.9% after reoperation	3 lines (SO group), 4 lines (C3F8 group)
Current study, 2018 (first comparison between ILM peel technique and IFT)	40	PPV-ILM-C2F6 PPV-IFT-C2F6	75% 92%	2.5 lines 5 lines

BCVA, best-corrected visual acuity; C2F6, hexafluoroethane; C3F8, octafluoropropane; IFT, ILM flap technique; ILM, internal limiting membrane; no., number; PPV, pars plana vitrectomy; SF6, sulfur hexafluoride; SO, silicone oil.

Table 7: Review of studies on PPV and ILM peel versus PPV and inverted ILM flap for different types of macular holes.

Author	Macular hole type	Surgical technique	No. of eyes	Anatomical closure (%)	Functional outcome (mean final BCVA)
Michalewska et al. [24]	Idiopathic	PPV, ILM peel, air	51	88%	(Pre-op 0.12)–(post-op 0.17); Snellen
		PPV, inverted ILM flap, air	50	98%	(Pre-op 0.07)–(post-op 0.2); Snellen
Chen et al. [25]	Idiopathic	PPV, inverted ILM flap, C3F8	8	100%	(Pre-op 1.3)–(post-op 0.6); logMAR
Sasaki et al. [26]	Macular hole-associated retinal detachment	PPV, ILM peel	9	55.5%	(Pre-op 1.00)–(post-op 1.02); logMAR
		PPV, inverted ILM flap C3F8 or SF6	6	100%	(Pre-op 1.04)–(post-op 0.6); logMAR
Mete et al. [27]	Myopic	PPV, ILM peel, SF6	36	61%	(Pre-op 0.6) –(post-op 0.58); logMAR
		PPV, inverted ILM flap, SF6	34	94%	(Pre-op 0.7)–(post-op 0.39); logMAR
Casini et al. [28]	Idiopathic	PPV, inverted ILM flap, SF6	41	97.6%	(Pre-op 20/120)–(Post-op 20/30); Snellen
		PPV, modified inverted ILM flap, SF6	40	97.5%	(Pre-op 20/132)–(Post-op 20/35); Snellen
Kannan et al. [29]	Idiopathic	PPV, ILM peel, SF6	30	70%	1.4 lines
		PPV, inverted ILM flap, SF6	30	90%	2.1 lines
Rizzo et al. [30]	Idiopathic, myopic	PPV, ILM peel	300	78.75%	(Pre-op 0.77)–(post-op 0.52); logMAR
		PPV, inverted ILM flap C3F8 or SF6	320	91.93%	(Pre-op 0.74)–(post-op 0.43); logMAR
Current study, 2018	Traumatic	PPV, ILM, C2F6	28	75%	2.5 lines
		PPV, IFT, C2F6	12	92%	5 lines

BCVA, best-corrected visual acuity; C2F6, hexafluoroethane; C3F8, octafluoropropane; IFT, ILM flap technique; ILM, internal limiting membrane; logMAR, logarithm of minimum angle of resolution; no., number; PPV, pars plana vitrectomy; SF6, sulfur hexafluoride.

between baseline MLD and macular hole closure or restoration of foveal microstructure in both groups. By extrapolation, the cause of worse final BCVA in group I was related to inferior macular hole closure rate rather than baseline MLD, which adds to the strength of our results as it corroborates the higher efficacy of IFT.

5. Conclusion

PPV and IFT is associated with significantly superior anatomic and functional outcomes of traumatic FTMH compared to PPV and ILM peel. Randomized comparative clinical trials focused on surgical management of traumatic

FTMH are needed to assert noninferiority or equivalence of PPV and IFT to emerging surgical alternatives before recommending it as a standard surgical approach to traumatic FTMH.

Data Availability

The statistical data used to support the findings of this study are included within the article. The data collected from history taking and clinical examination of patients recruited in the current study are confidential. Access to these data is restricted by Magrabi Eye Hospital, Tanta, Egypt, in accordance with the hospital's patients' data protection policy. Data are available for researchers who meet the criteria for access to confidential data through contacting the hospital's medical director Professor Hammouda Ghoraba.

Additional Points

Traumatic FTMH acquired notoriety of morbid outcome due to sequelae of trauma as tissue loss and retinal atrophy. Despite a myriad of surgical maneuvers, there is no current consensus on the ideal surgical technique. IFT is a promising approach that would improve the final outcome compared to ILM peel.

Disclosure

The study was conducted in Magrabi Eye Hospital, Tanta, Egypt. The manuscript involves the use of triamcinolone acetonide (TA) as an adjuvant for ILM peel. Currently, TA is used as an off-label ocular therapeutic agent that is not approved by FDA.

Conflicts of Interest

None of the authors has competing financial, professional, or personal interest that might have influenced the performance or presentation of the work described in this manuscript. None of the authors has commercial associations that might pose a conflict of interest in connection with the submitted article. None of the authors has proprietary interest in any of the materials discussed in the study.

Supplementary Materials

Supplemental digital content 1. Video demonstrates the IFT using TA.mp4. (*Supplementary Materials*)

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Research Article

Lamellar Macular Holes: The Role of Microperimetry in Functional Assessment

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Introduction. The aim of our observational cross-sectional study was to evaluate the association between visual function and anatomical characteristics of LMH, considering in particular different subtypes of LMH and their features. *Materials and Methods*. This observational clinical study has been conducted in the Ophthalmology Clinic, ASST-Sette Laghi, University of Insubria of Varese-Como, Italy. Included patients underwent a complete ophthalmological examination, as well as MP1 microperimetry evaluation and optical coherence tomography (OCT). Two experienced masked observers evaluated OCT imaging in order to assess the integrity of the photoreceptor layer (interdigitation zone and ellipsoid zone: IZ/EZ) and the external limiting membrane (ELM). *Results*. Twenty-five patients affected by an LMH were evaluated. Eighteen eyes of 18 patients met the study criteria and were included. Based on morphological and functional data, LMHs were divided into two subgroups: tractional (tLMH) and degenerative (dLMH). We identified 11 tLMHs and seven dLMHs. Functional parameters showed a significative difference in visual acuity and retinal sensitivity between the two groups, respectively: (sample median and the interquartile range) 0.0 (0.0; 0.09) LogMAR vs 0.15 (0.09; 0.52) LogMAR and 16.2 (14.2; 17.7) dB vs 10.0 (7.5; 11.8) dB ($p < 0.05$). Fixation was predominantly central in 90.9% of tLMH vs 71.4% of dLMH and stable in 81.8% tLMH vs 42.9% dLMH, but the differences were not statistically significant. Tractional and degenerative LMHs showed no significant differences in central foveal thickness. Conversely, LMH depth and horizontal diameters appeared different between the two groups. Tractional LMH showed a greater depth 257 (205; 278) μm vs 190 (169; 249) μm, whereas degenerative LMH showed a greater horizontal diameter 653 (455; 750) μm vs 429 (314; 620) μm ($p < 0.05$). IZ/EZ line was unaffected in 81.8% of tLMHs eyes versus 14.3% of dLMHs eyes ($p < 0.05$). Visual acuity and retinal sensitivity were higher in eyes with integrity of both IZ/EZ and ELM compared to those with a disruption of one or both layers ($p < 0.05$). *Conclusion*. Two different subtypes of LMH showed peculiar functional aspects due to their morphological features. Tractional LMHs revealed higher visual acuity and retinal sensibility due to the relative preservation of the outer retinal layers compared to degenerative LMHs. Moreover, we underlined the importance of microperimetry to better identify functional defects in macular degenerative pathologies.

1. Introduction

Lamellar macular hole (LMH) is a retinal pathology characterized by a morphologic alteration of the structure of the fovea, which could lead to metamorphopsia and a reduction in best-corrected visual acuity (BCVA) [1, 2].

Spectral-domain OCT (SD-OCT) provides an excellent visualization of the retinal structure and retinal layers [3]. Its role in characterizing LMHs has been fundamental for investigating subgroup characteristics and visualizing pathological lesions such as epiretinal membranes and proliferations [1, 4].

Recently, the International Vitreomacular Study Group suggested optical coherence tomography (OCT) features to identify LMHs: defect in inner fovea; irregular foveal contour; intraretinal schisis; and preservation of the ellipsoid zone (EZ). The pathogenesis of LMHs still has to be fully understood, as well as its indication for surgical treatment [5].

Microperimetry is used to test sensitivity to light stimulus, with a precise point-to-point analysis. An eye-tracking

system is used to correct noncentral fixation, and an infrared fundus image is constantly and simultaneously provided along the light sensitivity test. Microperimetry is of particular importance to assess the functional status of the macula in those pathologies characterized by subclinical symptoms, such as LMHs [6, 7].

The aim of our study was to evaluate the association between visual function and anatomical characteristics of LMH, considering in particular different subtypes of LMH and their features.

2. Materials and Methods

In this observational cross-sectional study, we included consecutive patients with a diagnosis of an LMH examined at the Vitreoretinal Outpatient Service, Ophthalmology Clinic, University of Insubria of Varese, Italy, between September 2017 and July 2018.

An LMH was diagnosed based on SD-OCT characteristics as proposed by Witkin and as classified by Duker [2, 3]. Inclusion criteria were as follows: (1) break in the inner fovea; (2) irregular foveal contour; (3) separation of the inner/outer foveal retinal layers, leading to an intraretinal split; (4) absence of a full-thickness foveal defect (Figure 1).

Exclusion criteria were as follows: (1) the presence of myopia of more than three diopters in the affected eye (axial length more than 25 mm if pseudophakic eyes); (2) retinal pathologies that could influence a correct diagnosis or functional evaluation, such as age-related macular degeneration (AMD), diabetic retinopathy or retinal vascular occlusion; (3) vitreous hemorrhage; (4) cataract graded more than N03 or NC3, according to the Lens Opacity Classification System; (5) ocular surgery other than uncomplicated cataract surgery. Patients presenting low-quality SD-OCT imaging or unable to perform microperimetry evaluation due to weak cooperation were excluded.

All subjects underwent a complete ophthalmologic examination along with intraocular pressure measurement. Instrumental examination included microperimetry, and SD-OCT evaluation. Our study followed the methods published on Reibaldi et al. [8].

All subjects signed an informed consent for clinical examination and data management. Hospital ethical committee considered all clinical procedures as standard evaluation not requiring specifically intended approval.

BCVA was measured by Snellen charts and then converted to LogMAR for statistical analysis.

An MP-1 microperimeter (Nidek Technologies, Padua, Italy) was used to test retinal sensitivity and fixation. After the pupils were dilated (1% tropicamide), a reference frame was obtained with the integrated infrared camera. We used a 4-2-2 double-staircase test strategy with white background illumination set at 4 apostilbs and a starting stimulus light attenuation set at 10 dB. A grid of 45 stimuli with a Goldmann III stimulus size and a time between the stimuli of 1 s was projected onto the central 8° (Figure 2). A bright red cross of 2° was used for the fixation target. For the assessment of fixation, the fundus movements were tracked during examination.

The mean retinal sensitivity (total sensitivity, mTRS) and the mean sensitivity of the central 13 points within 2° (mean central sensitivity, mCRS) were calculated. The fixation pattern was evaluated as fixation stability and fixation location. Fixation stability was divided into three categories: stable, relatively unstable, or unstable. If 75% of fixation points were located within a two-degree diameter circle, regardless of their position in relation to the foveal center, the fixation was classified as stable. If 75% of fixation points were located within a two-degree circle, but 75% of fixation points were located within a four-degree circle, the fixation was classified as relatively unstable. If 75% of fixation points were located within a four-degree circle, the fixation was classified as unstable. Fixation location was divided into three categories: central, pericentral, and eccentric. If 50% of fixation points were within 0.5 mm of the foveal center, the fixation was classified as central. If 25% to 50% of the fixation points were within 0.5 mm of the foveal center, the fixation was classified as pericentral. If 25% of fixation points were within 0.5 mm of the foveal center, the fixation was classified as eccentric (as in the work of Donati et al. [9]).

To rule out potential learning effects, all patients performed a preliminary test microperimetry examination. All imaging sessions were performed after 5 min of visual adaptation. The same experienced ophthalmologists carried out the examinations (P.D.; L.L.).

SD-OCT images were obtained with a Zeiss Cirrus HD OCT 500 version 7.0.1.290 (Carl Zeiss Meditec, Jena, Germany). All OCT examinations were carried out by a certified operator (S.D., CORC certification 2017). According to the protocol, OCT macular cube 512×128 and five-line scans, centered on the fovea, were obtained for each eye. More than 15 scans were averaged for each measurement. Only images with a quality score of more than five were selected as high-quality images.

According to the morphology of the LMH, all included eyes were divided into two subgroups based on the classification published by Govetto et al. [10]: tractional LMH and degenerative LMH (Figures 1 and 3).

The following dimensional parameters of LMHs were measured in μm on grey-scale SD-OCT images by means of a Cirrus software inbuilt manual caliber: horizontal diameter, base diameter, depth of LMH, and central foveal thickness (CFT) (Figure 3). Further analysis was applied considering the integrity of the photoreceptor layer (interdigitation zone and ellipsoid zone: IZ/EZ) and the external limiting membrane (ELM). Retinal layers were evaluated on five-line scans centered on the fovea; they were defined as intact when the line was continuous and disrupted when the line was interrupted by gaps larger than 30 μm. Based on the integrity of two lines, eyes were divided into three groups: Group A = integrity of ELM and IZ/EZ; Group B = integrity of ELM and disruption of IZ/EZ; Group C = disruption of both layers. Two masked expert investigators (E.P.; M.M.) interpreted the SD-OCT images. In case of disagreement, a third investigator (C.A.) was consulted for a final decision.

Continuous variables were summarized using the sample median and the interquartile range due to the low number of observations and the skewed distribution of most

(a) (b)

Figure 1: SD-OCT evaluation of tractional (a) and degenerative (b) lamellar macular hole.

Figure 2: Fundus color picture with retinal sensitivity grid.

(a) (b)

Figure 3: OCT Morphological parameters analyzed in tractional (3.1) and degenerative LMH (3.2): horizontal diameter (A); central foveal thickness (B); depth of LMH (C); base diameter (D).

parameters. Stable fixation and predominantly central fixation were dichotomized as yes vs. no and summarized using absolute and relative frequencies. To test the null hypothesis of no difference in functional and morphological parameters between the patients' populations with tractional and degenerative LMH, we used the Wilcoxon rank test and Fisher's exact test for continuous and dichotomic variables, respectively. We adopted the same descriptive and inferential approaches to investigate differences in patients' populations defined according to the presence of interruptions in the ELM and IZ-EZ segment. All the analyses were conducted using the SAS software, 9.4 release.

3. Results

Twenty-five eyes affected by an LMH were evaluated: of these, seven eyes were excluded (three due to the presence of concomitant macular diseases, two due to excessive refractive error, one due to a significant cataract, and one due to previous vitreoretinal surgery). Therefore, 18 eyes of 18 patients met the study inclusion criteria and were enrolled. Demographic and main clinical characteristics of the enrolled patients are reported in Table 1.

In Table 2, we report morphological and functional data eyes divided into two subgroups: tractional and degenerative LMH. We identified 11 tractional LMHs and seven degenerative LMHs.

Functional parameters showed a significative difference in both visual acuity ($p = 0.03$) and retinal sensitivity between the two groups. In particular, we observed a significative difference in both central ($p = 0.0008$) and total retinal sensitivity ($p = 0.0001$) between tractional and degenerative LMHs (Table 3). Fixation status and stability were different in patients affected by tractional compared to degenerative LMH. Fixation was predominantly central in 90.9% vs 71.4% of eyes and stable in 81.8% vs 42.9% of eyes, respectively, but the differences were not statistically significant.

Considering morphological parameters, tractional and degenerative LMHs showed no significant differences in central foveal thickness: 170 (160; 186) μm vs 157 (112; 175) μm, respectively. Conversely, LMH depth and horizontal diameters appeared different. Tractional LMHs showed a greater depth 257 (205; 278) μm vs 190 (169; 249) μm, whereas degenerative LMHs showed a wider horizontal diameter 653 (455; 750) μm vs 429 (314; 620) μm ($p < 0.05$).

Table 1: Demographics and main clinical data of enrolled patients.

Patient	Age	Study eye	Funduscopic examination		Visual acuity	
			Study eye	Fellow eye	SE	FE
1	70	RE	Degenerative lamellar macular hole	No abnormalities	0	0
2	68	LE	Degenerative lamellar macular hole	Macular pucker	0.09	0.3
3	75	RE	Tractional lamellar macular hole	Previous surgery for macular hole	0	0.6
4	71	LE	Degenerative lamellar macular hole	Previous surgery for macular pucker	0.5	0.6
5	73	RE	Tractional lamellar macular hole	Macular membrane	0	0
6	82	RE	Degenerative lamellar macular hole	Previous surgery for macular hole	0.15	0.6
7	72	RE	Tractional lamellar macular hole	VMT	0	0
8	68	LE	Tractional lamellar macular hole	No abnormalities	0	0
9	68	LE	Tractional lamellar macular hole	No abnormalities	0	0
10	67	RE	Tractional lamellar macular hole	No abnormalities	0.15	0.09
11	76	LE	Degenerative lamellar macular hole	No abnormalities	0.09	0.04
12	63	RE	Tractional lamellar macular hole	Macula pucker	0.15	0
13	71	RE	Degenerative lamellar macular hole	No abnormalities	0.5	0.15
14	78	LE	Degenerative lamellar macular hole	Macular pucker	0.15	0.6
15	77	RE	Tractional lamellar macular hole	No abnormalities	0.09	0.15
16	74	RE	Tractional lamellar macular hole	Retinal vein occlusion	0	0.04
17	80	LE	Tractional lamellar macular hole	No abnormalities	0.09	0.04
18	76	RE	Tractional lamellar macular hole	No abnormalities	0.04	0.04

Age: years; RE: right eye; LE: left eye; VMT: vitreomacular traction; SE: study eye; FE: fellow eye.

Table 2: Morphological and functional data for both studied groups.

Patient	Age	BCVA	mCRS	mTRS	LMH depth	LMH base	LMH diameter	CFT	Integrity ELM	Integrity IZ-EZ	Fixation stability	Fixation status
Tractional LMH												
1	75	0.00	17.90	15.85	287	844	537	186	+	+	Stable	Predominant central
2	73	0.00	16.21	16.67	310	1325	650	193	+	+	Relatively instable	Predominant central
3	72	0.00	14.21	13.82	202	1280	601	165	+	+	Instable	Poorly central
4	68	0.00	15.75	16.30	278	560	410	170	+	+	Stable	Predominant central
5	68	0.00	16.62	15.50	205	672	200	232	+	+	Stable	Predominant central
6	67	0.15	15.72	15.65	257	1201	620	176	+	+	Stable	Predominant central
7	63	0.15	11.75	17.25	268	1190	346	185	+	−	Stable	Predominant central
8	77	0.09	16.51	14.85	254	1287	634	162	+	+	Stable	Predominant central
9	74	0.00	18.62	18.06	167	499	243	160	+	+	Stable	Predominant central
10	80	0.09	17.65	17.00	263	1946	429	157	+	+	Stable	Predominant central
11	76	0.04	10.25	15.68	217	1107	314	138	+	−	Stable	Predominant central
Degenerative LMH												
1	70	0.00	12.75	13.77	222	nd	397	164	+	−	Instable	Predominant eccentric
2	68	0.09	11.75	12.45	169	nd	653	186	+	+	Stable	Predominant central
3	71	0.52	8.00	14.00	249	nd	750	103	−	−	Instable	Poorly central
4	82	0.30	7.50	8.50	190	nd	678	149	−	−	Relatively instable	Predominant central
5	76	0.09	10.00	9.10	180	nd	542	175	+	−	Stable	Predominant central
6	71	0.52	3.37	6.25	261	nd	920	112	−	−	Instable	Predominant central
7	78	0.15	10.60	10.20	134	nd	455	157	+	−	Stable	Predominant central

LogMAR best-corrected visual acuity; mean central and total retinal sensitivity (mCRS and mTRS) in dB; LMH diameters and central foveal thickness (CFT) in microns; interdigitation zone and ellipsoid zone (IZ/EZ) and the external limiting membrane (ELM).

Table 4 shows collected data according to ELM and IZ/EZ integrity. We identified 10 eyes with integrity of ELM and IZ/EZ and 8 eyes with disruption of IZ/EZ associated or not to ELM interruption. Data analysis showed a statistically significant difference in visual acuity and retinal sensitivity between these two groups.

In particular, visual acuity decreases in presence of IZ/EZ disruption: 0.00 (00; 0.09) LogMAR vs 0.15 (0.07; 0.41) LogMAR, respectively. Retinal sensitivity showed the same trend: both mCRS and mTRS decreased from 16.4 (15.7; 17.7) dB to 10.1 (7.8; 11.2) dB and from 15.8 (14.9; 16.7) dB to 12.0 (8.8; 14.8) dB, respectively ($p < 0.05$).

Table 3: Statistical analysis of demographical characteristics and functional and morphological parameters, considered for all patients and according to tractional and degenerative LMH groups. LogMAR best-corrected visual acuity; mean central and total retinal sensitivity (mCRS and mTRS) in dB; LMH diameters and central foveal thickness (CFT) in microns.

	All patients	Morphology		p value
		Tractional LMH	Degenerative LMH	
N	18	11	7	—
Age	72.5 (68.0; 76.0)	73.0 (68.0; 76.0)	71.0 (70.0; 78.0)	0.61[a]
BCVA	0.09 (0.0; 0.15)	0.0 (0.0; 0.09)	0.15 (0.09; 0.52)	**0.03**[a]
mCRS	13.5 (10.3; 16.5)	16.2 (14.2; 17.7)	10.0 (7.5; 11.8)	**0.0008**[a]
mTRS	15.2 (12.5; 16.3)	15.9 (15.5; 17.0)	10.2 (8.5; 13.8)	**0.0001**[a]
LMH depth	235.5 (190.0; 263.0)	257.0 (205.0; 278.0)	190.0 (169.0; 249.0)	0.06[a]
LMH diameter	539.5 (397.0; 650; 0)	429.0 (314.0; 620.0)	653.0 (455.0; 750.0)	**0.04**[a]
CFT	164.5 (157.0; 185.0)	170.0 (160.0; 186.0)	157.0 (112.0; 175.0)	0.12[a]
Stable fixation, n (%)	12 (66.7%)	9 (81.8%)	3 (42.9%)	0.14[b]
Predominantly central fixation status, n (%)	15 (83.3%)	10 (90.9%)	5 (71.4%)	0.53[b]

Median (25° percentile; 75° percentile) for continuous variables; n (%) for categorical variables. [a]Wilcoxon rank test. [b]Fisher's exact test.

Table 4: Statistical analysis of demographical characteristics and functional and morphological parameters, considered for all patients and according to IZ/EZ-ELM alteration groups. LogMAR best-corrected visual acuity; mean central and total retinal sensitivity (mCRS and mTRS) in dB; LMH diameters and central foveal thickness (CFT) in microns. Interdigitation zone and ellipsoid zone (IZ/EZ) and the external limiting membrane (ELM).

	All patients	IZ/EZ-ELM integrity		p value
		No alteration	Layers alteration	
N	18	10	8	—
Age	72.5 (68.0; 76.0)	72.5 (68.0; 75.0)	73.5 (70.5; 77.0)	0.56[a]
BCVA	0.09 (0.0; 0.15)	0.0 (0.0; 0.09)	0.15 (0.07; 0.41)	**0.02**[a]
mCRS	13.5 (10.3; 16.5)	16.4 (15.7; 17.7)	10.1 (7.8; 11.2)	**0.0001**[a]
mTRS	15.2 (12.5; 16.3)	15.8 (14.9; 16.7)	12.0 (8.8; 14.8)	**0.04**[a]
LMH depth	235.5 (190.0; 263.0)	255.5 (202.0; 278.0)	219.5 (185.0; 255.0)	0.36[a]
LMH diameter	539.5 (397.0; 650; 0)	569.0 (410.0; 634.0)	498.5 (371.5; 714.0)	0.70[a]
CFT	164.5 (157.0; 185.0)	173.0 (162.0; 186.0)	153.0 (125.0; 169.5)	**0.02**[a]
Stable fixation, n (%)	12 (66.7%)	8 (80.0%)	4 (50.0%)	0.32[b]
Predominantly central fixation status, n (%)	15 (83.3%)	9 (90.0%)	6 (75.0%)	0.56[b]

Median (25° percentile; 75° percentile) for continuous variables; n (%) for categorical variables. [a]Wilcoxon rank test. [b]Fisher's exact test.

Considering fixation parameters, the eyes showing integrity of both layers present a more frequent stable fixation and a predominantly central fixation status. These data, however, did not reach a statistical significance, probably due to the relatively small sample size.

Considering the morphological parameters of macular hole, the disruption of retinal layers is associated with a reduction in CFT, respectively, 173 (162; 186) μm vs 153 (125.0; 169.5) μm. LMH depth and central foveal thickness did not show significant correlations with IZ/EZ and ELM status.

Considering the integrity of IZ/EZ and ELM in both tractional LMHs and degenerative LMHs, we found that more than 81% of tLMHs present a preservation of external layers compared to 14.2% of dLMHs ($p = 0.0128$).

Figure 4 shows patients' distribution according to IZ/EZ and ELM integrity, analyzing functional and morphological parameters.

4. Discussion

Nowadays, LMHs represent a defined macular pathology, classified inside the large chapter of vitreomacular pathologies secondary to an alteration to the vitreoretinal interface [1–3].

The gold standard for the diagnosis and clinical characterization of LMHs is currently OCT imaging, which provides not only qualitative but also quantitative data on this pathology.

Govetto et al. in 2016 defined tractional and degenerative subtypes of LMH by means of OCT examination [10]. The first type is characterized by the schitic separation of the neurosensory retina between the outer plexiform and outer nuclear layers; it presents an intact ellipsoid zone and is associated with tractional epiretinal membranes and/or vitreomacular traction. The second type presents intraretinal cavitations, which could affect all retinal layers; it is associated with nontractional epiretinal proliferation and a retinal "bump"; it often presents with an early ellipsoidal zone defect and its pathogenesis, although chronic and progressive, remains poorly understood.

LMH subgroups were characterized by the same origin, but with different structure and evolution, in particular due to the evidence of an epiretinal tissue proliferation [11]. Published studies identified different characteristics of excised epiretinal membrane (ERM), defined as dense or tractional based on their appearance and behaviour on the retina. They showed different collagen structures as well as

Figure 4: Distribution of eyes according to IZ/EZ and ELM integrity, analyzing functional and morphological parameters. Best-corrected visual acuity (BCVA) in LogMAR; mean central and total retinal sensitivity (mCRS and mTRS) in dB; LMH depth, LMH diameter and central foveal thickness (CFT) in microns.

different immunoreactivity to glial or smooth muscle actin proteins [12, 13].

In our study, we combined a detailed description of OCT retinal modifications in LMHs with a complete functional evaluation by means of visual acuity and microperimetry examination. Microperimetry is able to quantify foveal and perifoveal retinal sensitivity in an exact fundus-related modality, thus adding detailed information regarding the degree and pattern of macular alteration. The importance of microperimetry was recently underlined by our group into two published clinical studies, in which we investigated the correlation between morphological modifications, retinal sensibility, and fixation status in patients who underwent surgery for epiretinal macular membranes and in patients treated with an intravitreal slow-releasing steroid implant for retinal vein occlusion [9, 14].

The present study underlines the morphological differences between tractional and degenerative LMH. The presence of a tractional ERM in the tLMHs increases LMH depth (median 257 μm vs 190 μm, $p = 0.06$) and produces an intraretinal schisis that we measure as LMH base (Figure 3). As previously described, the schisis changes according to OCT scan's orientation, so we did not consider it for statistical purposes.

Degenerative LMHs present larger LMH diameter than tLMHs probably due to progressive retinal degeneration and less tangential traction. Conversely, CFT was similar, despite a different morphology of the foveola (foveal bump in degenerative LMHs and foveolar sparing in tractional LMH).

Considering visual function, we showed a difference between tractional and degenerative LMHs, reflecting different morphological characteristics, as we showed above. Visual acuity, total and central retinal sensitivity appeared significantly higher in tractional LMHs. Considering stability and status of the fixation, tractional LMHs eyes show a prevalent central (90% of eyes) and stable (81.8% of eyes) fixation compared to degenerative LMH eyes. The ability of patients to maintain stability of fixation ensures high quality of visual function while reading or for near activities, as documented also in the case of macular pucker and macular hole, in pre- and postsurgery follow-up [9, 15].

As the second step, we evaluated the integrity of the outer retinal layers, which represents a pathognomonic sign of visual acuity preservation. Several authors have described impaired visual recovery in patients affected by diabetic macular edema or exudative AMD when the IZ/EZ was damaged [16, 17]. Tractional LMHs showed integrity of the IZ/EZ line in 81.8% of the eyes; conversely, in degenerative LMH, IZ/EZ was present only in 14.3% of eyes ($p < 0.05$). Moreover, we documented an alteration of the ELM, which represents the direct connection between photoreceptor and intraretinal architecture. A damage to the ELM, as reported in the literature, is consecutive to that of the IZ/EZ [18], and indicates that morphological changes are not limited to the photoreceptor junction level but extend toward the Muller cell cone. Parravano et al. showed similar results: they compared two type of LMH considering only the aspect of ERM and concluded that the dense not tractional ERM (corresponding to dLMH) correlates with outer retinal layers degeneration. The authors underline, as in our study, the influence of IZ/EZ and ELM on visual acuity and retinal sensitivity preservation [19].

To better understand the role of ELM and IZ/EZ, we divided patients according to outer retinal layers integrity (Table 4). We showed that eyes with no alterations of ELM and IZ/EZ had higher visual acuity, central retinal sensitivity, and stable fixation status (80% of eyes). Eyes presenting a damage to IZ/EZ associated or not to ELM disruption showed a significantly lower visual acuity and retinal sensitivity. As already reported by Reibaldi et al. [8], we showed that retinal morphological characteristics are correlated to central retinal sensitivity more than visual acuity, probably due to the different investigation of visual function. This suggests that microperimetry could be more sensitive in identifying morphological alteration of photoreceptor layer [15].

Tractional and degenerative LMHs present different morphological features due to specific ERM characteristics.

Despite inner modification of the fovea due to tractional schisis or horizontal traction with foveal bump, the visual function is influenced by outer retinal layers alterations that involve the photoreceptor complex and cause qualitative and quantitative visual impairment.

Early identification of these alterations may be useful to retina experts for LMHs follow-up or to evaluate the surgical approach.

Limitation of our study was the relatively small patient population, influenced by the low prevalence of this type of pathology and its subclinical symptoms. High-resolution OCT and deep functional analysis (OCT and superimposed microperimetry) may allow us to effectively characterize patients and evaluate their clinical status. A prospective study could be helpful in order to investigate clinical progression of different LMH subtypes and to evaluate the opportunity for surgical intervention [20, 21].

5. Conclusions

Our research revealed interesting elements about LMHs: tractional and degenerative LMHs show distinctive functional features that reflect their morphological differences. In particular, tractional LMHs revealed higher visual acuity and retinal sensitivity due to the relative preservation of the outer retinal layers compared to degenerative LMHs.

In order to correctly evaluate foveal degenerative pathologies with slow progression, such as LMH, a multimodal imaging is of fundamental importance. High-resolution OCT associated with microperimetry reveals the morphological and functional modifications of the retina.

Data Availability

The statistical data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Review Article

Inner Retinal Layer and Outer Retinal Layer Findings after Macular Hole Surgery Assessed by means of Optical Coherence Tomography

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Aim. To summarize the spectrum of optical coherence tomography (OCT) and OCT angiography (OCTA) features after full-thickness macular hole (MH) repair surgery. *Methods*. A PubMed engine search was carried out using the terms "Macular Hole," "Optical Coherence Tomography," and "Optical Coherence Tomography Angiography." All reports published in English up to October 2018, irrespective of their publication status, were included. Tomographic signs analyzed were divided according to the involved portion of the retina in "inner retinal layers" and "external retinal layers." Despite predominantly involving the inner retinal layers, cystoid macular edema (CME) has been treated as a separate entity. Finally, report on vessel density (VD) changes and the foveal avascular zone (FAZ) area modifications have been included. *Results*. Different clinical findings can be observed on OCT of patients who underwent MH repair surgery. There is general consent that retinal thinning involving primarily the retinal nerve fiber layer and the ganglion cell layer takes place after surgery. In the postoperative period, the outermost retinal layers get progressively restored. Persistent defects in the ellipsoid zone or in the external limiting membrane correlate with worse postoperative visual outcome. OCTA has globally demonstrated that eyes after MH closure show a reduction in macular and paramacular VD and smaller FAZ areas, compared with control or fellow eyes. *Conclusion*. Clinicians should be aware of the most common tomographic findings to properly manage each condition. In addition, significant advantages for the postoperative application of OCT and OCTA include noninvasiveness, rapid and simple execution, repeatability, and precise measurements.

1. Introduction

Vitreoretinal surgery has been an object of great innovation during the last years. New intraoperative instrumentation, such as vitrectomy probes [1, 2], illumination techniques [3], and wide-angle viewing systems, has increased the safety, the effectiveness, and the repeatability of the surgical maneuvers. On the other hand, the usage of noninvasive imaging techniques, such as optical coherence tomography (OCT), has enhanced the detection of many subtle vitreal, retinal, and choroidal changes, which are difficult or impossible to be visualized by indirect ophthalmoscopy [4].

The application of the OCT and its newest developments, such as enhanced-depth imaging (EDI) [5] or swept-source OCT [6], has widened the spectrum of vitreoretinal conditions, leading to the introduction of new clinical entities and the better understanding of the traditional ones, including macular hole (MH).

The preoperative assessment of MH by means of OCT is fundamental for the evaluation of several important features that have been recognized to contribute to the anatomical and functional outcome after surgical repair. The noninvasive morphological investigation of these lesions has allowed for the fundamental distinction between full-thickness macular

hole (FTMH) [7], characterized by an interruption in the neuroretina involving all the sensory layers, and lamellar MH (LMH) [8]. LMH, in turn, can be divided into degenerative and tractional, on the bases of specific morphologic features. The former is characterized by the presence of a foveal bump, lamellar hole-associated proliferation, a disrupted ellipsoid zone in the large majority of the cases, and a round-edged intraretinal cavitation involving outer retinal layers. The latter is almost invariable associated with the presence of tractional epiretinal membrane, an intact ellipsoid layer, and a sharp-edged schisis between the outer plexiform and the outer nuclear layer [9]. According to some authors, tractional LMH should be considered as being part of the pseudohole category with stretched foveal edges [10].

In the recent years, a new OCT-based classification of MH has been published by the International Vitreomacular Traction Study (IVTS) Group (Table 1) [11]. This classification accounts for the size, the cause, and the vitreous state at the macular region, known as vitreomacular interface (VMI), and its interaction with the neuroretinal layers and is one of the leading criteria driving the therapeutic approach to MHs.

Thanks to the recently published pieces of evidence, several OCT features have been identified as important prognostic parameters to be considered in the surgical planning, including the presence of an epiretinal membrane (ERM) or a lamellar hole-associated epiretinal proliferation (LHEP) [12, 13] and the state of the internal or external retinal layers [14].

Besides preoperative OCT studies, the intraoperative and postoperative monitoring of the surgical outcomes has been giving unattended insights on the response of the retinal tissue to the closing procedures [15, 16]. In fact, biomicroscopy is seldom able to evaluate the extent of retinal morphologic changes that take place after the surgery and is not able to establish any correlation between the anatomical and functional findings. On the other hand, visual symptoms are too dependent on patients' subjective perception and their psychophysical state to become a reliable parameter for the surgical outcome.

Conversely, postoperative OCT has demonstrated undeniable ability to capture microscopic anatomical details. In fact, especially in cases in which vitreal substitutes, like silicone oil or expansible gas, impair the view of the posterior pole, noninvasive imaging monitoring of the macula is a precious instrument for patients' evaluation and follow-up. Qualitative assessment of the OCT includes the analysis of the different retinal structures, the remnants of the ERM and the internal limiting membrane (ILM), and the release of any point of vitreomacular attachment (VMA) or vitreomacular traction (VMT). In parallel, quantitative evaluation relies on standard objective parameters offered by the modern OCT software, including the central macular thickness (CMT), retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and inner plexiform layer (IPL) thickness. Finally, the introduction of OCT angiography (OCTA) [17], a relatively new, dyeless, depth-resolved technique that allows the visualization of retinal microvasculature by detecting intravascular blood flow, has been used to noninvasively investigate retinal capillary networks and foveal avascular zone (FAZ) changes in patients who underwent macular surgery.

Table 1: The International Vitreomacular Traction Study (IVTS) Group classification of macular hole (MH).

Size	Small (250 mm)
	Medium (>250–400 mm)
	Large (>400 mm)
Status of vitreous	With VMT
	Without VMT
Cause	Primary or idiopathic
	Secondary (caused by other pathologies, without any preexisting or concurrent VMT)

VMT: vitreomacular traction. Source: Duker et al. [11].

The aim of this review is to summarize the spectrum of OCT features after MH repair surgery, focusing on the prognostic signs a retinal surgeon should be aware of in order to predict the final visual outcome.

2. Methods

A PubMed engine search was carried out using the terms "Macular Hole," "Lamellar Macular Hole," "Optical Coherence Tomography," and "Optical Coherence Tomography Angiography." All reports published in English up to October 2018, irrespective of their publication status, were reviewed. From the results, articles were selected based on the degree of relevance as determined by the authors: original studies were preferred; case reports or case series were included only if deemed of particular interest. The majority of the articles taken into consideration were referred to FTMH. However, due to paucity of articles published so far about OCTA in MHs, data from LMH were also included in the review.

Tomographic signs analyzed in this review were divided according to the involved portion of the retina; "inner retinal layers" included all the structures between the ILM and the external limiting membrane (ELM) (RNFL, GCL, and IPL). On the contrary, "external retinal layers" included the structures comprised between the ELM and Bruch's membrane, namely, the four hyper-reflective outer lines on SD-OCT: the external limiting membrane (ELM); the inner segment ellipsoid zone (EZ, previously called the junction between the inner and the outer segments (IS/OS junction)); the cone outer segment tips (COST) or interdigitation zone (IZ); and the retinal pigment epithelium (RPE) [5] (Figure 1). The photoreceptor outer segments (PROS) length was considered as the distance between the EZ and the RPE. Despite predominantly involving the inner retinal layers, cystoid macular edema (CME) has been treated as a separate entity.

Finally, report on vessel density (VD) changes and the FAZ area modifications in patients with MH undergoing surgery, investigated by means of OCTA, have been included in the present review. The generally accepted classification in superficial capillary plexuses (SCP), deep capillary plexuses (DCP), and choriocapillaris (CC) has been maintained.

3. Inner Retinal Layers

ILM peeling during vitrectomy has become a routine surgical procedure for the treatment of idiopathic MH, as the

(a) (b)

Figure 1: A spectral domain optical coherence tomography (SD-OCT) scan passing through the fovea in a patient with a large macular hole. (a) Color fundus of the patient; (b) SD-OCT scan showing a small operculum on the roof of the macular hole. Bottom right: magnification of the scan showing a detail of the four external retinal layers.

procedure significantly increases the MH closure rate and lowers the recurrence rate [18]. ILM is the basement membrane of Müller cells, the inner barrier of the neural retina, and anatomically adjacent to RNFL and GCL. Functionally, delay in the recovery of the b-waves of focal macular electroretinograms has been described; [19] anatomically, changes in the inner retinal layers thickness and alterations of their architecture correspond to the functional impair after ILM removal in MH surgery.

Based on the shape of the inner foveal layers and their tomographic contour, four macular hole closure types have been distinguished: a *U*-shape closure type, described with a contour similar to that of the healthy fovea; a *V*-shape closure type, described as a steep foveal outline; an irregular closure type, presenting as a closed hole that cannot be defined either as *U*-shape or as a *V*-shape closure type; and a flat/open closure type, described as having flat borders of the macular hole with bare RPE. Better postoperative visual acuity statistically correlates with the U-shape closure [20].

Based on the thickness of the inner foveal layers, reduction in the width of the inner retinal tomographic bands has been described by different authors [21, 22]. Kumagai et al. found that the four inner Early Treatment Diabetic Retinopathy Study (ETDRS) sectors showed a significant reduction in the average retinal thickness at 1 month, and this damage was progressive throughout the 24 months after surgery, with exception of the nasal sector [23]. From the functional point of view, a significantly positive correlation between the foveal thickness at 1 month and the visual acuity at 12 months after MH surgery has been reported. This must be interpreted that a thicker fovea in the early postoperative phase may indicate a higher degree of filling with neuronal tissue, and, therefore, a major chance of MH defect closure [24].

The changes in macular retinal thickness are not uniformly distributed at the posterior pole but rather involve specific macular quadrants and certain retinal layers. In detail, the temporal quadrants show the most severe thinning, followed by the superior and the inferior ones; conversely, in the nasal quadrant, the global thickness often increases [22, 25].

There is general consent that retinal thinning involves primarily the RNFL and GCL, with a relative sparing of the outermost retinal layers. Sabater et al. presumed that a mechanical damage due to ILM peeling involving the GCL (the layer in its whole or only the Müller cells within the GCL) is the main responsibility of these tomographic findings [26]. Faria and associates found that 6 months after ILM peeling, the RNFL, GCL, and IPL had a decreased thickness in both the nasal ($-12.8\,\mu$m) and the temporal regions ($-29.6\,\mu$m). As a possible explanation, the authors hypothesized that, after ILM peeling, inner retinal cells were particularly affected by local inflammation, microcirculatory ischemia, and stretching effects [27]. The same group found a shortening of papillofoveal distance and thickening in the outer retinal layers (ORLs) in both nasal and temporal regions during the follow-up [28].

Qualitatively, more than 50% of the eyes that underwent successful MH repair surgery developed either superficial or deep structural alterations in the extrafoveal retina [29]. These alterations appeared on fundus photography as arcuate, slightly dark, extramacular striae along the course of optic nerve fiber and on OCT as dissociated optic nerve fiber layer (DONFL) (Figure 2) [30, 31].

Further studies have characterized DONFL with en face OCT, as multiple dark dots along the course of RNFL, called concentric macular dark spots (CMDSs), which can be eventually associated with localized defects in the underlying GCL-IPL [32, 33]. A strong association with ILM peeling has been proved: DONFLs do not develop in eyes without ILM peeling and are detectable only in the areas where the ILM peeling was performed. On the contrary, the dye used for the peeling (indocyanine green, triamcinolone acetonide, or/and trypan blue) does not seem to affect the prevalence of these lesions [34]. DONFLs appear between 1 and 3 months after ILM removal and progressively increase in number and proportionate area in the subsequent 3 to 6 months after surgery; in general, no new cases are usually observed beyond 6 months. Increase in the first months has been related to progressive deturgescence of the RNFL in the postoperative period [35].

Figure 2: Optical coherence tomography (OCT) of dissociated optic nerve fiber layer (DONFL). B-scan OCT (a) illustrates the presence of a localized defect in the retinal nerve fiber layer and the underlying ganglion cell and inner plexiform layers in a patient who underwent macular hole repair surgery with internal limiting membrane peeling. A strong association with ILM peeling has been proved by different reports. (b) The color-coded altitude map shows a relative thinning of the retinal layers.

DONFL-related defects tend to locate majorly in the temporal macular quadrant [36] and to progress with time [37, 38] but do not affect the visual acuity or the macular function [29, 39]. Earlier investigations suggested that the DONFL appearance is not due to injury to the retinal nerve fibers, but to the Müller cells, causing a cleavage in the retinal nerve fiber bundles [30].

4. External Retinal Layers

Physiologically, the outer retina appears on OCT as four separate bands, that correspond, starting from inside to outside, to: (1) the ELM; (2) the boundary between the ellipsoid portion of the IS; (3) the OS tips/RPE junction (contact cylinder); (4) the RPE, Bruch's membrane, and the choriocapillaris. The integrity of each of these bands, especially of bands 2 and 3, is fundamental for effective signal transmission and, in the end, for visual acuity. The prognostic relationship between preoperative morphological features of these external retinal layers and postoperative visual outcome in patients with MH has long been established. Poorer preoperative and postoperative best-corrected visual acuity (BCVA) has been correlated with larger horizontal MH basal diameter and larger preoperative diameter of the EZ defect [40].

In the postoperative period, the ELM, EZ, and COST line got restored in 100%, 69%, and 17% of eyes, respectively, after successful hole closure according to a prospective clinical series recently published [25]. This restitution is slow but progressive and takes place in the first 6 months after the surgical procedure [20, 41]; before the process gets completed, three different tomographic signs can be recognized in the foveal area.

First, a foveal detachment can persist in the first months in up to 43% of closed MHs [42], similar to that one occurring in spontaneous closure of traumatic MHs, suggesting that bridging of the inner neuroretinal tissue may be the initial step in MH repair. Secondarily, outer foveolar defects (OFDs), also called "outer retinal defects," "foveolar lucencies," or "foveolar cysts," can be transiently identified in the first postoperative stage and have been associated with smaller preoperative MH [43, 44]. Once detected, the outer foveolar defects disappear, at the earliest, in 1 month, and the main time of defect disappearance is of 183 days after the surgery. Recently, the development of these lesions has been interpreted as a normal state of recovery after MH repair, associated with a more favorable surgical outcome and less-advanced preoperative MH stage [45].

Finally, a foveal hyper-reflective lesion can be noticed, which has been interpreted as a cluster of proliferative glial cells (Müller cells or astrocytes), reapproximating the normal photoreceptors to the central fovea. In different studies, the maintenance of this tissue at longer follow-up has been associated with worse visual recovery [46]. On the basis of their size, these lesions can be divided into two groups: those with larger diameter replacing the entire intraretinal foveal defect, and those with smaller diameter localized in the inner foveal layers only [47]. According to Wakabayashi and associates, the type of foveal hyper-reflective lesion is able to influence the postoperative centripetal reapproximation of the ELM on SD-OCT. If the bridging of the ELM advances faster than glial cell proliferation into the foveal defect, the hyper-reflective line corresponding to the ELM will restore. Otherwise, if the foveal defect is filled by the proliferating glial cells before the bridging of the reapproximating ELM takes place, subsequent reestablishing of the normal

tomographic external retina profile at the central fovea is impeded [48]. The authors conclude that only eyes with an intact ELM have a higher chance of achieving subsequent restoration of the EZ postoperatively, and therefore, the ELM rather than the EZ acts as a critical structure predictive of the restoration potential of the foveal photoreceptor integrity in surgically closed MHs.

The relationship between the integrity of the foveal microstructure, and especially of the EZ and the ELM, and the foveal sensitivity after MH surgery has been studied by different groups (Table 2). Timely recovery of these specific layers is associated with better postoperative BCVA [14, 46, 48, 49]. In particular, the restitution of the ELM had a superior postoperative functional prognosis and acted mostly as an indirect sign of functional recovery of the foveal photoreceptors in surgically closed MHs, regardless or in association with the restoration of the EZ [48, 50, 51]. The integrity and the length of the foveal COST line were also identified as important predictors of the final BCVA: the COST line recovery begins in the peripheral region and progresses toward the center of the closed macular hole even though not always symmetrically [49, 52]. In parallel to COST line defect reduction, the BCVA progressively increases postoperatively (correlation significant at 1, 3, 6, 9, and 12 months after surgery) [53].

As far as it concerns the RPE, atrophic changes have been found both within the area of the previous MH and outside the fovea. In the former case, foveal RPE atrophy has been related to the direct contact of indocyanine green or trypan blue dye on the RPE through the retinal defect; atrophic changes outside the macula can be secondary to initial ILM incisions with the microvitreoretinal blade [54]. Engelbrecht and his group advocated that the use of minimum indocyanine green concentration and shorter time to allow for adequate staining of the ILM would reduce the potential risk for toxicity to the RPE [55]. Finally, some authors have hypothesized that the usage of the inverted internal limiting membrane (ILM) flap technique for large MH could be complicated by the expansion of submacular RPE atrophy at the long-term follow-up [56].

5. Cystoid Macular Edema

Postoperative CME is a major cause of visual impairment after ocular surgery. Almost any intraocular procedure can be complicated by the development of CME, including surgery for cataract, glaucoma, and cornea and vitreoretinal disorders. However, while many advances have been made in our knowledge regarding the incidence, predisposing factors, visual outcomes, and therapeutic options for CME after cataract surgery, less information is available for CME after vitreoretinal surgery [57].

Any sign of CME has been observed by structural OCT in 47% of eyes undergoing vitrectomy for nonemergent vitreoretinal indications, including epiretinal membranes, MH, vitreous hemorrhage, vitreous opacity, or tractional retinal detachment [58]. CME was more common in eyes undergoing vitrectomy for epiretinal membranes as compared to MH or nonclearing vitreous hemorrhage (incidence rate of 64% versus 29% and 29%, respectively). These significant differences can be partly explained by the tractional forces associated with epiretinal membranes, which may require more time for a full recovery, and by the different surgical and postoperative management. Also, the technique used to detect the presence of CME is important to compare the results of different studies [59].

Surgical trauma with subsequent ocular inflammation has a major role in the development of this postoperative complication, which can be suspected on fundus examination as an abnormal foveal reflex associated with a variable degree of visual disturbances. However, subtle forms of CME cannot be easily recognized without additional exams. OCT is a simple and noninvasive way to identify and monitor the presence of CME, which appears as hyporeflective cysts predominantly located in the parafoveal area (Figure 3). In more severe cases, OCT reveals the presence of a serous retinal detachment, usually of a scarce entity. The incidence rate of CME is as high as 80% of patients operated for MH far, according to the studies based on fluorescein angiography; studies based on OCT suggest an inferior prevalence of this entity.

Different factors may contribute to explain this discrepancy; it is possible that not all the vascular changes seen after vitreoretinal surgery lead to significant retinal thickening and intraretinal cysts formation. However, OCT provides more objective and reproducible measurements and can be particularly useful for assessing changes during the follow-up and for monitoring the response to treatment. Sacconi et al. observed that the main alterations in CME after cataract surgery were located at the level of the deep capillary plexus and were partially reversible after therapy [60].

Different therapeutic options have been used in postsurgical CME. Topical treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids aims at decreasing the production of inflammatory molecules involved in the breakdown of the blood-retinal barrier. Topical NSAIDs have been shown to be able to reach the vitreous chamber in significant concentrations to produce structural and clinical changes [57]. Systemic steroids, on the opposite, were not able to give significant functional and anatomical improvements in patients with postsurgical CME after vitreoretinal procedures. For refractory cases of CME after vitrectomy, sustained-release dexamethasone intravitreal implant proved to be useful in different studies. This treatment was effective by improving visual acuity by one or more Snellen lines in most of the treated eyes, with effect duration up to 9 months. Functional results after a single injection of dexamethasone implant correlated with a significant decrease of mean central retinal thickness measured by structural OCT [61]. Another treatment option described in cases of recalcitrant CME includes the use of intravitreal injection of triamcinolone acetonide. This treatment was effective in reducing CME, but the visual improvement was transient. In persistent cases of CME, intravitreal injections of anti-VEGF have also been tried and showed no significant benefits on central macular thickness and visual improvement [62]. It is possible that intravitreal injections of anti-VEGF in vitrectomized eyes have a limited duration because of a more rapid clearance.

Table 2: Prognostic value of postoperative optical coherence tomography (OCT) external retinal layers after macular hole (MH) repair surgery.

OCT layer	Authors	Year	Type of study	Eyes/ patients	ILM peeling (yes/ no)	Dye	MH diameter (μm, mean ± SD and/or range)	Mean follow-up (months)	Comment
OFD	Kang et al. [43]	2010	Retrospective	96/93	NA	NA	333.5 ± 126.3 with OFD 504.2 ± 155.6 without OFD	14.4	OFD associated with better preoperative and postoperative BCVA
	Powers et al. [45]	2018	Retrospective	104	Yes	NA	NA	NA	ORD may represent a normal state of recovery after MH repair with ILM peeling
ELM	Wakabayashi et al. [48]	2010	Retrospective	40/40	Yes	Indocyanine green dye or triamcinolone acetonide	623 ± 303 (144–1235)	12	Reconstruction of ELM at 3 months associated with better BCVA at 3 and 12 months
	Bottoni et al. [44]	2011	Prospective	19/19	Yes	Indocyanine green or brilliant blue G	NA	12	Combined recovery of ELM, EZ, and ONL determined VA improvement, but ELM was first structure to recover after MH closure
	Ooka et al. [50]	2011	Prospective	43/43	Yes	Indocyanine green dye or triamcinolone acetonide	NA	6	Length of both EZ and ELM defects significantly correlated with postoperative BCVA and foveal sensitivity
EZ	Sano et al. [42]	2009	Retrospective	28/27	Yes	Indocyanine green	NA	7.7	EZ was the only relevant factor affecting postoperative BCVA at six months
	Michalewska et al. [20]	2010	Retrospective	71/66	Yes	Trypan blue	666–1386	12	BCVA correlated with EZ. 93% had EZ defects at 1 week; only 29.5% had EZ defects at 12 months
	Oh et al. [46]	2010	Retrospective	23/23	Yes	None or indocyanine green dye or triamcinolone acetonide	104–998	3	Larger diameter of EZ defect and apparent glial sealing correlated with worse postoperative BCVA
	Chang et al. [51]	2015	Retrospective	60/56	Yes	Indocyanine green	NA	12	Postoperative BCVA correlated with restored ELM and EZ line and resolved glial cells

Table 2: Continued.

OCT layer	Authors	Year	Type of study	Eyes/ patients	ILM peeling (yes/ no)	Dye	MH diameter (μm, mean ± SD and/or range)	Mean follow-up (months)	Comment
COST or PROS length	Itoh et al. [53]	2012	Retrospective	51/51	Yes	Indocyanine green dye or triamcinolone acetonide	336 ± 152 (136–946)	12	Preoperative length of COST line defect correlated with postoperative BCVA at 12 months
	Hashimoto et al. [49]	2015	Retrospective	24/23	Yes	Triamcinolone acetonide	NA	28.7	Postoperative BCVA correlated exclusively with foveal PROS elongation

SD: standard deviation; NA: not assessed; OFD: outer foveolar defects; ELM: external limiting membrane; EZ: ellipsoid zone; COST: cone outer segment tips; PROS: photoreceptor outer segment.

(a) (b)

Figure 3: Optical coherence tomography (OCT) of macular edema following macular hole repair surgery. (a, b) Persistent hyporeflective intraretinal cyst after vitrectomy with internal limiting membrane peeling for MH.

In conclusion, the development of CME can complicate MH repair surgery, and the noninvasive diagnosis and follow-up with OCT is a simple and fast way to identify and monitor this condition and its response to medical treatment.

6. Macular Perfusion

Up to the present, few pieces of evidence have been published analyzing the VD changes and the FAZ modifications in patients with MH undergoing surgery. At baseline, qualitative analysis of en face OCTA slabs shows a central, round flow defect in the SCP and DCP, surrounded by perifoveal hyporeflective pseudocysts more consistent at the DCP. These cysts appear either as large, regular, and well-defined radial cystic areas with a petaloid or "grapefruit" configuration or as small, dispersed lesions with a "sponge-like" appearance [63]. Quantitatively, the investigations of the structural preoperative SCP and the DCP have proven a diffuse compromising, more pronounced in the DCP in long-standing, large MHs and a larger FAZ compared to controls [64]. The apparent expansion or enlargement of the FAZ can be interpreted as the loss of retinal tissue at the center of the fovea happening in MHs. However, it might be related to centrifugal tractional forces acting on the foveal center; dilatation of the FAZ would be in this case the result of mechanical factors.

Postoperatively, OCTA has globally demonstrated that eyes after MH closure feature a reduction in macular and paramacular vasculature, compared with control or fellow eyes. At the same time, different authors have described, independently, a reduction in the FAZ area at both the SCP and the DCP after the surgical repair [65–67], symmetrical to the size of the fellow eye [68]. The FAZ area tends to be inversely correlated to the postoperative foveal thickness [66] and the postoperative BCVA, suggesting that eyes with smaller FAZ areas disclose a better postoperative visual outcome up to 6 months after the surgery. The reduction in FAZ size has been interpreted either as the result of the release of tractional forces after MH closure or a consequence of the centripetal dragging of retinal tissues after ILM peeling [69]. On the other hand, the link between larger FAZ and worse functional outcome is consistent with findings in retinal diseases other than MH, including age-related macular degeneration, diabetic retinopathy, or central retinal vein occlusion [70, 71]. Therefore, the FAZ area is advocated as a surrogate indicator of the neurovascular integrity of the fovea.

Similar to FAZ, also the retinal VD of SCP and DCP was associated with postoperative retinal thickness, and in particular, with mean GCL-IPL thickness [72]. An issue that has been raised with repeated FAZ and VD measurements before and after MH closure deals with macular displacement secondary to ILM peeling. Comparative analysis of preoperative and postoperative fundus photographs has shown that the fovea is generally displaced toward the optic disc after surgery, with the temporal vessels shifted more than the nasal vessels. This macular dragging nasally and inferiorly has been recently demonstrated also by means of OCTA; using the fovea as a fixed point, a centripetal displacement of the vessel bifurcations has also been confirmed [17].

Figure 4: Optical coherence tomography (OCT) angiography in a case of degenerative lamellar macular hole. Superficial vascular plexus (top left panel) and deep vascular plexus (top middle panel) illustrate alterations of the foveal avascular zone, corresponding to the lamellar loss of inner retinal tissue. Segmentation at the level of the choriocapillaris (top right panel) demonstrates normal perfusion. The exact segmentation of the superficial vascular plexus, deep vascular plexus, and choriocapillaris (bottom panel) is illustrated on B-scan OCT with blood flow superimposed (red flow for retinal circulation and pink flow for choroidal circulation).

In the parafoveal region, eyes after MH surgery had a tendency to have a lower vascular density at the DCP, closely linked to the global retinal thickness in that area. This is true for generative LMH also (Figure 4) [63, 66, 73]. The explanation for this finding seems to be linked to the presence of intraretinal pseudocysts preoperatively seen at the edge of the MH. These pseudocystic areas localize between the inner nuclear layer (INL) and the outer plexiform layer (OPL), where the capillary bed of the DCP is embedded; despite a successful MH closure and anatomical reapposition of the walls of the pseudocysts, vascular atrophy corresponding to the pseudocystic cavity remains and appears as a darker hole on OCTA.

As far as it concerns the CC, Teng et al. found that the flow area and the parafoveal VD of CC in the macular area were significantly lower in eyes with MH than unaffected fellow eyes and healthy controls; this diminished CC circulation was partially restored after surgery [74]. Findings confirming CC perfusion defects were then confirmed by Ahn et al., who also observed that VD in the CC in LMH was not significantly different from that seen in fellow eyes and normal controls [75].

In conclusion, the quantitative evaluation of vascular capillary networks and of the FAZ may serve as a useful anatomic biomarker for assessment of macular perfusion parameters before and after MH repair.

7. Conclusions

Different devices have been recently added to the diagnostic tools available for the postoperative assessment of vitreoretinal surgery and for the prompt recognition of surgical complications. Among all these newly introduced devices, OCT and OCTA have added great value and significant benefits for the monitoring of the clinical course after vitreoretinal surgery. Different clinical findings can be observed on OCT of patients who underwent MH repair surgery, including inner retinal changes, outer retinal changes, CME, and macula perfusion abnormalities. Clinicians should be aware of these tomographic findings in order to properly manage each of the aforementioned condition. In addition, significant advantages for the postoperative application of OCT and OCTA include its noninvasiveness, rapid and simple execution, repeatability, and precise measurements. Taking together all these points, the OCT integrated into the clinical monitoring of patients after MH surgery is an invaluable diagnostic tool, critical for proper therapeutic management.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Research Article

Multifocal Electroretinography in Assessment of Macular Function after Internal Limiting Membrane Peeling in Macular Hole Surgery

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Purpose. Internal limiting membrane (ILM) peeling is important for macular hole (MH) surgery but may have secondary effects visible on spectral domain optical coherence tomography (OCT) and multifocal electroretinography (mfERG). We relate integrity of inner and outer macular layers with functional results with mfERG. *Methods*. Nonrandomized prospective study of 33 consecutive eyes of 33 patients with macular hole who underwent vitrectomy with ILM peeling. Best-corrected visual acuity was assessed, and integrity of external layers was measured using OCT. Each component of mfERG, N1 and P1 amplitude and latency, was also measured. *Results*. All eyes showed macular hole closure. Visual acuity improved from 20/400 to 20/40 in the Snellen visual acuity chart ($P < 0.001$), and OCT external lines were intact in 19 eyes and disrupted in 14 eyes. Postoperatively, N1 and P1 amplitudes in ring 1 increased compared to preoperative values ($P < 0.001$ for both). Latency remained delayed for both N1 and P1 wave. In the group of 19 eyes with integrity of outer retinal layers, N1 amplitude in ring 1 was superior to the group of 14 patients with disrupted outer retinal layers ($P = 0.042$). *Conclusions*. In macular hole surgery, structure analysis in OCT is one of the important outcomes for the retinal surgeon. Functional results are parallel with anatomic results, but visual gain is limited. The limited recovery in mfERG suggests an alteration of retinal physiology that could explain limited vision recover.

1. Introduction

Currently, macular hole is a common surgical feature, practiced in most vitreoretinal centers with high rate of closure [1]. Peeling of the internal limiting membrane (ILM) and inverted flap technique allows this high closure rate [2]. Indications for surgery and surgical technique to be used are based on structural images. Also, postoperative results are based on foveal anatomy. With ocular coherence tomography (OCT), it has become much easier to define and understand the retinal anatomy before and after macular hole surgery. In addition, it has also helped to explain poor visual acuity (VA) in cases where the retina appeared normal at biomicroscopic examination. Most efforts have focused on surgical technique to realign photoreceptors and improve VA. However, exploring retinal function is another way of understanding the healing process of macular holes.

After successful hole closure, patients refer less metamorphopsia and an improved ability to read [3]. Nevertheless, even with hole closure, visual function improves but the gain in visual acuity is often limited. Visual function before and after macular hole surgery is usually assessed by visual acuity measurement [4]. However, the visual acuity level represents only a part of the visual function resulting from macular hole development, which includes metamorphopsia, scotoma, and blurred vision [5].

Because ILM is the basement membrane of Müller cells, the inner barrier of the neural retina and anatomically adjacent to the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL), ILM removal may alter the architecture of

the inner retinal layer and also alter the function of Müller cells, responsible for the generation of electroretinogram [6]. Nerve fibers are joined and fixed at the lamina crivosa, and after ILM peeling, a dissociated optic nerve layer has been referred by Tadayoni et al. [7]. Also, nasal displacement and contraction of this neural layer and ganglion cell axon allow the underlying macular tissue to react with the alteration of cytoarchitecture of external retinal layers [8]. All these structural alterations may have consequences on postoperative macular function. Moreover, the direct trauma of surgery to the nerve fiber layer, the gas tamponade, the stain used to visualize the transparent ILM, and the endoillumination light probe are all factors to consider as possible toxic effects to macular function.

Multifocal electroretinography (mfERG) is an objective clinical tool to assess visual function and selects the multiple retinal locations of the macular area to provide a topographic map of local central retinal electrophysiological activity [9]. The purpose of this prospective study was to characterize macular function by means of mfERG, before and after surgery.

2. Methods

2.1. Setting and Patients. In a nonrandomized prospective study, 33 consecutive eyes of 33 patients with MH underwent surgery between January 2015 and June 2017 at the Department of Ophthalmology of Santa Maria Hospital, Lisbon. Exclusion criteria were maculopathy other than MH, surgeries for MH recurrence, other retinal diseases, or an axial length greater than 26.0 mm. Mean follow-up time was at least 12 months after surgery. This study was approved by the Ethics Committee of Santa Maria Hospital. The tenets of the Declaration of Helsinki were followed. All subjects have given written informed consent to the surgical and the study procedures.

2.2. Collected Data. Preoperative data included age, gender, and complete ophthalmic examination. Best-corrected visual acuity (BCVA) was measured using a Snellen chart and converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Hand motion was considered as logMAR 3 and counting fingers as logMAR 2.

2.3. Optical Coherence Tomography. All macular holes were staged based on recent OCT-based classification [10], and only full thickness macular hole, grade 2 to 4, was considered for the study. Retinal images were acquired using Spectralis SD-OCT (Heidelberg Engineering, Heidelberg®, Germany), using the eye-tracking feature with software posterior pole images centered on the fovea (61 acquisitions, 120 μm interval).

The status of the foveal ellipsoid zone (EZ) and the external limiting membrane (ELM) were examined for each eye to test integrity: intact and disrupted. The intact eyes had a regular continuation of the hyperreflective line corresponding to the EZ or ELM. The disrupted eyes were characterized by hyporeflective discontinuities in the EZ or ELM line (Figure 1). These classifications were assessed by agreement of two authors (MF and NF).

2.4. Multifocal Electroretinography. RETIscan Multifocal ERG (Version 6.12.5.12; Roland Consult) was used for mfERG recording. The recording procedures were the same as those described by the International Society for Clinical Electrophysiology of Vision [11]. The stimulus consisted of 61 hexagons that scale concentrically and covered the central 25 degrees of the fundus area. The viewing distance was 29 cm, which allowed a viewing angle of approximately 30 degrees. Each hexagon was modulated temporally between black (2 cd/m^2) and white (200 cd/m^2). Pupils were dilated with tropicamide and phenylephrine hydrochloride. After topical anesthesia, a contact lens jet electrode was placed, and signals were recorded. During the recordings, the patients' fixations were monitored. The signal was amplified (100,000) and bandpass filtered (10–300 Hz). Three-dimensional topography represents the retinal response density (amplitude per retinal area, nV/deg^2).

The mean simultaneous response was recorded. The typical waveform of the basic mfERG response is a biphasic wave with an initial negative deflection followed by a positive peak. Implicit times (latencies) and the amplitude relative to their respective areas (nV/deg^2) of the first negative peak (N1) and the first positive peak (P1) were measured using regional averages derived from 5 concentric rings (Figures 2 and 3). Three-dimensional topography (Figure 4) represents the retinal response density (amplitude per retinal area, nV/deg^2). The studied field contained 61 hexagons in 5 rings within a field diameter of 25 degrees, 12.5 degrees radially centered on the fovea [12], and was analyzed with RETIscan software. Five rings correspond to 5 degree areas. Only ring 1 and ring 2 were considered, as they roughly parallel a 3 mm diameter ILM peel during surgery.

Multifocal ERG was recorded preoperatively and at 12 months after surgery. In the present study, we focused on amplitude and latency of N1 and P1, before and after surgery.

2.5. Surgical Procedure. A standard surgical procedure consisted of 23- or 25-gauge, three-port pars plana vitrectomy (PPV). Except in pseudophakic patients, every patient underwent combined cataract surgery, in order to avoid confounding results. Standard small-incision phacoemulsification and implantation of a standard foldable intraocular lens were associated with vitrectomy. In every eye, Brilliant Peel® Dual (Geuder, Germany) assisted ILM peeling was performed, in an area of approximately 3 mm, engaged with end-grip intraocular forceps. A flap is created, then peeled in a rosette way all around the hole, and trimmed until the border of the macula but leaving a flap big enough to invert and cover the hole. BSS was exchanged with 15% SF6 (sulfur hexafluoride) gas. The patients were instructed to maintain a face-down position for at least 5 days. All surgeries were performed by the same experienced surgeon (MF).

2.6. Postoperative Follow-Up. In postoperative observations, at day 1, month 3 and month 6, a thorough ophthalmic examination, including BCVA, mfERG, and OCT, whenever

(a) (b)

Figure 1: OCT with closed macular hole: integrity of ELM and EZ zone (a) and disrupt ELM and EZ (b).

(a) (b)

Figure 2: Amplitude of P1 nV/deg^2 in patient no. 4 in five rings centered in fovea, before surgery (a) and after surgery (b) Ring 1 (green) and ring 2 (red) are considered for study.

(a) (b)

Figure 3: Amplitude of P1 in nV/deg^2 in patient no. 4 in topographic display around fovea, before (a) and after (b) surgery.

possible, and fundus revision were performed. Hole status, ELM, and EZ integrity at the fovea were measured in OCT. N1 and P1 waves of mfERG were measured for amplitude and implicit time.

2.7. Statistical Analysis. The results are expressed as medians (range). Only ring 1 and ring 2 of mfERG were considered as they correspond to the area of the ILM peel. Amplitude and latency of N1 and P1 of mfERG were compared before and after surgery. BCVA and amplitude of N1 and P1 of mfERG were compared between the groups with intact or disrupted photoreceptor. For comparisons before and after surgery, the Wilcoxon signed-rank test was used. Between group analyses were performed with the Mann–Whitney U test. Correlations were tested using Spearman's ρ correlation coefficient. Statistical significance was established at $P < 0.05$.

3. Results

3.1. Demographic and Clinical Data. The median (range) age of the patients was 71 (21) years, and the study group

Figure 4: Three-dimensional topography of amplitude P1 of patient no. 4, before and after surgery for macular hole.

included 14 men and 19 women. Thirty-three eyes were studied, 26 patients underwent concomitant cataract surgery, and 7 were already pseudophakic. None of the patients required further treatment during the 12-month follow-up.

3.2. Amplitude of P1 and N1 and Respective Latency Times before and after Surgery. There was an increase in amplitude of P1 and N1 waves, in ring 1, after surgery ($P < 0.001$ for both). Ring 2 increase was only statistically significant for P1 wave ($P = 0.040$). Pre- and postoperative latency was not significant for neither waves (Table 1).

3.3. Visual Acuity and Amplitude of P1 and N1 by Photoreceptor Status before and after Surgery. The median (range) visual acuity, in logMAR, improved from 2.10 (2.90) to 0.70 (4.80), $P = 0.007$ and from 1.80 (1.60) to 1.10 (2.0), $P = 0.008$, from baseline to 12 months in the intact and disrupted photoreceptor groups, respectively. P1 and N1 in the first ring region of the retina increased both in the intact photoreceptor group and the disrupted photoreceptor group ($P < 0.001$ and $P = 0.001$, respectively), with no differences in the second-ring regions of the retina (Table 2).

3.4. Difference between Post- and Presurgery in BCVA, N1 Amplitude, and P1 Amplitude. Median (range) increase in visual acuity from pre to postsurgery was −0.80 (7.60) logMAR and −0.40 (1.40) logMAR, in the intact photoreceptor group and the disrupted photoreceptor group, respectively ($P = 0.114$). Increase in N1 ring 1 was 30.20 (75.20) nV/deg^2 and 10.25 (116.90) nV/deg^2, and increase in P1 ring 1 was 12.00 (99.10) nV/deg^2 and 20.95 (97.90) nV/deg^2 in the intact photoreceptor group and the disrupted photoreceptor group, respectively ($P = 0.042$ and $P = 0.418$, respectively), as assessed by the Mann–Whitney U test. There was no correlation between BCVA increase and N1 increase in any of the groups, intact or interrupted, as assessed by Spearman's ρ correlation coefficient.

4. Discussion

In macular hole surgery, removing the ILM may eliminate almost all traction, anterior-posterior and tangential, and lead to a higher probability of hole closure [13]. ILM peeling was introduced as an additional maneuver to improve anatomical and functional outcomes [14], allowing 100% closure of idiopathic macular holes, especially with the inverted flap technique [2]. With the latest spectral domain OCT, with increased depth of resolution, it has become much easier to define and understand the retinal anatomy before and after macular hole surgery. In our study, peeling was performed in every surgery. However, the effects of ILM removal on retinal function remain unknown. Multifocal electroretinography is a noninvasive method that objectively measures visual function by selecting multiple retinal locations around macular area to provide a topographic map of electrophysiological activity in the central retina [9]. Based on the International Society for Clinical Electrophysiology of Vision (ISCEV), mfERG responses show greater amplitudes in the fovea where cone photoreceptors and bipolar cells are in greater number. It is believed that N1 is generated by photoreceptors in the outer retinal layer and P1 is generated by Müller and bipolar cells [15, 16].

If outer retinal layers are intact after surgery, photoreceptors will probably recover function, N1 will probably increase and influence internal layers, in recovering P1 functions. However, that is not always true, as peeling of ILM may negatively influence these internal layers.

Several previous studies with mfERG on eyes before and after MH surgery were published. Machida et al. [17] found no toxic effect of brilliant blue G, indocyanine green, or triamcinolone acetonide in macular hole surgery with ILM peel, as measured with focal macular electroretinograms. Scupola et al. [18] compared triamcinolone acetonide and infracyanine green in thirty eyes studied with focal electroretinogram and found late toxic effect with infracyanine green-assisted ILM peeling. Bellerive et al. [19] also compared toxicity of trypan blue and infracyanide green in macular hole surgery using mfERG before and after surgery and concluded that, at 12 months, there was improvement of P1 amplitude and implicit time, BCVA, and contrast sensitivity was not different between groups. Ferencz et al. [20] studied mfERG in 30 eyes with MH, found preoperative subnormal responses, and only at 20 months found significant improvement in both groups by probable toxicity with infracyanine green in surgery.

Studying macular hole before and after its closure is a unique situation where outer retinal cells do not exist at full thickness hole. After successful surgery, there is a closed hole with or without integrity of ELM, EZ, and retinal pigment

Table 1: Amplitude of P1 and N1 and respective latency times before and after surgery.

Parameter	Before surgery (n = 33)	After surgery (n = 33)	P value
P1 amplitude (nV/deg^2)			
Ring 1	36.00 (77.20)	59.20 (92.60)	**<0.001**
Ring 2	45.70 (62.30)	55.30 (97.30)	**0.040**
P1 latency (ms)			
Ring 1	33.30 (30.40)	34.30 (38.20)	0.806
Ring 2	33.30 (20.60)	34.30 (30.40)	0.955
N1 amplitude (nV/deg^2)			
Ring 1	28.30 (127.30)	46.30 (155.30)	**<0.001**
Ring 2	20.80 (85.80)	22.60 (47.40)	0.550
N1 latency (ms)			
Ring 1	17.60 (48.80)	18.60 (22.50)	0.330
Ring 2	17.60 (13.70)	17.60 (27.40)	0.977

Amplitude of P1 and N1 are expressed in nanovoltage (nV)/area degree^2 (deg^2) and implicit time (latency) in milliseconds (ms). All values are expressed as median (range). P values are obtained from the Wilcoxon signed-rank test.

Table 2: Visual acuity and amplitude of P1 and N1 by photoreceptor status before and after surgery.

Parameter	Before surgery (n = 33)	After surgery (n = 33)	P value
Intact photoreceptor			
Visual acuity (logMAR)	2.10 (2.90)	0.70 (4.80)	**0.007**
P1 amplitude (nV/deg^2)			
Ring 1	37.70 (77.20)	59.00 (92.60)	**<0.001**
Ring 2	51.50 (39.70)	67.30 (97.30)	0.231
N1 amplitude (nV/deg^2)			
Ring 1	31.40 (120.80)	67.90 (117.80)	**<0.001**
Ring 2	20.30 (30.80)	24.80 (47.40)	0.571
Disrupted photoreceptor			
Visual acuity (logMAR)	1.80 (1.60)	1.10 (2.00)	**0.008**
P1 amplitude (nV/deg^2)			
Ring 1	35.65 (48.10)	60.80 (82.20)	**0.001**
Ring 2	35.15 (62.30)	45.85 (80.20)	0.084
N1 amplitude (nV/deg^2)			
Ring 1	23.35 (127.30)	31.65 (155.30)	**0.001**
Ring 2	21.30 (85.80)	21.50 (40.20)	0.861

Amplitude of P1 and N1 are expressed in nanovoltage (nV)/area degree^2 (deg^2). All values are expressed as median (range). P values are obtained from the Wilcoxon signed-rank test.

epithelium. Also, there is a reduced thickness of internal macular layers after ILM peeling in macular hole surgery [8], especially ganglion cell layers and internal nuclear layers, measured at 3 mm diameter centered on fovea, roughly the degree reached by the second ring in mfERG.

In this macular hole study, mfERG recorded before surgery showed almost undetectable retinal response in foveal and parafoveal areas, in ring 1 and ring 2. After surgery, the improvement in the retinal response density of mfERG in the same ring seems to be consequent to closure of the macular hole with realignment of photoreceptor cells and glial cell activation. Resolution of the central scotoma seems to be attributed to anatomical repair and, in our study, we found a statistically significant increase in N1 and P1 in ring 1. Comparing ring 1 in N1 and P1 amplitude and outer retinal layer status, we found that P1 wave increased both in the intact and disrupted groups ($P < 0.001$ and $P = 0.001$, respectively), which is consistent with increase of P1 amplitude with closure of hole, whatever the outer layer status is. As to the N1 wave, the increase in the intact group was superior to the increase in the disrupted group ($P = 0.042$). All other results were not significant. Therefore, in our results, correct restoration with intact hyperreflective photoreceptor lines in OCT, ELM and EZ, results in improvement in outer retina response, as measured by the N1 wave. It has generally been thought that photoreceptor status by OCT is associated with visual recovery [21]. Although the N1 amplitude was reduced by the presence of MH, the increase in 66% of its amplitude after ILM peeling, hole closure, and realignment of photoreceptors agrees well with that the N1 amplitude was related to and generated from the outer retina.

The median BCVA of patients included in the study improved after surgery. The mechanism by which visual function improves after surgery is not clearly understood. However, the centripetal movement of the previously displaced photoreceptors to its original site as proven by OCT images may be the simplest explanation [4]. However, even with integrity in photoreceptor lines, vision improvement is limited.

BCVA increased in both the intact and disrupted groups ($P = 0.007$ and $P = 0.008$, respectively). Even though clinically the results are better in the intact group, there is a large

variability, which may have prevented a higher statistical significance in this group.

Besides the low recovery of P1, there was also a delay of implicit time. After ILM peeling and closure of the macular hole, implicit time of the P1 wave in ring 1 maintained delay of 33.96 (38.20) millisecond in this study compared to normative data [22]. The delay may be related to surgical aggression of ILM peeling, or even ischemia in the macular area [23]. Implicit time was delayed before surgery and never recovered, even after closure and visual recovery. Andréasson and Ghosh already referred [24] to a very slow cone function recovery even after successful anatomical healing.

Hood et al. [9] already suggested that the multifocal ERG value might affect numerous factors we could not detect and control. As to the N1 wave, the increase in the intact group was superior to the increase in the disrupted group ($P = 0.042$), and therefore, the P1 wave in the intact group was expected to increase superiorly than that in the disrupted group. However, P1 ring 1 increased both in the intact and disrupted groups, with no statistical differences, suggesting a loss of interaction with outer retinal layers.

Thus, we suspect that ILM peeling may damage inner retinal layers and Muller cell function which have some negative effect on the P1 wave of multifocal ERG and visual acuity.

In eyes with successful MH surgery, there is disappearance of central scotoma and improvement of visual acuity. This improvement is enhanced if there is realignment of photoreceptors and integrity of outer retinal layers. This results in N1 increase in mfERG of 66% compared to 53% increase in the disrupt photoreceptor group.

P1 wave in mfERG also increases after surgery, 69% in intact and 109% in disrupted outer retinal layers, but below age-related normative data. This uneven increase of the P1 wave, whatever the outer retinal status is, may explain the functional impairment between inner and outer retinal layers. ILM is the end feet of glial cells, and an alteration of retinal physiology in inner retinal layers, where bipolar and glial cells interact with photoreceptors, may explain the limited improvement in BCVA.

The present study had several limitations. The number of patients included is small, which may limit the reliability of the statistical results. Also, only BCVA was measured, and no other visual functions were tested. We did not have a control group in which the ILM was not peeled in macular hole surgery. Performing the surgery without ILM peeling could lead to lower closure rates in grade 3 or 4 macular hole, and therefore, generating such a control group would be unethical. The peeled area of ILM is around 3 mm in diameter, but no film registration of each surgery was made in every patient to ensure the exact diameter of the peel.

Lastly, contrary to most diagnostic equipment in ophthalmology, normative data in mfERG may vary with each equipment, and laboratory and healthy fellow eyes were not used as control. Also, population-specific factors such as age, ethnicity, pupil size, axial length, and diurnal variation may influence normative data.

5. Conclusion

In eyes with successful MH surgery, there is disappearance of central scotoma and improvement of visual acuity. This improvement is enhanced if there is realignment of photoreceptors and integrity of outer retinal layers. However, functional results may not be parallel with anatomic results as visual gain is limited. ILM is the end feet of glial cells, and an alteration of retinal physiology in inner retinal layers, where bipolar and glial cells interact with photoreceptors, may explain the limited improvement in BCVA. The limited recovery in mfERG suggests an alteration of retinal physiology that could explain limited vision recover.

Data Availability

All data used to support the findings of this study are at Ophthalmology Department, Hospital Santa Maria, Centro Hospitalar Universitário Lisboa Norte, and available from the corresponding author upon request.

Conflicts of Interest

None of the authors has any conflicts of interest.

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Review Article

Traumatic Macular Hole: Diagnosis, Natural History, and Management

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Traumatic macular hole occurs most often in young men and can present after various types of injuries. Traumatic macular holes result from anteroposterior and tangential vitreoretinal traction and may exhibit concurrent additional pathologies such as Berlin's edema and subretinal fluid. Optical coherence tomography can play an essential role in patient management both at presentation and during follow-up. Initial management consists of observation, but macular hole repair can be performed if spontaneous resolution does not occur. Upon macular hole closure, vision may improve, on average, by two lines or more but may be limited by associated macular pathology.

1. Introduction

A macular hole (MH), a full-thickness defect of the neurosensory retina at the fovea, occasionally can result after trauma. The first case of traumatic MH was described by Knapp in 1869 [1]. While idiopathic MHs occur more commonly among women older than 65 years of age [2], traumatic MHs are found more often in young men in their early twenties [3, 4]. Because traumatic MHs frequently are associated with sports and work-related accidents, they occur predominantly in younger persons. The incidence of traumatic MHs is 1.4% in closed-globe trauma [5] and 0.15% in open-globe injuries [6]. Traumatic MHs also can occur following laser injury [7], surgical trauma [8], lightning strikes [9], and shock with electrical current [10].

Vision at presentation ranges from Snellen 20/30 to 20/400 [3, 4]. The functional prognosis often is uncertain due to the accompanying trauma-induced retinal pathologies, such as commotio retinae, vitreous hemorrhage, retinal hemorrhage, choroidal rupture, retinal pigment epithelium (RPE) damage, and subretinal choroidal neovascularization and fibrosis.

Treatment includes observation, as spontaneous closure has been reported [11–15], as well as surgical closure with vitrectomy if necessary.

2. Pathogenesis

In contrast to idiopathic MHs which develop gradually over months [16], MHs more commonly form immediately after trauma [17] although there are reports of holes developing weeks following injury [14]. Two hypotheses exist to explain the development of traumatic MHs, and these are similar to their idiopathic counterparts, in that tangential and anteroposterior vitreoretinal traction are the main culprits.

One theory proposes anteroposterior vitreous traction on the fovea causing true loss of foveal tissue. This scenario could be thought of as a trauma-induced force vector with a component orthogonal to the corneal surface resulting in anteroposterior compression of the globe with equatorial globe expansion followed by a rebound contrecoup resulting in vitreofoveal traction. However, a flaw with this theory is that many studies have not found a posterior vitreous detachment (PVD) in traumatic MHs nor has evidence of vitreomacular traction consistently been observed with optical coherence tomography (OCT) [4, 6, 17]. Additionally, following surgical closure vision typically improves at least two lines [6, 17], which would not likely be the case if true loss of foveal tissue had occurred. However, Yamashita et al. reported a hole developing a few days following trauma which showed OCT evidence of vitreomacular traction. The

hole closed spontaneously one month later after the vitreous fully detached from the fovea [14]. Thus, it is possible that anteroposterior vitreous traction without true foveal loss can be causative and may contribute to MH formation in some cases.

Likely, a more frequent cause proposed by Johnson et al. [17] is as follows. Blunt trauma to the eye occurs in the axial direction, causing a decrease in the axial length of the globe. Subsequently, there is an expansion of the globe along its equatorial dimension. This expansion results in tangential vitreoretinal forces that are transmitted to the macula, with centripetal forces separating the neurosensory retinal layers at the fovea, resulting in a central defect without any loss of foveal tissue.

It is likely that a combination of anteroposterior vitreoretinal and tangential retinal traction is the cause in many cases. However, given that commotio retina sometimes resolves with substantial photoreceptor atrophy and given that the predominant cell type in the foveal center is the specialized cone photoreceptor, loss of foveal photoreceptors may cause full-thickness macular holes in some patients after globe trauma [18]. In these cases, closure of the hole may not be possible, and, even if it is, recovery of precision vision is not likely to occur.

3. Examination

Patients usually complain of decreased vision and metamorphopsia. The vision may range from 20/30 to 20/400. If there are no additional injuries, there is no afferent pupillary defect (APD). On clinical examination, a round or ellipsoid full-thickness defect of the neurosensory retina in the macula is seen with a rim of subretinal fluid (Figures 1 and 2). Retinal edema and subretinal hemorrhage may be evident in many eyes if examined immediately after the traumatic event. Posterior vitreous detachment is absent in most cases. Usually, the traumatic MHs involve the foveal center, but they can have an eccentric location, particularly if they arise from surgical trauma [8].

The Watzke–Allen sign is usually positive [9]. A laser aiming beam directed in the central defect may not elicit any perception of the light spot. The Amsler grid usually will show central metamorphopsia [9]. A fluorescein angiography may reveal late central hypofluorescence or hyperfluorescence [19], depending on the RPE changes that have developed. OCT shows a full-thickness defect in the neurosensory retina occasionally with a cuff of subretinal fluid, usually without PVD or evidence of vitreomacular traction [12, 15]. Intraretinal cysts may be noted in some cases, particularly at the edge of the full-thickness retinal defect [15].

Fundus autofluorescence (AF) has been used to stage and monitor idiopathic MHs [20–22]. Relative hypoautofluorescence is normally noted at the fovea due to the presence of lutein and zeaxanthin pigments that attenuate the RPE autofluorescence [21, 22]; in eyes with MH, however, the lack of these pigments results in hyperautofluorescence which disappears with successful anatomic closure. Stellate hyperautofluorescence with striae may be associated with cysts in the outer plexiform layer and present with better VA and lower stage MH than eyes without a stellate appearance [20].

A large study comparing OCT findings in traumatic MHs to idiopathic MHs was completed by Huang et al. [4]. They found that traumatic MHs are more eccentric, or less circular, than idiopathic MHs, with the horizontal diameter significantly longer than the vertical diameter. This eccentricity is consistent with the tangential traction theory of development. As the equatorial horizontal diameter of the globe itself is longer than its vertical diameter [23], a stronger shearing force is likely applied at the macula in the horizontal meridian, resulting in the greater horizontal hole diameter observed in traumatic MHs. Huang et al. also reported significant differences in the average size of traumatic versus idiopathic MHs—a larger basal diameter and basal area of 1338.45 μm and 176.85 μm^2 versus 958.57 μm and 77.92 μm^2, respectively, with retinal thickness much lower at 248.4 μm compared to 408.8 μm at the edge of the defect. They noted that there was no correlation between visual acuity (VA) and size of traumatic MH. This finding is in contrast to idiopathic MHs, the diameter of which is positively correlated with worse VA. No evidence of PVD or operculae was seen on OCT in this study.

Teng et al. using OCT angiography showed an association between decreased subfoveal choroidal blood flow in eyes with idiopathic MHs compared to healthy fellow eyes [24] but, to date, this has not been studied in eyes with traumatic MHs.

4. Management

4.1. Observation. Most spontaneous closures of traumatic MHs occur in children or young adults [12, 14, 15]. Miller et al. described a 50% spontaneous closure rate in children and a 28.6% rate in adults in a long-term follow-up series of traumatic MHs [12]. The holes closed spontaneously at a median of 5.6 weeks, and none closed without intervention after 67.3 weeks [12]. Other series also report a spontaneous closure rate of 37%–44% within two months after injury [14, 15]. OCT plays an important role in the management of traumatic MHs to delineate the anatomic details of the defect, associated retinal pathology, and also to assess its progression objectively on a weekly or monthly basis.

Many investigators have noted that smaller traumatic MHs have a higher chance of spontaneous resolution [12, 14, 15]. The majority of such eyes have no PVD [14, 25]; the posterior hyaloid may play a tamponading role to prevent fluid from entering the hole. Chen et al. found that holes with spontaneous closure were less likely to have intraretinal cysts compared to the holes that did not close spontaneously (10% versus 76.5%, respectively) [15]. They suggested that the absence of intraretinal cysts on OCT may predict spontaneous traumatic MH closure. Of note, case reports describe topical nonsteroidal anti-inflammatory drugs, resulting in closure of traumatic holes associated with cystoid macular edema [26].

One proposed mechanism for spontaneous hole closure is glial cell proliferation from the level of the RPE to the basal surface of the hole, thus promoting closure [13]. If there is an

(a)

(b)

Figure 1: An 18-year-old male, punched in the face, presented with visual acuity of 20/60 with Berlin's edema and a full-thickness macular hole. He underwent surgical repair of the hole with pars plana vitrectomy, induction of a posterior vitreous detachment, and internal membrane peel, two months later. (a) OCT, two months after presentation, shows a full-thickness macular hole with intraretinal fluid. (b) OCT, two months after surgical repair, shows a closed macular hole and parafoveal disruption of the ellipsoid zone. Visual acuity was 20/40.

element of anteroposterior vitreomacular traction, formation of a complete PVD may also foster closure of the hole. As Berlin's edema resolves, the edges of the hole may return closer to the RPE, resolving the central full-thickness defect.

There is no consensus on when to operate on a traumatic MH that does not close spontaneously. As noted above, many reports describe spontaneous closure within two months of trauma [12, 14, 15]. Additionally, Miller et al. noted that traumatic MHs that underwent delayed vitrectomy, on average approximately one year after presentation, were less likely to close than those operated on earlier [12]. Thus, the vitreoretinal surgeon should strive to balance waiting long enough for spontaneous closure but not so long that the likelihood of an anatomically successful outcome is materially reduced. Waiting one to three months before intervening with surgery seems prudent.

4.2. Surgery

4.2.1. Basic Technique. Vitrectomy to surgically induce the closure of idiopathic MHs was described originally by Wendel et al. as comprising five steps: (1) pars plana vitrectomy; (2) induction of a posterior vitreous detachment (PVD), if not present; (3) epiretinal membrane peel; (4) fluid-gas exchange; and (5) one week of occiput-up positioning [27]. They reported a 73% overall single-operation anatomic success rate; patients with symptom duration less than six months had an 80% overall single-operation anatomic success rate. Since the introduction of this technique, many variations have been described in an attempt to improve the anatomic success rate of traumatic MH closure.

Surgical adjuvants such as TGF-beta 2, platelet concentrate, and serum were used to close idiopathic MHs following Kelly and Wendel's report [28]. Subsequently, these adjuvants were used in the repair of traumatic MHs. The adjuvants are placed into the hole following the fluid-air exchange and prior to the instillation of the tamponade agent. One proposed mechanism for the use of these adjuvants is that they could assist in the formation of a chorioretinal adhesion that would act as a barrier preventing more fluid from entering the subretinal space [29], thus enabling MH closure.

(a)

(b)

(c)

Figure 2: A 19-year-old male who sustained a firework explosion to his face presented with a macular hole that resolved spontaneously within three months of follow-up. (a) OCT at presentation shows a full-thickness macular hole and extensive subretinal fluid. Visual acuity was 20/400. (b) OCT a week after presentation shows a closed macular hole with some residual subretinal fluid. Visual acuity was 20/400. (c) OCT at the three-month follow-up visit shows a closed hole with resolved subretinal fluid but with extensive outer retinal atrophy and an increase in subretinal deposits. Visual acuity was finger counting.

4.2.2. TGF-Beta 2. Rubin et al. utilized TGF-beta 2 in a series of 12 eyes with a traumatic MH and noted a 67% (8/12) single-operation success rate, which improved to 92% (11/12) after repeat surgery in the four eyes that failed initially [30]. In contrast to the procedure described by Kelly and Wendel, their method called for 24 hours of supine positioning to allow for the TGF-beta 2 to maintain contact with the macula before beginning two weeks of face-down positioning; 67% of eyes gained two lines of vision or more.

4.2.3. Serum. Johnson et al. reported 25 eyes that underwent vitrectomy for traumatic MH, 12 of which received serum as a surgical adjuvant in addition to perfluoropropane (C3F8) tamponade [17]. They noted MH closure in all cases treated with serum, with two or more line visual improvement in 75% of eyes. However, there were no significant differences between the rate of closure or visual improvement between eyes treated with or without serum.

4.2.4. Platelet Concentrate. García-Arumí et al. infused the platelet concentrate over the traumatic MH before infusing sulfur hexafluoride gas (SF6) in a series of 14 eyes [19]. These patients were kept supine for 1 hour after surgery before adopting strict face-down positioning. They reported an 86% (12/14) single-surgery success rate, which improved to 93% (13/14) after the second surgery. Visual acuity improved at least two lines in all eyes in which the MH closed, and at least 50% of eyes had a final visual acuity better than or equal to 20/30.

4.2.5. Internal Limiting Membrane (ILM) Peeling. Kuhn et al. were among the first to report peeling the ILM before the fluid-air exchange in eyes with traumatic MHs in a series of 17 eyes utilizing SF6 tamponade [6]. The single-surgery success was 100% with 94% of patients improving at least two lines of vision and a mean improvement of six lines. Bor'i et al. published a series of 26 eyes that underwent vitrectomy and ILM peeling and reported a 92% single-surgery success rate [31].

4.2.6. ILM Flap Techniques. An inverted ILM flap, initially proposed by Michalewska et al. for the treatment of idiopathic MHs [32], involves an ILM peel circularly some distance away from the hole while keeping the ILM attached to the border of the hole and then directing the inner layer of the ILM flap over the surface of the MH. Abou Shousha utilized this technique for traumatic MHs in a series of 12 eyes with SF6 tamponade [33]. The closure rate was 100% with a median final visual acuity of 20/100. An alternative technique proposed by Morizane et al. [34] has been described for refractory idiopathic MHs. In this method, the surgeon creates a free ILM flap the same size as the hole; the flap is then placed into the MH and covered with a viscoelastic material. The proposed mechanism for both techniques is that the ILM flap contains residual Mueller cells that can use the flap as a scaffold on which to proliferate and subsequently seal the hole [32].

4.2.7. Plasmin-Assisted Vitreolysis. Pediatric patients have very strong adhesion between the posterior hyaloid and the ILM. Plasmin is an enzyme that can hydrolyze fibronectin and laminin, two extracellular matrix proteins responsible for the strong adhesion [35]. Wu et al. injected plasmin intravitreally before vitrectomy with the goal of weakening the hyaloid-ILM adhesion and thus making the surgical induction of PVD easier in a series of 13 pediatric eyes with a traumatic MH [35]. They noted 38% (5/13) of these patients already had a partial or complete PVD at the start of surgery, and in the remaining 62%, inducing the PVD was much easier and required less than 50 mmHg of suction; 92% of patients had their holes close, and 92% achieved two-line or greater visual improvement with 50% achieving a final vision better than or equal to 20/50. No studies have reported using ocriplasmin for traumatic MHs, which was approved for the use of idiopathic MHs 400 μm or less with evidence of vitreomacular traction [36].

4.2.8. Tamponade Agents. SF6, C3F8, and silicone oil all have been used as tamponade agents in traumatic MH surgery with air tamponade also being described for idiopathic MHs [37].

SF6 tamponade has attained as high as 86–100% anatomic success for traumatic MHs with face-down positioning for one or two weeks [6, 19, 33]. Oil tamponade is used uncommonly, and two studies have retrospectively compared silicone oil and C3F8 for traumatic MH surgery [31, 38]. The use of both agents involved two weeks of face-down positioning. Silicone oil has reported anatomic success rates of 67%–90%, while C3F8 has a higher anatomic success rate of 90–92.3%.

Typically, gas tamponade is preferred to silicone oil for the closure of traumatic MHs to obviate the need for an additional surgery to remove the oil, unless face-down positioning would be difficult or impossible as in pediatric cases or incarcerated patients.

4.3. Visual Outcome of Traumatic Macular Hole Closure. Whether spontaneous or vitrectomy-induced, traumatic MH closure is generally associated with visual acuity improvement of at least two lines; however, there is potential for greater improvement. Kuhn's series on vitrectomy with ILM peel noted mean improvement of six lines of vision [6].

Trauma can cause photoreceptor and RPE damage, limiting the visual potential of these eyes even with successful MH closure. Many eyes exhibit commotio retinae or faint subretinal hemorrhage immediately after the injury. Rapid resolution of retinal edema and hemorrhage with no clinical sequelae can follow. In many cases of traumatic MHs, however, RPE changes are observed a few weeks after the injury, suggesting RPE and photoreceptor damage. OCT may reveal disruption of the RPE and ellipsoid layers. Johnson et al. alluded to Berlin's edema being associated with photoreceptor and RPE damage and mentioned a few eyes that had significant RPE changes after surgery with final visual outcome ranging from 20/30 to 20/200 [17]. Miller et al. noted no significant difference in final visual acuity in eyes that had foveal Berlin's edema on presentation versus those that did not [12]. Additionally, Miller et al. noted a statistically insignificant trend for better final visual acuity among eyes that had an intact ellipsoid zone on OCT, suggestive of an intact healthy photoreceptor layer, as compared to those that did not [12].

A literature review of traumatic MH studies by Liu and Grzybowski noted an anatomic success rate of 45% to 100% (median, 92.5%) and a functional success (Snellen visual

acuity two or more lines improvement) rate of 27% to 100% (median, 84%) [39].

While the vast majority of cases in the literature are secondary to direct ocular trauma with generally good prognoses, two case reports of traumatic MHs secondary to lightning or electrical shock injuries have both resulted in light perception vision and recurrent retinal detachments following pars plana vitrectomy [9, 10].

5. Conclusion

Traumatic MH can result from tangential and anteroposterior vitreomacular traction. It may also result from foveal photoreceptor atrophy following commotio retinae. As compared to idiopathic MHs, traumatic holes tend to be more common in younger male patients. Spontaneous closure can occur; however, vitrectomy, induction of PVD, and ILM peeling (with or without an ILM flap to cover the MH) is associated with anatomic success rates of up to 100% [6, 33]. Functional success despite anatomic closure may be limited by trauma-induced concurrent macular pathology.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Characteristics and Risk Factors for Spontaneous Closure of Idiopathic Full-Thickness Macular Hole

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Idiopathic full-thickness macular hole is a severe visual impairment disease. Pars plana vitrectomy remains the primary treatment option for idiopathic full-thickness macular holes, and over 90% idiopathic full-thickness macular holes are closed by vitrectomy surgery. However, the full-thickness macular hole may close spontaneously, with a good visual acuity progress. Since recent studies are small-sample studies and case reports, the characteristics for spontaneous closure of idiopathic full-thickness macular holes are not fully understood. Here, we review the articles in PubMed database from 1999 to 2018 and discuss the characteristic and the risk factors, especially OCT structure features, for spontaneous closure of idiopathic full-thickness macular holes.

1. Introduction

Idiopathic macular hole (IMH) is a kind of disease that seriously affects the visual quality of patients, showing obvious central visual loss and visual deformation. The AAO guidelines suggest that stage 2–4 IMHs have a good prognosis after vitrectomy surgery, which can effectively improve the central vision acuity and reduce metamorphopsia. The closure rate after vitrectomy has been reported to be from 91% to 98% in the last 5 years [1–4]. Currently, vitrectomy is recognized as a primary and effective treatment option. However, it is noted that the IMH can spontaneously close without any intervention, which has been consistently reported in recent years. The mechanism of spontaneous closure of IMHs and the risk factors have not been fully elucidated. Therefore, it is necessary to summarize the general characteristics and OCT structural features of spontaneous closure of IMHs and discuss the risk factors of spontaneous closure of full-thickness IMHs.

A structured literature search in PubMed was performed on October 1, 2018, and a search strategy of "((spontaneous closure) OR (spontaneous closed) OR (spontaneous resolution)) AND (macular hole)" executed in "title and/or abstract" was applied. We also checked all the references of relevant reviews and eligible articles that our search retrieved. Language restrictions were not used. Title and abstract screening of all retrieved articles was performed using prespecified criteria. Studies were included if all following criteria were fulfilled: (1) adults with IMHs and (2) the IMH closed spontaneously during the follow-ups. Criteria for exclusion were as follows: (1) adults with systemic diseases, such as diabetes and hypertension; (2) adults with ophthalmic diseases, glaucoma, high myopia, diabetic retinopathy, etc.; (3) adults with a history of ophthalmology surgery; and (4) surgery and drug intervention performed during the period from the onset of IMHs to closure.

We identified and screened a total of 186 articles and found 78 relevant articles. Among these, 30 articles were excluded for non-IMHs. 11 articles were excluded because patients also suffered from other ophthalmic diseases. 8 articles were excluded because the cases were not described in detail. Finally, we included 21 articles, including 58 eyes in 54 patients.

In our statistical result, the average age of spontaneous closure of IMHs was 69.0 ± 6.4 (50–81). Complete data on gender were recorded in 38 reports, with 26 females and 12

males. The stages of IMHs were described in 41 eyes, with 21 stage II, 13 stage III, and 7 stage IV IMHs. The course of disease (the time between patients' description of symptoms and visit time) ranged from 5 days to 31 months, with an average of 96.1 ± 178.0 d. The closure time was 100.9 ± 98.3 d on average. Follow-up time ranged from 3 months to 49 months. The average initial BCVA was 0.36 ± 0.20, and the average final BCVA after spontaneous closure of MH was 0.70 ± 0.17. The average diameter of MH was 178.6 ± 77.3 μm. The results of this query are shown in Table 1.

2. Incidence

The incidence of spontaneous closure of idiopathic macular holes varies from 4% to 11.5%. Yuzawa et al. retrospected 97 eyes with full-thickness IMH for a period ranging from 2 to 182 months, and 6 eyes (6.2%) showed spontaneous closure within 24 months of the initial examination [26]. A multicentered, controlled, randomized clinical trial by Freeman et al. studied 129 eyes of 122 patients with stage III or IV IMH [27]. In their studies, 64 eyes were randomized to surgery, and 65 eyes were randomized to observation. 2 (4%) of the holes in 56 eyes randomized to observation were spontaneously closed. Another randomized clinical trial by Ezra et al. studied 185 eyes of 174 patients, which also randomized to surgery group and observation group [28]. Their results showed that spontaneous closure of the FTMH occurred in 7 (11.5%) of 61 patients, with little or no change in overall acuity levels in 24 months. In 2012, Okubo et al. retrospectively reviewed the records of 142 eyes of 138 patients with full-thickness IMH [8]. The full-thickness IMHs were diagnosed by OCT with 45 stage II eyes (31.7%), 71 stage III eyes (50%), and 26 stage IV eyes (18.3%) using OCT. They found five eyes (3.5%) with spontaneous closure. However, vitrectomy was planned in all eyes between 11 days and 154 days (mean: 65.2 days) after the initial presentation, which means part of the IMHs may not have enough observation time. In conclusion, the incidence of spontaneous closure ranges from 4% to 11.5%, and further studies for a relatively fixation observation time by OCT will be needed to verify the incidence results.

3. Age, Gender, and Closure Time

So far, no researches have mentioned that basal characteristics, such as age, gender, and the course of disease, have relationship with spontaneous closure of IMHs. Among these, the age of patients reported by most of the articles was greater than 60, except a 50-year-old case reported by Kelkar et al. [9]. The average spontaneous closure time of IMHs was 99.5 ± 98.0 d. Morawski et al. [7] suggested a 2- to 3-month observation time before surgery in posttraumatic eyes, since a quite number of cases showed spontaneous closure. In our review data, it seems that a 3-month observation time may also be considered in IMHs. However, it should be mentioned that the course of disease (the time between patients' description of symptoms and visit time) varies from 5 days to 31 months, which create biases in suggesting observation time.

4. Visual Acuity

All cases with a spontaneous closure of IMHs acquired progress in visual acuity. The average initial BCVA was 0.36 ± 0.20, and the average final BCVA after spontaneous closure of MH was 0.70 ± 0.17. This shows that the spontaneous closure of MH may gain a well visual acuity, and the influencing characteristic needs to be explored.

5. IMH Diameter

Many articles mentioned that the spontaneous closure occurred in IMHs with a relatively small diameter. Sugiyama et al. suggested that MHs of less than 250 μm diameter have more opportunity to close spontaneously [11]. Privat et al. believed that the diameter of MHs is probably the main factor for the spontaneous closure, since the diameters in their study are between 70 and 250 μm in 13 patients, except in one patient who had a 350 μm macular hole [21]. In our review data, the diameter of 34 IMHs are smaller than 250 μm and that in 13 IMHs are between 250 μm and 400 μm. It seems that the small diameter of IMHs gives the chance to both edges of the IMHs to combine together. Also, in a case studied by Fernández and Navarro [10], the minimum diameter of IMHs is much smaller than basal diameter. They suggested that this may be a recovery phenomenon, which indicates the inner layer of macular retinal concentrates to the center. Although most studies did not provide metrical data of basal diameter, we observed that about half of the IMHs shows much larger basal diameter than minimum diameter. However, the hypothesis needs to be confirmed by a larger sample study.

6. VMT

It is widely believed that spontaneous release of the vitreomacular traction (VMT) may account for the closure of IMHs [21], which is also the theory of vitrectomy surgery, since many MHs closed after the relieve of VMT [5, 6, 8–10]. Indeed, in our review data, more than half of the IMHs were in stage II, and most VMT relieve during their spontaneous closure of IMHs. However, Privat et al. also mentioned 6 stage III or IV MHs in which vitreous already detached from the MH edge at the first examination [21]. In Morawski et al.'s study, 5 out of 9 eyes (one excluded for trauma history) showed no vitreous detachment in foveal during closure [7]. Since the VMT was relieved in stage III and stage IV IMHs, the mechanism of spontaneous closure may be complicated. Fernández and Navarro thought this phenomenon may due to the different first examine time, which means these macular holes may already have undergone spontaneous closing after the relief of VMT [10]. Kelkar et al. reported a stage II full-thickness MH spontaneously closed without the relieve of VMT, which is also shown in the report of Freund et al. [9, 29]. These results indicate that the

Table 1: Literature review of articles on spontaneous closure of idiopathic full-thickness macular holes.

No.	Author	Year	Age	Gender	Stage	Diameter	VMT	Bridge	CD time	SC time	Follow-up	EZ recover time	Initial BCVA	Final BCVA
1OD	Gonzalez-Cortes et al. [5]	2018	67	F	4	136	y	n	3 w	4 w	12 m	4 w	20/40	20/20
1OS	Gonzalez-Cortes et al. [5]	2018	67	F	2	272	n	y	3 w	4 w	12 m	20 w	20/60	20/25
2	Zvornicanin, et al. [6]	2017	64	M		213	y	y	5 d	56 d	6 m	56 d	20/80	20/20
3a	Morawski et al. [7]	2016	64			<250	n	y	28 w	32 w			20/40	20/50
3b	Morawski et al. [7]	2016	66			250–400	y	y	10 w	8 w			20/150	20/25
3c	Morawski et al. [7]	2016	74			<250	y	y	20 w	64 w			20/50	20/30
3d	Morawski et al. [7]	2016	65			<250	n	y	12 w	12 w			20/60	20/80
3e	Morawski et al. [7]	2016	81			<250	n	y	6 w	40 w			20/100	20/25
3f	Morawski et al. [7]	2016	66			<250	n	y	8 w	12 w			20/40	20/30
3g	Morawski et al. [7]	2016	70			<250	y	y	2 w	8 w			20/100	20/40
3h	Morawski et al. [7]	2016	75			250–400	y	y	24 w	48 w			20/80	20/50
3i	Morawski et al. [7]	2016	79			250–400	n	y	8 w	8 w			20/100	20/100
4	Okubo et al. [8]	2013	71	M	2	396 (b)	y	y	5 w	5 m	7 m	—	20/80	20/40
5	Kelkar et al. [9]	2013	50	F	2		n	n	1 m	6 w	3 m	—	20/125	20/30
6	Fernández and Navarro [10]	2012	67	M	4	60	n	y	11 m	3 m	2 y	7 m	0.5	0.7
7a	Sugiyama et al. [11]	2012	64	F	3	150				57 d	85 d		0.8	0.8
7b	Sugiyama et al. [11]	2012	62	M	2	240				49 d	226 d		0.2	0.6
7c	Sugiyama et al. [11]	2012	71	M	4	125				70 d	511 d		0.4	0.8
7dOD	Sugiyama et al. [11]	2012	72	M	2	250				56 d	1146 d		0.1	0.8
7dOS	Sugiyama et al. [11]	2012	72	M	3	210				70 d	579 d		0.4	0.9
8a	Inoue et al. [12]	2012	78	F	4	135		n		3 m	40 m	6–9 m	20/40	20/20
8b	Inoue et al. [12]	2012	76	F	2	280		n		2 m	36 m	9–12 m	20/100	20/25
8c	Inoue et al. [12]	2012	73	M	2	156		y		3 m	49 m	3–9 m	20/50	20/20
8d	Inoue et al. [12]	2012	65	F	2	333		y		1 m	43 m	33–36 m	20/63	20/32
8e	Inoue et al. [12]	2012	73	M	3	197		n		3 m	42 m	6–9 m	20/100	20/30
8f	Inoue et al. [12]	2012	65	F	3	152		n		4 m	36 m	1–4 m	20/100	20/30
9	Lipkova et al. [13]	2011	65	F					31 m				20/100	20/60
10OS	Imasawa et al. [14]	2010	72	M	2	210	y	y	10 d	2 m	37 m	6 m	0.4	0.9
10OD	Imasawa et al. [14]	2012	72	M	3	250		n		2 m	19 m	6 m	0.1	0.7
11	Petropoulos et al. [15]	2009	63	M				n		2 m	12 m	5 m	0.6	1
12	Chen et al. [16]	2008	71	M	3	524 (b)	n	n	3 m	9 m	27 m	27 m	20/50	20/15
13a	Michalewska et al. [17]	2008	67	F	4	289	n	y	3 w	3 m	3 m		0.05	0.5
13bOD	Michalewska et al. [17]	2008	72	M	3	87	n	y		1 m	2 m	2 m	0.5	0.8
13bOS	Michalewska et al. [17]	2008				274	n	n		1 m	2 m		0.2	0.5
14	Milani et al. [18]	2007	70	F	2	50–150	y	y	2 m	10 m	15 m	10 m	0.3	0.8
15a	Hamano et al. [19]	2007	63	F	2	95		y		6 w	5 m	5 m	20/40	20/20

Table 1: Continued.

No.	Author	Year	Age	Gender	Stage	Diameter	VMT	Bridge	CD time	SC time	Follow-up	EZ recover time	Initial BCVA	Final BCVA
15b	Hamano et al. [19]	2007	59	F	4	70		y		3 w	8 w	8 w	20/100	20/30
16	Schweitzer and García [20]	2007	76	F	3	200	n	n	2 w	1 m	9 m	1 m	20/60	20/25
17a	Privat et al. [21]	2007	72	M	2	200				14 m			0.05	0.2
17b	Privat et al. [21]	2007	79	F	3	350				2 m			0.4	0.7
17c	Privat et al. [21]	2007	77	M	3	95				4 m			0.6	0.9
17d	Privat et al. [21]	2007	74	F	2	250				1 m			0.2	0.6
17e	Privat et al. [21]	2007	60	F	3	160				3 m			0.4	0.9
17f	Privat et al. [21]	2007	73	F	2	200		y		3 m			0.8	0.8
17g	Privat et al. [21]	2007	70	M	2	200		y		2 m			0.3	0.6
17h	Privat et al. [21]	2007	65	F	2	90				3 m			0.4	0.5
17i	Privat et al. [21]	2007	81	M	3	80				1 m			0.5	0.6
17j	Privat et al. [21]	2007	71	F	2	100				3 m			0.3	0.8
17k	Privat et al. [21]	2007	61	M	2	120		y		1 m			0.3	0.6
17l	Privat et al. [21]	2007	75	M	4	70				7 m			0.5	0.6
17m	Privat et al. [21]	2007	70	F	3	250				1 m			0.3	0.5
17n	Privat et al. [21]	2007	62	F	2	100				2 m			0.2	0.8
18a	Punjabi et al. [22]	2007	66	F	2			y	7 d	3 m	3 m	3 m	20/40	20/25
18b	Punjabi et al. [22]	2007	80	M	2			n	30 d	4 m	4 m	—	20/50	20/25
19	Win and Young [23]	2007	65	F				y	2 m	1 m	1 m		20/70	20/30
20	Lai et al. [24]	2006	62	F		137		y	2 w	3 w	3 w		20/40	20/30
21a	Ishida et al. [25]	2004	62	F					1 m	5 w	7 m	5 m	20/67	20/20
21b	Ishida et al. [25]	2004	65	F					2 m	3 m	3 m		20/33	20/22

relieve of VMT promotes the spontaneous closure in IMHs, but it may not be the indispensable reason.

7. Sharp Edge and Bridge-Like Structure

Previous literature has suggested that some of the edges of macular holes become sharp and stretch out bridge-like structure. This sharp edge was stated by Michalewska et al. [17], who believed the phenomenon may facilitate the spontaneous closure. Morawski et al. [7] supposed that the sharp edge facilitates bridging and spontaneous MH closure. We statistically analyzed the results of OCT images in the cases and found that 27 cases (69%) had obvious sharp edges, while 12 cases did not. It has been reported that this may be the result of collagen secretion by outer retinal cells such as Müller cells. The extension and proliferation of the Müller cells may also form this bridge-like structure [8]. We speculate that the occurrence of this phenomenon may be gradually obvious with the occurrence of spontaneous closure. Due to the differences in the follow-up time between the cases, the 12 cases without obvious bridge-like structure may miss the phenomenon occurring time. Therefore, the bridge-like structure may be an important manifestation of spontaneous closure process. However, we reviewed some cases of macular hole occurrence that were not closed, and the appearance of this bridge-like structure was also observed. Therefore, the bridge-like structure may be an important, but maybe not unique, manifestation during the spontaneous closure process of macular holes.

8. Epiretinal Membrane Formation

Few articles found the epiretinal membrane formation during the spontaneous closure of MH. Smiddy [30] and Petropoulos et al. [15] each found one IMH with epiretinal membrane formed during the spontaneous closing process, but this phenomenon has not been found in other cases at present. Petropoulos et al. believed that the formation of a contractile epiretinal membrane can facilitate the macular hole closure. However, the epiretinal membrane formation was not widely seen in spontaneously closed macular holes. This suggests that epiretinal membrane formation may be one of the reasons for spontaneous closure of IMHs.

9. Cystic Structure

In the meantime, there are some spontaneously closed macular holes with cystic structure [17]. This kind of macular hole has a thicker fovea, and the thickness of the macular hole decreases obviously after the spontaneous closure. RPE cells have the function of absorbing extracellular fluid in the cyst cavity [17]. We speculate that the closure of this kind of macular hole may be related to the absorption of cystic structure.

10. Autofluorescence and OCT Angiography

Resent studies has focus on the autofluorescence and OCT angiography in macular hole closure. Zhang et al. believed that postoperative area of high AF in macula can be an

evaluating indicator for poor macular function recovery [31]. Teng et al. suggested that choroidal circulation in the macular area, which is detected by OCT angiography, might be affected by the intact structure of the fovea [32]. However, whether these characteristics have correlations with spontaneous closure of macular holes remains unclear.

11. Conclusion

In conclusion, there exists a percentage of idiopathic full-thickness macular holes to be spontaneously closed, which occur in about 3 to 4 months after initial examination. The macular hole with the diameter of less than 400 μm, especially less than 250 μm, may have more chance to close spontaneously. Also, these spontaneously closed macular holes have some distinctive OCT characteristics, such as the relieve of VMT, bridge-like structure, epiretinal membrane, and cystic structure. In our review results, these characteristics give the macular hole tendency to close spontaneously. Although these characteristics may not be irreplaceable and unique risk factors, they give the doctor a consideration to observe for a few months before surgery. Further research is needed to understand the pathophysiology underlying the development of spontaneous closure of idiopathic full-thickness macular holes [33, 34].

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Review Article

Sulfur Hexafluoride (SF_6) versus Perfluoropropane (C_3F_8) in the Intraoperative Management of Macular Holes: A Systematic Review and Meta-Analysis

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Purpose. A systematic literature search was conducted to identify and review studies comparing SF_6 to C_3F_8 as a tamponade agent in the intraoperative management of macular holes. *Methods*. Publications up to October 2018 that focused on macular hole surgery in terms of primary closure, complications, and clinical outcomes were included. Forest plots were created using a weighted summary of proportion meta-analysis. Analysis was performed separately for SF_6 and C_3F_8. A random effects model was used, and corresponding I^2 heterogeneity estimates were calculated. *Results*. Nine pertinent publications studying a total of 4,715 patients were identified in 2000 to 2017, including two randomized studies (n = 206), two prospective studies (n = 170), and five retrospective or registry-based studies. Similar rates of closure between SF_6 and C_3F_8 were reported in eight out of nine studies, regardless of subgroup analyses. All studies reporting visual outcomes showed similar results when comparing SF_6 to C_3F_8 at one to six months of follow-up. Neither agent was clearly associated with increased risk of ocular hypertension, cataract formation, or other adverse events. Meta-analytic pooling of the closure rates in the SF_6 group resulted in 91.73% (95% confidence interval: 88.40 to 94.55, I^2: 38.03%), and for C_3F_8, the closure rate was 88.36% (95% confidence interval: 85.88 to 90.63, I^2: 0.0%). *Conclusions*. Both SF_6 and C_3F_8 appear to have achieved similar visual outcomes and primary closure rates and neither was associated with an increased risk of adverse events. Considering the more rapid visual recovery with SF_6, there appears to be no evidence to support C_3F_8 as the tamponade agent of choice for macular hole surgery.

1. Introduction

Macular hole surgery was first described by Kelly and Wendel in 1991 [1]. Although their 5-step technique has remained largely unchanged, debate still exists concerning several key aspects of the procedure [2]. These include whether to peel the internal limiting membrane (ILM), the use and type of dye, and the duration of face-down positioning following surgery [3, 4].

Another heatedly debated aspect is the choice of tamponading agent [3, 5, 6]. The most commonly used compounds are sulfur hexafluoride (SF_6) and perfluoropropane (C_3F_8). However, hexafluoroethane (C_2F_6), room air, and silicone oil are also employed [7]. Although the procedure was initially described with use of SF_6, subsequent clinical trials used C_3F_8 further adding to the debate [1, 8–10]. To the authors' best knowledge, no systematic review or meta-analysis has yet been published, comparing the two agents.

The aim of this study was to systematically review the literature for studies that compared SF_6 to C_3F_8 as a tamponade agent in the intraoperative management of macular hole surgery, perform a pooled meta-analysis of the data, and discuss any differences found with respect to clinical outcomes and adverse effects.

2. Materials and Methods

2.1. Literature Search. A systematic literature search was conducted using MEDLINE, Scopus, Google Scholar, and The Cochrane Library, reviewing all available published

clinical studies up to October 2018. The following keywords were used, in various combinations: macular hole, MH, sulfurhexafluoride, sulfur hexafluoride, SF_6, perfluoropropane, C_3F_8, gas, short-acting, long-acting, tamponade, bubble, pneumatic, and retinopexy. A bibliographic search of relevant studies identified additional publications. A flow diagram of the screening and inclusion process is illustrated in Figure 1.

2.2. Eligibility Criteria. Full publications in English that directly compare SF_6 and C_3F_8 in the intraoperative management of macular hole surgery, in terms of primary closure, complication rates, and clinical outcomes were included (not abstracts or letters to the editor). Studies performed on animal or cadaver eyes, as well as case reports and nonempirical opinion articles, were excluded.

2.3. Screening and Synthesis. The review process was conducted under the guidance of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria to support reporting [11]. Two reviewers (IH and MM) independently implemented the search strategy for relevant publications. Selected publications were then approved by the senior investigator who also devised the search strategy (YB).

2.4. Statistical Analyses. To better illustrate the main anatomical outcome of primary closure, forest plots were created using a weighted summary of proportion meta-analysis. Analysis was performed separately for SF_6 and C_3F_8. A random effects model was used (as implemented by DerSimonian and Laird, 1986 [12]), and corresponding I^2 heterogeneity estimates were generated. Data were tabulated and analyzed using SPSS for Windows version 22.0 software by IBM Inc. (Armonk, NY, USA). Graphs were created using MedCalc software version 16 (Mariakerke, Belgium).

3. Results

Data comparing the use of SF_6 and C_3F_8 for macular hole surgery were extracted from nine studies published during 2000 to 2017 (Table 1), studying a total of 4,715 patients. Two of the studies were randomized by design and included a total of 206 patients. Two studies prospectively enrolled patients without randomization (170 patients), and the remaining five were retrospective or registry based. Figure 1 illustrates the flow of the inclusion process.

3.1. Intraoperative Management. Several differences existed between the studies with respect to the surgical technique. The first relates to ILM removal as a routine part of the operation.

ILM peeling was routinely performed in six of the nine studies. In two studies (Essex et al. [4] and Tognetto et al. [7]), a majority of patients (97.7% and 67.7%, respectively) underwent ILM peeling while the remainder did not. The authors elected not to routinely perform ILM peeling of prospectively enrolled patients in only one study (Mulhern et al.) [16].

Tognetto et al. expanded their investigation, comparing the outcomes of patients who underwent ILM peeling with those who had not [7]. They analyzed the retrospective data of 1,627 patients from different countries, who had been operated on for idiopathic macular hole. They found that ILM peeling improved hole closure only for longstanding macular holes or those in advanced stages [7].

A second aspect in which studies differed was the choice of gas concentration. The SF_6 concentration was 20% in four of the nine studies. Mulhern et al. used 23%, Kumar et al. used 25%, and Briand et al. used between 20 and 25% SF_6. The C_3F_8 concentrations similarly varied, ranging from 13% used by Modi et al. to 18% by Kumar et al. However, most used concentrations ranged between 14% and 16% C_3F_8 (Table 1).

3.2. Postoperative Management. Face-down positioning varied between studies. Most studies recommended two to seven days of prone positioning; however, some (e.g., Mulhern et al.) requested patients who received SF_6 maintain a prone head position for up to 4 weeks [16].

A registry-based analysis by Essex et al. sheds further light on this topic [4]. They analyzed the outcome of 2,367 patients from Australia and New Zealand who underwent primary idiopathic macular hole surgery. Approximately 26% of these patients were not advised to remain in prone position postoperatively, and among those who were advised, most were instructed to remain prone between three and seven days. Essex et al. further compared the outcomes between patients who were not advised a postoperative face-down position to those who were and found that no prone positioning was noninferior for holes of less than 400 μm in diameter, while for larger holes noninferiority could not be concluded [4].

3.3. Primary Anatomical Closure. Most studies used anatomical closure as the primary outcome; their results are summarized in Table 1. Closure rates ranged from 85% to 100%, with most in the 90% to 95% range.

A comparison of SF_6 and C_3F_8 showed similar rates of closure in eight of the nine studies, including the two randomized controlled studies by Casini et al. [3, 5]. One study by Essex et al. using a more stringent noninferiority analysis with a relatively narrow noninferiority margin (5%) also demonstrated noninferiority of SF_6 compared to C_3F_8 [4]. Only one study by Tognetto et al. reported a higher success rate with SF_6 (93.6% versus 87.2%); however, the authors provide no statistical foundation for this claim [7].

Several studies further analyzed subgroups in an attempt to detect a subset of patients, which might benefit from one agent over the other. Modi et al. examined different hole sizes, stages, and durations; Casini et al. also examined different stages; and Kim et al. compared the agents independently for different stages, durations of symptoms, presence of posterior vitreous detachment, and whether indocyanine green dye was used for ILM peeling [3, 6, 15].

Figure 1: Flow diagram of the inclusion process. Flow diagram of the search and inclusion process based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11].

They all found SF_6 to produce results similar to C_3F_8 regardless of the subgroup analyzed (Table 1).

3.4. Visual Acuity. Six studies reported visual acuity outcomes following surgery [3, 5, 6, 14–16]. All showed similar results when comparing SF_6 to C_3F_8 at one to six months of follow-up (Table 1). Improvement following SF_6 gas ranged from 2.7 to 5.9 Early Treatment Diabetic Retinopathy Study (ETDRS) lines, while following use of C_3F_8 ranged between 2.7 and 6.9 ETDRS lines. Five of the six studies report comparative statistics on visual improvement between groups, and all find no significant differences (Table 1). The randomized trial by Casini et al. as well as the prospective cohort study by Xirou et al. showed that visual acuity was initially better in the group treated with SF_6 but was eventually found to be similar [3, 14].

3.5. Complications. Most studies reported on short-term and long-term complication rates in each group. The randomized controlled trial by Briand et al. showed similar results in terms of cataract development and extraction, a similar time interval between surgery and cataract extraction ($p = 0.184$) and similar rates of retinal tears (4% vs. 7%), retinal detachment (4% vs. 0%), and ocular hypertension (21% vs. 19%, all $p = 1.0$) [5]. The retrospective report by Modi et al. on 177 patients revealed a decreased incidence of cataract and ocular hypertension (1.99 vs. 4.02 mmHg) in the group treated with SF_6, as well as a nonsignificantly lower incidence of glaucoma (9.0% vs 6.1%) [6]. Xirou et al., in a prospective study on 46 patients, revealed similar elevations of intraocular pressure [14]. Kim et al. reported similar rates of cataract development; however, myopic shift rates were greater in the C_3F_8 group (SF6: −0.82 diopters vs. C_3F_8: −1.42 diopters for phakic patients, $p = 0.016$). Finally, in the prospective trial by Mulhern et al., similar rates of posterior subcapsular cataract were seen (55% after C_3F_8 vs. 37% after SF_6; $p = 0.20$) and mean intraocular pressure spike maximum was nonsignificantly higher in the SF_6 group (32.5 mmHg vs. 23.7 mmHg; $p = 0.131$) [16].

3.6. Pooled Analysis of Primary Closure. Forest plots of proportion of patients who achieved anatomical closure with each compound are presented in Figures 2 and 3. Meta-analytic pooling of the closure rates in the SF_6 group resulted in 91.73% (95% confidence interval: 88.40 to 94.55, I^2: 38.03%, p value for heterogeneity = 0.126). For the patients who received C_3F_8, the pooled anatomical closure rate was 88.36% (95% confidence interval: 85.88 to 90.63, I^2: 0.0%, p value for heterogeneity = 0.864).

4. Discussion

In this study, a systematic review and meta-analysis of studies comparing SF_6 and C_3F_8 gas tamponades for macular hole surgery was performed. Macular hole closure rates were found to be similar regardless of whether SF_6 or C_3F_8 was used and were typically in the 90–95% range. Visual acuity outcomes were also similar but tended to improve faster with SF_6. Rates of complications (including cataract formation, ocular hypertension, and retinal tears) varied among studies and appeared to be inconsistently related to either agent.

Table 1: Publications reporting on clinical outcomes of macular hole repair using either SF_6 or C_3F_8 gas tamponade.

Study [Ref]	Year	Design	Number of patients	Postoperative face-down positioning duration	Gas concentration	ILM peeling	Anatomical closure	Results: primary closure	Results: visual improvement*	Results: complications
Modi et al. [6]	2017	Retrospective comparative study	SF_6: 67 C_3F_8: 111Total: 177	SF_6: 45 minutes of every hour (duration NR) C_3F_8: 45 minutes of every hour (duration NR)	20% SF_6 13% C_3F_8	All cases	SF_6: 86.4% C_3F_8: 86.5%	Similar ($p = 0.982$), irrespective of hole size, stage, or duration	SF_6: 2.7 lines (0.900 ± 0.383 to 0.629 ± 0.375 logMAR) at 3–6 months C_3F_8: 4.2 lines (1.03 ± 0.39 to 0.61 ± 0.40 logMAR) at 3–6 months No significant difference ($p = 0.066$)	SF_6 exhibited a decreased incidence of cataract and ocular hypertension (1.99 vs. 4.02 mmHg) as well as a nonsignificantly lower incidence of glaucoma (9.0% vs. 6.1%)
Casini et al. [3]	2016	Randomized controlled trial	SF_6: 70 C_3F_8: 77 Total: 147	SF_6: 2 days C_3F_8: 2 days	20% SF_6 14% C_3F_8	All cases	SF_6: 90% C_3F_8: 91%	Similar, independent of stage	SF_6: 5.9 lines (0.894 to 0.301 logMAR) at 1 month C_3F_8: 6.9 lines (0.965 to 0.272 logMAR) at 1 month	Patients treated with SF_6 experienced greater improvement of visual acuity at 1 week postoperatively ($p < 0.01$) but not at 1 month
Essex et al. [4]	2016	Registry-based study	SF_6: 1,653 C_3F_8: 702 Total: 2,456	SF_6: 0–14 days C_3F_8: 0–14 days	NR	97.7% of cases	Mean of both 95.0% (individually NR)	SF_6 noninferior, regardless of macular hole size	NR	NR
Briand et al. [5]	2015	Randomized controlled trial	SF_6: 31 C_3F_8: 28 Total: 59	SF_6: 7 days C_3F_8: 14 days	20–25% SF_6 15% C_3F_8	All cases	SF_6: 93.3% C_3F_8: 92.9%	Similar ($p = 0.943$)	SF_6: 3.5 lines at 12 months C_3F_8: 3.4 lines at 12 months No significant difference ($p = 0.787$)	Similar in terms of cataract development and extraction and adverse events
Kumar et al. [13]	2014	Prospective cohort study	SF_6: 20 C_3F_8: 42 Total: 62	SF_6: 18 hours daily for 3 days C_3F_8: 18 hours daily for 3 days	25% SF_6 18% C_3F_8	All cases	SF_6: 85% C_3F_8: 90.5%	Similar ($p = 0.67$)	NR	NR
Xirou et al. [14]	2012	Prospective cohort study	SF_6: 23 C_3F_8: 23 Total: 46	SF_6: 2 days C_3F_8: 2 days	20% SF_6 14% C_3F_8	All cases	SF_6: 100% C_3F_8: 96%	Similar	SF_6: 3.8 lines (0.67 ± 0.20 to 0.29 ± 0.12 logMAR) at 6 months C_3F_8: 2.8 lines (0.90 ± 0.10 to 0.62 ± 0.23 logMAR) at 6 months No significant difference ($p = 0.06$)	Patients treated with SF_6 experienced greater improvement of visual acuity initially but was similar in the following 6 months. Similar elevations of intraocular pressure

Table 1: Continued.

Study [Ref]	Year	Design	Number of patients	Postoperative face-down positioning duration	Gas concentration	ILM peeling	Anatomical closure	Results: primary closure	Results: visual improvement*	Results: complications
Kim et al. [15]	2008	Retrospective comparative study	SF_6: 38 C_3F_8: 41 Total: 79	SF_6: 7 days C_3F_8: 7 days	20% SF_6 16% C_3F_8	All cases	SF_6: 90% C_3F_8: 91%	Similar ($p = 0.91$), regardless of stage, duration of symptoms, presence of PVD, and use of ICG dye for ILM peeling	SF_6: 4.9 lines (0.86 ± 0.41 to 0.37 ± 0.43 logMAR) at 12 months C_3F_8: 5.4 lines (0.99 ± 0.43 to 0.45 ± 0.35 logMAR) at 12 months No significant difference ($p > 0.30$)	Cataract development was similar. Myopic shift was greater in the C_3F_8 group ($p = 0.016$)
Tognetto et al. [7]	2006	Retrospective cohort study	SF_6: 1,004 C_3F_8: 337 Total: 1,627	SF_6: NR C_3F_8: NR	NR	67.7% of cases	SF_6: 93.6% C_3F_8: 87.2%	Higher success rates with SF_6	NR	NR
Mulhern et al. [16]	2000	Prospective comparative study	SF_6: 31 C_3F_8: 31 Total: 62	SF_6: 14–30 days C_3F_8: 6 days	23% SF_6 16% C_3F_8	Not routinely performed	SF_6: 96.7% C_3F_8: 93.5%	Similar ($p = 1.0$)	SF_6: 2.8 lines (0.86 ± 0.18 to 0.575 ± 0.31 logMAR) at 3 months C_3F_8: 2.7 lines (0.88 ± 0.21 to 0.61 ± 0.37 logMAR) at 3 months No significant difference ($p = 0.719$)	Incidence of posterior subcapsular cataract was similar. Mean IOP spike maximum was nonsignificantly higher in the SF_6 group

NR, not reported; C_3F_8, perfluoropropane; SF_6, sulfur hexafluoride; ILM, internal limiting membrane; PVD, posterior vitreous detachment; ICG, indocyanine green; IOP, intraocular pressure. *Expressed in Early Treatment Diabetic Retinopathy Study (ETDRS) chart lines.

Figure 2: Forest plot of the proportion of patients who achieved anatomical closure following the use of SF_6 gas. Meta-analytic pooling of the proportion of patients who achieved anatomical closure following surgery in the SF_6 group. Pooled estimate was 91.73% (95% confidence interval: 88.40% to 94.55%, I^2: 38.03%, p value for heterogeneity = 0.126). Size of the squares is proportional to the number of cases in the study. Error bars represent 95% confidence intervals. The diamond shape represents the pooled estimate.

Figure 3: Forest plot of the proportion of patients who achieved anatomical closure following the use of C_3F_8 gas. Meta-analytic pooling of the proportion of patients who achieved anatomical closure following surgery with C_3F_8: pooled estimate was 88.36% (95% confidence interval: 85.88% to 90.63%, I^2: 0.0%, p value for heterogeneity = 0.864); size of the squares is proportional to the number of cases in the study. Error bars represent 95% confidence intervals. The diamond shape represents the pooled estimate.

Following macular hole repair, contact of the gas bubble with the retina causes the extrusion of subretinal fluid and maintains anatomical position, as well as possibly providing a scaffold for cellular proliferation [14]. It therefore seems reasonable that a larger, longer-acting, bubble would provide further benefit. However, some evidence suggests that hole closure occurs very early in the postoperative period, perhaps as early as the first 24 hours [17]. A recent study by Masuyama et al. showed that repair of the macular hole typically occurs between 4 and 7 days postoperatively and is presumed to be facilitated by ganglion and Muller cells [18]. Long-lasting gasses (such as C_3F_8) may offer more extensive tamponade; however, they also impair vision longer. It is possible that such longer-acting agents are not required, considering the short timescales in which macular hole repair occurs. The outcomes of this review appear to support this notion, as use of SF_6 produced similar clinical outcomes to C_3F_8 in terms of both primary closure and visual outcomes.

This study has several limitations. It included non-randomized trials in the analysis. However, given the small number of randomized studies performing a direct comparison of SF_6 and C_3F_8 for macular hole surgery, we elected to include relevant retrospective and registry-based studies, in order to increase the power of the meta-analysis. Given the findings of this study, the need for more prospective randomized studies evaluating this comparison may be questionable. In addition, several differences between the studies concerning the surgical technique may have introduced biases to the analyses. However, we discussed and compared variations in surgical technique found across these studies.

5. Conclusions

To the authors' best knowledge, this is the first systematic review and meta-analysis comparing SF_6 and C_3F_8 as a tamponading agent for macular hole surgery. We found that SF_6 and C_3F_8 resulted in both similar visual outcomes as well as similar primary closure rates. Neither agent was clearly associated with increased risk of ocular hypertension, cataract formation, or other adverse events. Visual recovery with SF_6 tended to occur earlier. It is probable that shorter-acting tamponade agents such as SF_6 may be sufficient for macular hole surgery; we found no evidence to support C_3F_8 as the tamponade gas of choice.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Macular Hole in Myopic Eyes: A Narrative Review of the Current Surgical Techniques

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Macular hole (MH) in myopic eyes is a disease arising from complex tractional forces exerted by vitreomacular interface, epiretinal tissue, and progressive scleral ectasia of the posterior ocular globe wall. This retinal disease requires vitreoretinal treatment for its repair, and the surgical intervention remains a challenge also for experienced surgeons. The aim of this review is to describe the current knowledge regarding the pathogenesis of MH in myopic eyes and to detail novel surgical techniques and technological advancements in its surgical management.

1. Introduction

Idiopathic macular hole (MH) is an important cause of central visual loss [1] characterized by a round full-thickness defect in the center of the macular area involving the anatomical fovea [2, 3]. The estimated prevalence in the general population is approximately 3.3 per 1000 people [4, 5], with a cumulative incidence of MH formation of 41.1 cases per 100 000 person/years [6]. This incidence increases with age, and the disease usually affects individuals in their sixth or seventh decade of life [7]. Females have a 64% increased risk of being diagnosed with MH when compared with males [6]. MH is a common complication in pathological myopic eyes with an axial length greater than 26.5 mm and/or a refraction greater than −6.00 diopters [8, 9], and a prevalence of 8.4% has been reported [10]. The incidence of myopic MH is greater in Asian ethnicity compared to Caucasian or black individuals due to the high prevalence of myopic refractive defect in Asian population [6].

For many years, MH was considered an untreatable disease resulting in irreversible vision loss. In the early 90s, new surgical strategies to treat this anatomical macular defect in order to improve the visual acuity were described. The surgical procedure consisted of three-port pars plana vitrectomy (PPV) with posterior hyaloid removal in combination with intraocular gas tamponade to allow the flattening and the repositioning of MH edges [11, 12]. A remarkable success rate and a clear benefit from this type of surgical management were reported [13–16].

Although pars plana vitrectomy with posterior hyaloid removal, internal limiting membrane (ILM) peeling, long-acting gas tamponade, and face-down positioning is still the gold standard for a successful closure of idiopathic MH, the treatment of large, persistent, or myopic MH remains a challenge [17–19]. Nowadays, several methods have been proposed to allow high rate of success, particularly for the abovementioned MH such as the inverted ILM flap [20], inverted ILM flap insertion [21] with or without blood coverage of the hole [22], temporal or superior single-layer inverted ILM flap [23, 24], free ILM insertion [25], and double [26] or multiple free ILM flap insertion [16] into the MH.

The purpose of this review is to describe the current knowledge regarding the pathogenesis of MH in myopic eyes and to detail novel surgical techniques and technological advancements in the surgical management of this retinal disease.

2. Pathogenesis

The biomicroscopic identification of MH in highly myopic eyes may be difficult due to several factors such as the typical

low contrast between the anatomical foveal defect and the retinal pigmented epithelium (RPE), the chorioretinal atrophy, or the presence of a deep posterior staphyloma [27].

The introduction of optical coherence tomography (OCT), which provides an in vivo analysis of the relationship between the macula and the vitreous, has allowed identifying the perifoveal vitreous changes that may lead to MH formation. In particular, OCT is able to detect the localized adhesion between vitreous cortex and fovea, the incomplete posterior vitreous detachment associated with a full-thickness MH [28–30] and the ILM contraction that creates a tangential traction responsible of MH enlargement [19].

The anteroposterior traction caused by vitreous cortex on the fovea leads to MH formation [28–30]. It is widely accepted that the genesis of this dynamic force is localized in the precortical liquified vitreous pocket, immediately in front of the macula area, resulting in a passive contraction of the posterior hyaloid undetached from the fovea [31, 32]. Subsequently, the tangential traction due to the ILM stiffening promotes the progressive MH enlargement.

In contrast, in high myopic eyes, MH formation is related to more complex pathogenetic mechanisms [33–38]. In addition to the anteroposterior traction caused by the strong adhesion of vitreous cortex and to the tangential traction from the tightening of the ILM, an important role is reserved to the abnormal growth of myopic eyes that may result in the development of posterior staphyloma (PS) defined as a progressive scleral ectasia of the posterior ocular globe wall (Figure 1(a)) [39].

The PS introduces new pathogenetic forces in myopic MH formation and increases the spectrum of tractional forces in relation to different depths and location of the scleral ectasia with respect to the macular area. The centripetal vector forces are more relevant in case of deeper PS compared to the flatter staphyloma [40]. Due to the relative inelasticity of the inner retinal layers and retinal vessels, deep PS promotes a progressive retinal split which initially results in the development of a myopic foveoschisis (FS) (Figure 1(b)) and finally may lead to a retinal detachment involving the posterior pole.

In the case of flat PS, vitreoretinal tractions are not sufficient to produce the concomitant FS or retinal detachment [41, 42], and the pathogenetic mechanism of MH formation seems to be similar to those of emmetropic eyes [43].

Recently, several mechanisms regarding the development of MH in highly myopic patients were analyzed, and different pathways of MH formation were reported [44]. In detail, a normal foveal depression with abnormal vitreoretinal relationship characterized the first pathway. According to the main tractional forces recognized, two different processes can be distinguished. Similar to MH in emmetropic eyes, in high myopic eyes, the anteroposterior vitreomacular traction (VMT) induces a vitreomacular separation with the disruption of the inner laminar layers and the formation of inner foveal cysts with or without small foveal detachment (Figure 1(c)). The rupture of intraretinal cysts results in a disruption of outer laminar layers followed by the progression in a full-thickness MH. Alternatively, the posterior hyaloid may separate from the fovea, and the development of a tangential traction exerted from the surrounding preretinal membrane leads to a lamellar MH formation. The progressive foveal disruption results in a full-thickness MH [44].

A second pathway is characterized by the presence of FS that may occur with or without macular detachment. FS is not an uncommon finding in highly myopic eyes (9–34%) [43] and is believed to be one of the main causes of MH formation in these patients [45–47]. A macular schisis promotes a tangential or multidirectional traction with the development of lamellar MH. The continuous traction caused by the preretinal membrane induces the evolution in a full-thickness MH [44]. When macular schisis occurs with foveal detachment, an outer laminal dehiscence can be observed (Figure 1(d)). If preretinal traction induces inner laminar dehiscence, a full-thickness MH may develop with a macular retinal detachment (Figure 1(e)) [44, 48].

Finally, the third pathway includes MH with concomitant chorioretinal atrophy or underlying macular scar. Both progressive retinal thinning over the lesion and tangential traction promote the MH formation that may occur adjacent to the margins or within the lesion area [44].

In a recent report, Lai et al. [49] analyzed the lamellar hole-associated epiretinal proliferation (LHEP) in lamellar MH and full-thickness MH in high myopic eyes. This epiretinal proliferation is a noncontractile membrane localized at the edge of a deep and wide retinal defect. Several OCT studies have demonstrated the tight connection between the inner retinal tissue and LHEP [50] characterized by a homogeneous mound at OCT examination [51]. Two morphological LHEP findings, typical of highly myopic eyes, were described: the broad LHEP extension and LHEP-posterior hyaloid (PH) adhesion. In eyes with high myopia, a broader extension of LHEP (>1.500 μm from the foveal center) was observed when compared with nonhighly myopic patients. Moreover, a greater prevalence of LHEP-PH adhesion in eyes with high myopia was detected. The LHEP-PH adhesion was described as the growth of the LHEP along the PH surface when the PH remains attached to the margins of the MH and to the space between the hole edge and the hyaloid.

Although several mechanisms of MH formation are clearly described in the literature, the exact evolution of this retinal disease in myopic eyes is not always predictable and rapid changes from a typical configuration to another pattern may be observed [44].

Figure 1 shows different myopic macular hole patterns.

3. Surgical Techniques

Since the introduction of three-port PPV with gas tamponade in the 90s [11, 12], several surgical strategies have been developed for the MH repair in high myopic eyes, including silicone oil tamponade, episcleral posterior buckling, suprachoroidal buckling, and scleral shortening technique [52–55].

(a)

(b)

(c)

(d)

(e)

Figure 1: Different myopic macular hole (MH) patterns. (a) Full-thickness MH with intraretinal cysts in deep posterior staphyloma. (b) Full-thickness MH with perilesional foveoschisis. (c) Vitreomacular separation with vitreofoveal adhesion which causes the dehiscence of the inner retinal layers and the formation of inner foveal cysts. (d) Vitreomacular traction with impending macular hole associated with diffuse macular schisis and foveal detachment which results in outer retinal layers disruption. Note: the important traction exerted by the thickened posterior hyaloid undetached from the fovea and the consequential retinal split due to the deep posterior staphyloma. (e) Complete disruption of the inner and outer retinal layers resulting in macular retinal detachment.

Although PPV with ILM peeling and intraocular gas tamponade leads to an anatomical closure rate more than 90% for idiopathic MH [56], in highly myopic eye the successful closure of MH varies considerably from 60% to 100% and some patients require multiple treatments in order to achieve the closure of the hole [20, 57]. The aim of vitrectomy is to release all vitreoretinal tractions from the vitreous and the epiretinal tissue and to reduce macular stretching caused by the ILM in order to promote retinal elongation and adaptation to the posterior staphyloma, if present.

In highly myopic eyes, the ILM appears thin, sticky, and strongly adhered to the retinal surface; moreover, preretinal membranes showed a multilayered and heterogeneous aspect composed of vitreous cortex residuals, ERM, and ILM [58]. Because of these features, ILM tends to break into several little sections rather than peel off in a sheet during its surgical removal [59]. This aspect may lead to difficult and dangerous ILM peeling because the subsequent ILM regrasping is associated with a higher risk of iatrogenic retinal breaks [60].

To avoid these difficulties, several tools have been introduced in vitreoretinal surgery for the treatment of myopic MH helping the surgeons to perform a safe and effective procedure. The chromovitrectomy helps to better identify the vitreous and the epiretinal membranes in myopic eyes. The use of triamcinolone acetonide increases the visualization of the vitreous body and vitreous cortex that remains tightly adhered to the retina plane in high myopic patients. Furthermore, the introduction of vital dyes allows to stain the posterior pole and correctly recognized the ERM (trypan blue) and the ILM (brilliant blue, lutein/zeaxanthin + brilliant blue). Moreover, the use of specific light filters can provide a better visualization of stained ILM in myopic eyes [61], reducing the retina light toxicity [62].

In order to avoid the inadvertent migration of vital dyes into the subretinal space, several substances have been used during the dye-assisted ILM peeling in MH surgery [63–65]. To promote the gentle injections of vital dyes and heavy liquids into the vitreous cavity and to avoid fluid turbulence, several devices with a steady and slow jet have been introduced [66]. Specific dual-bore cannula with a side port for fluid injection prevents the risk of retinal injury caused by a fluid jet stream and promotes a faster pressure relief during injection by multiple fluid egress vents [67].

The microscope-integrated intraoperative OCT in MH surgery allows a real-time visualization of the vitreoretinal interface [68]. This device provides an imaging of foveal architecture during the tissue-instruments interaction helping the surgeon to release in a safe manner the VMT and to identify and remove residual ERM or ILM if present [69].

In high myopic MH, several factors may influence the anatomical and functional outcomes after surgery [44] including the increased axial length, the retinal shortening over an elongated sclera [57], the presence of posterior staphyloma [70], the presence of severe traction maculopathy [63], the presence of foveoschisis [41], and the intraoperative peeling of rigid and stiff ILM [71].

The extension of ILM peeling is a matter of controversy. For a successful MH closure, no clear guidelines regarding the minimum area of ILM peeling are available [72]. Due to the adhesion between the ILM and the retinal nerve fiber layer—ganglion cell layer complex, the peeling maneuver might damage these inner retinal layers with consequently poor postoperative visual acuity [73]. Thus, a smaller ILM peeling might be more respectful of the retinal nerve fiber layer—ganglion cell layer complex [74]. On the other hand, a wider peeling extended up to the vascular arcades might be useful in order to reduce the complex tractional forces in the myopic retina [75].

However, ILM peeling in myopic FS is currently under debate. Due to thin central foveal tissue, an iatrogenic full-thickness MH could develop during ILM removal. The risk of this complication ranges from 16.7 to 20.8% [76] and significantly increases in case of outer lamellar macular hole [77]. To reduce the risk of this complication and to preserve the epifoveal ILM, foveal-sparing ILM peeling procedures were introduced [76–79]. Although these techniques have showed a better success rate and visual outcome when compared to the classic ILM peeling, no consensus regarding the ILM area to be preserve was developed. A range from 300 to 1000 μm diameter was reported in different studies [77]. Anatomical results showed the primary success rate limited to 50–73.3% with vitrectomy, ILM peeling, and gas tamponade in high myopic eyes [80].

Recently, for persistent myopic MH, the inverted ILM flap technique was introduced [81]. In this procedure, the remnant of an incomplete ILM peeling is left and then inverted inside the macular hole to provide a scaffold for MH closure [81]. At the beginning, many surgeons believed necessary to insert the flap into the hole like a plug. Now it is thought sufficient to cover the hole with the peeled ILM flap in order to obtain a division between the vitreous cavity and the intraretinal spaces and to promote the MH repair mechanism [82]. The original procedure consisted of circumferentially 2-disc-diameter ILM peeling around the MH to preserve the adhesion between the inner ILM outline and the MH edges. Afterwards, the ILM flap was folded and gently positioned inside the MH [81]. For ILM flap manipulation and positioning, different techniques have been described to prevent the flap dislocation during the fluid-air exchange or in the postoperative period. These strategies include the use of viscoelastic [83] or perfluorocarbon [84] before balanced saline solution-air exchange, fluid-air exchange with low intraocular pressure and passive aspiration [75], and the addition of autologous serum [14, 22] or platelet-rich plasma [85]. Platelet-rich plasma seems to achieve better anatomical results compared to the autologous serum due to its greater adhesiveness to the edges of the hole [82].

In order to increase the ILM flap maneuverability and to reduce its displacement, several studies suggested the use of a bigger ILM flap which is resized and trimmed using the vitrectomy probe and subsequently plugged into the hole [20, 75, 86]. If ERM is present, it may be inverted with the ILM into the hole [20]. To avoid macular hole packing with a folded multilayered ILM, the creation of a single-layer

inverted flap was suggested [84]. This large monolayer ILM flap seemed to promote regular glial cells proliferation and to create a physiological scaffold for the photoreceptors [84, 87]. To preserve the nasal maculopapillary nerve fiber layer, a 270-degree C-shaped temporal ILM flap has been suggested [23]. ILM flap is peeled towards the hole but stopped approximately 0.5 disc diameter from the center of the fovea, and a single smooth layer is used to cover the MH. This technique provides a reduction in dissociated optic nerve fiber layer [88] and is able to release more than 180° traction from the temporal side. A surgical variant of 180° superior ILM flap which does not require postoperatively prone positioning was also proposed [89].

The inverted ILM flap approach remains technically challenging even for an experienced surgeon [90]. To further steady the flap in an adequate position, the vitreous cavity can be filled with gas or silicone oil [20, 26, 75]. Compared to gas, silicone oil is characterized by long-lasting but weaker tamponade action, especially for myopic eyes with deep posterior staphyloma because of its difficulty to fit into this area. Nevertheless, silicone oil has been tested as a tamponade in highly myopic eyes, and it surprisingly demonstrated to be an effective tamponade for the treatment of MH [53]. It has been demonstrated that silicone oil creates a bursa inside the MH with a compartmentalization of chemotactic and nutrient substances. These substances might promote reparative mechanism which supports the closure of the hole [82].

Although the anatomic success of inverted ILM flap technique without retinal detachment range from 94% to 100% [75, 81], a previous PPV with complete ILM peeling precludes the feasibility of this surgical approach in case of MH reopening. In these cases, several alternatives have been described including the use of anterior and posterior lens capsular flap transplantation [91] or the autologous transplantation of the ILM [25]. Recently, autologous neurosensory retinal free flap transplantation (ANRFF) technique with gas or silicone oil tamponade was introduced [92, 93]. Chen et al. [91] described the use of anterior and posterior capsule lens to close refractory MH, due to its similar nature to ILM, reporting a significantly better closure rate with the anterior capsule flap but not a significantly VA improvement than eyes treated with the posterior one. Once obtained a circular anterior or posterior capsular flap, it is stained with 0.125% ICG and transplanted into the hole [91]. The advantages of a lens capsular flap are its higher density compared with ILM making it easier to settle down on the retinal surface and its easy feasibility.

Autologous transplantation of the ILM was first described by Morizane et al. [25]. This surgical approach consists of visualization of residual ILM using 0.25 mg/mL brilliant blue G solution and creation and transplantation of a free flap of ILM inside the macular hole. Grewal and Mahmoud [92] described the use of ANRFF transplantation for refractory myopic MH complicated by retinal detachment. This technique involves harvesting an autologous neurosensory retinal free flap and gently positioning it over the refractory MH using bimanual approach [92].

In highly myopic eyes, a macular hole with retinal detachment (MHRD) can occur. Vitrectomy with removal of cortical vitreous and ILM and gas or silicone oil tamponade has become the standard of care for MHRD treatment [94]. Although anatomic reattachment can be achieved, the success rate of MH closure ranges from 50% to 70% and poor postoperatively visual acuity was reported [23, 95, 96]. The inverted ILM flap technique has been demonstrated to be a useful strategy to increase the closure rate of the hole in MHRD [20, 22, 23]. Macular buckling has also been introduced as a treatment option for both primary MHRD and MHRD refractory to vitrectomy with an anatomical success rate ranging from 70% to 100% [97–101]. This technique aims to reduce the complex anteroposterior and tangential tractions resulting from PS in highly myopic eyes through the modification of macular shape from concave to convex profile. According to the intraoperative difficulty to check the correct position of the buckle and to place sutures posteriorly, several buckles with different designs and material have been described [102–104].

Considering that eyes with extremely high myopia can frequently exceed 30 mm in the axial length, surgical instrumentation, such as vitreous forceps, must be evaluated accurately during PPV. To overcome the inability to reach the retinal surface, surgeons can verticalize the instruments and carefully apply a pressure on the sclera wall in order to temporarily reduce the axial length of the globe [105]. However, these maneuvers are not free from complications, such as limited visibility due to erroneous contact and dislocation of the viewing system, corneal folds and impaired surgeon maneuverability which result in a longer operation time and challenging surgical procedures [106]. To prevent complications resulting from iatrogenic trauma, long-shaft forceps for ILM peeling specific for highly myopic eyes were developed [107]. Curved elongated instruments were also proposed [105].

Microincision vitrectomy surgery (MIVS) has potential advantages compared to conventional vitrectomy in highly myopic eyes. Despite the lowest incidence of complications with the small-gauge system compared to conventional vitrectomy, no statistically significant difference in visual outcomes has been reported [59]. With MIVS a small-diameter sutureless sclerotomies may be performed. This surgery is characterized by a faster postoperative recovery, less postoperative inflammation and patient discomfort, and reduction of iatrogenic peripheral breaks incidence [108, 109]. However, in some cases, the self-healing sclerotomies can remain open with spontaneous leakage and early postoperative hypotony. This condition mainly occurs in myopic patients due to the anatomical characteristic of these eyes with a thinner sclera and a deranged fibrillar architecture [110].

The intrascleral tunnel morphology plays a key role in avoiding the sclerotomy leakage. Both biplanar oblique-perpendicular-bevel-down trocar insertion and longer tunnel have a lower incidence of early hypotony when compared to straight bevel-up and shorter sclerotomies [111–114]. To promote the wound sealing, several options have been introduced, including the prolonged sclerotomy

massage [115, 116], transconjunctival and trans-scleral absorbable suture [117], releasable sutures [118], use of fibrin glue or polyethylene glycol hydrogel polymer [119, 120], and conjunctival cauterization [117]. The introduction of 27-gauge vitrectomy with scleral incision diameter of 0.4 mm does not require biplanar trocar insertion, thus reducing the risk of postoperative hypotony in myopic eyes [121, 122].

4. Conclusions

Several and complex tractional mechanisms are implicated in the development of MH in myopic eyes including the anteroposterior forces due to the strong adhesion of vitreous cortex, the tangential traction on the macula caused by the ILM, as well as the centripetal vector forces exerted by the PS. Related to these anatomical conditions, myopic eyes still remain a challenge for vitreoretinal surgeons. In the last decades, the introduction of significant innovations for the treatment of myopic MH has allowed vitreoretinal surgeons to perform a safe and effective surgery in these complicated eyes.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Clinical Study

An Internal Limiting Membrane Plug and Gas Endotamponade for Recurrent or Persistent Macular Hole

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Introduction. Recurrent or persistent macular holes (MHs) are rare today due to the tendency to carefully peel the internal limiting membrane. Conversely, their treatment is still a challenge for a vitreoretinal surgeon. *Materials and Methods*. This is a retrospective, consecutive, and nonrandomized study of patients affected by recurrent or persistent MHs treated using small-gauge pars plana vitrectomy (25- or 23-gauge) and an autologous ILM plug, at the Eye Clinic of Azienda Ospedaliera Universitaria Careggi (Florence, Italy) between January 2016 and May 2018. We included 8 eyes of 8 patients in the study. Five patients had a recurrent MH while 3 had a persistent MH. The case series includes patients with myopic eyes and with large macular holes (>400 μ). Patients were followed up with ophthalmoscopic examinations and swept-source optical coherence tomography (SS-OCT). *Results*. The mean age of the patients was 74 years (±4.81 standard deviation (SD)), 3 patients were men and 5 women. The average axial length was 26.28 mm (±2.84 SD). Four patients had an AL ≧ 26 mm. The mean MH diameter was 436.5 (±49.82 SD). Average preoperative best-corrected visual acuity (BCVA) was 0.81 logMAR (±0.16 SD) and 20/125 Snellen. The ILM plug has been found integrated in the MH in all the follow-ups. *Conclusion*. In our study, an ILM autologous macular transplant was used successfully in 5 cases of macular hole recurrence and 3 cases of macular hole persistence. The anatomical success was achieved in all the cases; 4 patients improved their BCVA, and 4 patients maintained it. No macular alterations such as RPE or retinal atrophy/dystrophy were observed after 6 months.

1. Introduction

Via pars plana (VPP) vitrectomy surgery for macular holes (MHs) has a high success rate, with recent reports of primary closure rates of more than 90% [1, 2]. Treatment of primary macular holes is mainly performed with macular peeling [3–7] or with inverted internal limiting membrane (ILM) flap [4, 6, 8–12], if the patient has a large hole or has high myopia. Unfortunately, macular holes can be persistent if they remain open after surgery, or recurrent if they reopen after initial closure. Previous studies showed an incidence of MH persistence or reopening after initial closure between 4.8% and 9.2% [13–16]. This may be due to residual epiretinal traction, insufficient gas tamponade, poor compliance by the patient in keeping a prone position, or an unknown cause [17]. Recurrent or persistent MH treatment is still a challenge for a vitreoretinal surgeon.

A technique of autologous ILM plug transplantation has already been proposed [18, 19].

This work aims at reporting the anatomical and functional results in a series of patients affected by recurrent or persistent MH treated using an autologous ILM plug transplant.

2. Materials and Methods

This is a retrospective, consecutive, nonrandomized, and comparative study of patients affected by recurrent or persistent MHs treated using small-gauge pars plana vitrectomy (PPV) (25- or 23-gauge) and an autologous ILM

plug at the Eye Clinic of Azienda Ospedaliera Universitaria Careggi (Florence, Italy) between January 2016 and May 2018. We included 8 eyes of 8 patients in the study (Table 1).

Five patients had a recurrent MH while 3 had a persistent MH.

All the patients were pseudophakic and had previously undergone pars plana vitrectomy with macular ILM peeling for a macular hole. The average time for reopening of the MH (5 eyes) was 15. 4 months.

The mean age of the patients was 74 years (±4.81 standard deviation (SD)); 3 patients were men and 5 women. The average axial length was 26.28 mm (±2.84 SD). Four patients had an AL ≧ 26 mm. The mean MH diameter was 436.5 (±49.82 SD).

Average preoperative best-corrected visual acuity (BCVA) was 0.81 logMAR (±0.16 SD) and 20/125 Snellen. The patients had previously undergone surgery in different centers (3 patients in our centre by 3 different surgeons and 5 patients in different Italian centers all by different surgeons). The study was approved by the Institutional Ethics Committee and complied with the Declaration of Helsinki. Written informed consent for participation was obtained from all patients. All the patients underwent a complete ophthalmologic examination, and optical coherence tomography (OCT) (SPECTRALIS; Heidelberg Engineering, Germany; RS300 Advance SD-OCT; Nidek Co, Ltd, Japan; and DRI OCT Triton OCT, Topcon, Japan) was conducted at the time of surgery and 1 month, 4 months, and 6 months later.

The macular hole minimum and maximum widths were measured using a foveal OCT scan, as described by Duker et al. [20]. Both widths are measured using the OCT calliper function, as a line drawn roughly parallel to the RPE.

Visual acuity was converted into logMAR to perform the statistical analysis.

2.1. Surgical Technique. A standard 3-port 23/25-gauge PPV was carried out (CONSTELLATION, Alcon Surgical, Fort Worth, TX). The choice of the calibre of the vitrector was made according to the axial length (AL) of the eye; the 23-gauge was used for eyes with an AL ≧ 28 mm. An ILM dye Brilliant Blue G (Brilliant Peel, Fluoron, Germany) or Membrane Blue Dual (DORC, the Netherlands) was injected onto the ILM withdrawing area to stain the ILM for approximately 30 seconds. All the residual epiretinal membranes (ERMs), which were present in 2 patients, were removed. The ILM was harvested in an area inside the vascular arcades, starting from the edge of the previously removed ILM, in a circular fashion for approximately 1 disk diameter, and inserted into the hole (see Video, Supplemental Digital Content 1). A balanced salt solution and air exchange was performed, and gas (C3F8 14% or SF6 20%) was injected at the end of surgery. The patients were subsequently kept in a face-down position overnight and were advised to take a prone position for 3 days after surgery. Topical therapy with tobramycin and dexamethasone drops was carried out after surgery for 30 days.

3. Results

Mean postoperative BCVA after 6 months was 0.68 logMAR (±0.14 SD) and 20/100 Snellen. The ILM plug was kept in place in all the cases and integrated in the MH to close it (see Figure 1). No eyes had postoperative macular degeneration such as RPE or retinal atrophy/dystrophy after 6 months. All 8 patients had successfully closed holes at 6 months and improved their BCVA (4 cases) or maintained it (4 cases). The myopic patients also had encouraging visual outcomes, which could be due to a preoperative absence of myopic patchy macular atrophy.

4. Discussion

The study shows 5 cases of recurrent MH and 3 cases of persistent MH who underwent VPP combined with autologous ILM plug transplant into the macular hole. The anatomical success was achieved in all the cases, and no cases of postoperative macular degeneration such as RPE or retinal atrophy/dystrophy were observed after 6 months.

This technique has already been described in the literature and has provided excellent results with success rates of 91–100% [21–26].

Concerning the inserting technique, the authors have tried to solve the problem of autologous ILM transplant instability within the MH in several ways. For example, some authors have used ocular viscoelastic devices (OVD) to stabilise the ILM flap [21, 23]. Morizane et al. [21] injected OVD over the ILM flap to position it in the hole and hold it in place. Dai et al. [23] instead used OVD to slightly lift the edge of the recurrent hole and prepare it to receive the ILM flap. Park et al. [22] used a drop of perfluoro-*n*-octane which, after stabilising the ILM flap inside the macular hole, was removed using a basic salt solution- (BSS-) air exchange.

We were able to insert the ILM flap without OVD or perfluoro-*n*-octane. The ILM flap floats into the vitreous cavity and can be easily lost during manipulation. We reduced the infusion to 10 mmHg to make the ILM plug easier to manoeuvre and avoid excessive flotation. The insertion of the plug must be carried out with great care to avoid damaging the macular edges. The thinness and the motility of the ILM plug allow good visualisation during the insertion manoeuvres, and the contact with the macular surface can be avoided (see supplemental digital content 1).

Risk factors for macular hole reopening include cataract surgery, intraoperative retinal tears, and cystoid macular oedema [27, 28]. High myopia is also a risk factor, and our series confirms that 4 out of 8 eyes (50%) had an axial length ≧ 26 mm.

All the patients had undergone phacoemulsification during the first vitrectomy; therefore, in our series, recurrence is independent of the lens removal. The pathophysiology causing the recurrence of the macular hole is not clear but probably relates to mechanical factors, inflammatory factors, or both [15, 29].

Previous studies reported that the average reopening time of a macular hole is between 12 and 15 months [30, 31]; although in 1 series, an average reopening time of 28 months

Table 1: Preoperative findings and postoperative outcomes of the patients.

Patient	Age (years)	Maximum MH diameter (μ)	MH type	Axial length (mm)	Preoperative visual acuity (Snellen)	Preoperative visual acuity (logMAR)	Postoperative visual acuity (Snellen) after 6 months	Postoperative visual acuity (logMAR) after 6 months	Macular hole reopening time (months)	Macular hole in the fellow eye
1	75	461	Recurrent	24.7	20/200	1	20/200	1	18	Yes
2	69	385	Persistent	24.2	20/100	0.7	20/100	0.7	0	No
3	81	376	Recurrent	25.1	20/125	0.8	20/80	0.6	19	Yes
4	77	440	Recurrent	23.9	20/200	1	20/80	0.6	12	Yes
5	73	420	Recurrent	27.1	20/200	1	20/100	0.7	11	No
6	68	510	Persistent	28.4	20/100	0.7	20/100	0.7	0	No
7	79	485	Recurrent	27.8	20/80	0.6	20/63	0.5	17	No
8	70	415	Persistent	29.1	20/100	0.7	20/100	0.7	0	No

Figure 1: (a) Preoperative OCT that shows a recurrent macular hole (max. MH diameter 461). (b) 1 month after the operation, the plug is positioned into the closed macular hole. (c) 4 months after the operation. (d) 6 months after the operation. We can observe a partial reconstruction of the outer retinal layers.

was observed [32]. We found a result more similar to the literature, because in our series, the reopening time in the eyes with recurrent MHs was 14.6 months. Surgical technological advances, and especially small-gauge surgery and modern phacoemulsification, have led to decreased rates of macular hole reopening. In fact, the decreased postoperative inflammation that could cause a cystoid macular edema possibly reduces the macular hole reopening rates. Moreover, better surgical instrumentation and the assistance of vital dyes to identify ERMs and ILMs can help the surgeon to perform a more thorough peeling.

A longer reopening time is probably related to more consistent and improved ILM peeling. Better staining and visualisation methods and better surgical instruments are permitting more extensive and less traumatic macular peeling. Internal limiting membrane peeling is thought to reduce the recurrence rate of ERMs after macular surgery by eliminating a scaffold for cellular reproliferation [13, 33, 34]. In fact, ERMs may create a "spillover" effect from the gliosis that induced the macular hole to close after the first operation. The "spillover" effect derives from tangential traction that acts centrifugally and could counterbalance the centripetal forces that close a macular hole.

Histopathologic studies of ERMs associated with recurrent holes have shown Muller cells and astrocyte cells similar to those seen proliferating inside successfully closed holes [35, 36]. These cells could generate the extracellular matrix and therefore the centrifugal forces that reopen the macular hole.

In our series, ILM peeling had previously been performed in all cases, but in 2 cases, we had to remove, during the second operation, an ERM that had formed even in the presence of ILM peeling. Each eye that had additional ERM peeling during the second operation had successful macular hole closure. Moreover, residual ERM can increase foveal fluid, and if there is a noncomplete outer retinal layers postoperative reconstruction, we can have a failure in the RPE pump and then an increased risk of hole reopening due to an uncontrolled cystic accumulation.

Chakrabaarti and Roufail [37] used the same shorter-acting gas tamponade (SF6) without posturing instructions with reasonable success rates in traumatic MHs. We also used SF6, but we preferred to tell patients to stay face down to facilitate closure in these complex recurrent or persistent MHs cases. Gases are thought to increase the contact between the neurosensory retina and the RPE pump and therefore reduce cystic macular accumulation.

Other tamponading tools, such as "heavy" silicone oils, have been successfully proposed by Rizzo et al. [38–40] for the closure of persistent holes. In our series, we preferred to use a gas tamponade because we believe that a strong tamponading force in the first postoperative period is crucial for surgical success. Moreover, we do not have to remove the silicone oil, risking MH reopening. Injecting silicone oil may cause inflammation and emulsion; so, we only use it if multiple peripheral retinal tears could lead to the formation of a rhegmatogenous retinal detachment.

Chakrabarti et al. [41] only used sterile air for the postoperative tamponading of the MHs, but we have preferred gas in order to have a more prolonged effect.

The frequencies of bilateral MHs among the reopened cases in earlier studies were between 33% and 59% [15, 42, 43]. In our cases, similarly, 3 out of 8 patients had had a macular hole in the fellow eye. Patients with recurrent holes may tend to form ERMs and tractional forces in general that cause macular holes to open.

By analysing microstructural changes in the fovea using swept-source optical coherence tomography (SS-OCT) in eyes with large refractory MH following autologous ILM transplantation, Pires et al. [24] showed that the closure was associated with the prolonged proliferation of glial tissues in the fovea with fibrotic and depigmentation phenomena. Moreover, Ra and Lee [44] also described these phenomena.

In our study, conversely, we found good recovery of the outer retinal layers, (see Figure 1) which they had already been correlated positively with postoperative visual improvement [45]. Once the external limiting membrane (ELM) is damaged, the breaching of the seal between the neurosensory retina and the RPE pump causes fluid accumulation in the fovea with an elevation of the edges of the hole and, consequently, its progression and enlargement.

When the hole is successfully repaired, the migration of the glial cells bridges the hole and reestablishes the seal between the neurosensory retina and the RPE. This allows a fluid reduction in the cystic retina and therefore the macular hole closure [46].

The myopic patients had stable or improved visual outcomes, which may be due to a preoperative absence of myopic patchy macular atrophy. Moreover, we did not observe macular pigment epithelium atrophy in myopic patients after surgery. Concerning the hydrostatic theory of macular hole closure [46], the presence of the ILM plug could possibly reduce the entering of fluids into the retinal layers of the macula.

The limitations of this study are its retrospective nature, the small number of patients, and short-term follow-up. A prospective study and a more extensive series of cases using this technique could provide reliable and conclusive data on the efficacy of ILM autologous plugs and gas endotamponade in recurrent/persistent macular holes.

5. Conclusion

In our study, an ILM autologous macular transplant revealed its usefulness and safety in the cases of recurrent and persistent macular holes that had previously undergone surgery with vitrectomy and ILM macular peeling.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

Each author warrants that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, and patent/licensing arrangements) that might pose a conflict of interest in connection with the article.

Supplementary Materials

Supplemental digital content 1: surgical video showing the ILM plug technique. (*Supplementary Materials*)

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Review Article

Perspectives of Autologous Mesenchymal Stem-Cell Transplantation in Macular Hole Surgery: A Review of Current Findings

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The main treatment available for idiopathic macular holes is represented by pars plana vitrectomy with internal limiting membrane peeling. However, late-stage macular holes are affected by a higher risk of surgical failure. Although adjuvant techniques can be employed, a satisfactory functional recovery is difficult to achieve in refractory macular holes. Given their neuroprotective and antiapoptotic properties, mesenchymal stem cells (MSCs) may represent an appealing approach to treat these extreme cases. The purpose of this review is to highlight the findings regarding healing mechanisms exerted by mesenchymal stem cells and preliminary application in cases of refractory macular holes. When compared with MSCs, MSC-derived exosomes may represent a feasible alternative, given their reduced risk of undesired proliferation and easiness of use.

1. Introduction

A macular hole is an anatomic gap in the retina occurring at the level of the fovea. The majority of macular holes is idiopathic, although they can be associated with highly myopic eyes or ocular trauma, especially in the elderly [1].

The general prevalence of full-thickness idiopathic macular holes found in the Beaver Dam Study is 0.3%, with rates increasing to 0.8% in people with 75 or more years of age [2]. The genesis of macular holes is supposed to be promoted by vitreous tractions or due to epiretinal membranes at the level of the fovea.

Occasionally, macular holes are associated with retinal detachments, leading to severe visual impairment, especially in elderly people with elevated myopia and in the presence of a posterior staphyloma [3, 4].

The typical progression of macular holes is characterized by a series of stages (reported by a biomicroscopic analysis by Gass) over a period of weeks, featuring retinal defects which in severe cases involve the macular region in all its thickness [5]. In the later years, optical coherence tomography (OCT) has become a useful method to confirm diagnosis and to better define the staging of macular holes. If left untreated, full-thickness macular holes lead to a poor visual prognosis, with visual acuity of 20/100 in more than 50% of all cases [6–10].

As a treatment for macular holes, Kelly et al. introduced in 1991 the use of pars plana vitrectomy, with removal of epiretinal membranes and introduction of long-acting gas tamponades [11]. Internal membrane peeling has been proposed by Eckardt et al. to further improve anatomical closure rates [12].

Other several advances in this surgical field allowed more satisfactory outcomes with a 98% closure rate of early-onset macular holes [13]. However, treatment of large (>400 μm) and late-diagnosed macular holes (>6 months) are affected by low success rates [14], particularly in highly myopic eyes [15]. In fact, size and stage of macular holes, duration of symptoms, and preoperative visual acuity have been reported as prognostic factors [16]. Moreover, a retrospective

chart review by Kim et al. concluded that large basal hole diameter and thin choroid are associated with poorer visual outcomes [17].

As of today, the goal of the surgical procedure focuses on the resolution of vitreal or epiretinal tangential tractions on the central retina and macular hole's margins, achieving its closure with good anatomical results in more than 90% of eyes with full-thickness macular holes [18–20]. Even if a review by Parravano et al. concluded that vitrectomy is effective in improving visual acuity and in achieving hole closure [21], surgical closure rates are relatively low in complex cases, such as large macular holes, myopic macular holes or refractory holes after the first surgery [15, 22–24]. Novel techniques have been introduced to improve anatomical and visual outcomes in complicated cases [25–29]. These techniques include outpatient fluid-gas exchange, the inverted internal limiting membrane (ILM) flap technique, ILM fragment transplantation, and the use of human autologous serum, platelet concentrate, transforming growth factor-beta 2, and heavy silicone oil endotamponades [26, 30–40]. Inverted ILM flap techniques may facilitate the proliferation of glial cells, which then fill the hole and facilitate its closure and are currently employed as a treatment of choice for macular holes in patients with severe myopia and posterior staphylomas. However, even if good anatomical outcomes (with successful macular hole closure) are achieved, functional recovery and regeneration of the retina are difficult to obtain, especially in case of late stages of the disease.

Retinal degenerative diseases can be characterized by loss of cellular elements, such as retinal ganglion cells (RGC), retinal pigment epithelium (RPE) cells, and photoreceptors, and the following visual impairment is typically irreversible, since retinal cells lack self-repair capability. Several cell-based treatments have been proposed and evaluated to overcome these limits.

Cell therapy represents an appealing alternative to obtain regeneration of damaged retina, potentially improving functional outcomes also in surgery of macular hole. Transplantation of retinal cells has been considered as a potential treatment for retinal degenerative diseases, particularly in late stages associated with severe cell damage. This approach aims at replacing lost retinal cells using stem cells, progenitor cells, and mature neural retinal cells with potential applications in a wide range of retinal degenerative conditions.

The purpose of this review is to highlight perspectives of cell-based treatment for refractory macular holes, focusing particularly on the current evidence regarding the application of autologous mesenchymal stem cells (MSCs) since they overcome the ethical and safety problems of embryonic and induced pluripotent stem cells (ESCs and iPSCs, respectively). In addition, mesenchymal stem cells can be easily extracted from different human tissues and possess neuroprotective and immunomodulatory properties.

2. Hints of Cell Therapy for Retinal Degenerations

Appealing anatomic and functional outcomes have been reported in animal models of retinal degeneration by various study groups evaluating the transplant of RPE cells, retinal progenitor cells, photoreceptor precursors, or full-thickness retinal sheets [41–44]. However, integration into the receiving retina and functional recovery still represent major obstacles for successful transplant. Submacular transplantation of autologous RPE, retrieved from the peripheral retina, has led to visual acuity improvements in patients affected by macular degeneration [45–48]. However, since ocular autologous cell sources are limited, a treatment based on stem cells seems more feasible, given their potentially unlimited proliferative properties.

In fact, it is possible to obtain a virtually unlimited source of different retinal cells (RPE cells, ganglion cells, and photoreceptors) from the expansion of pluripotent stem cells, both embryonic and iPSCs, as shown in numerous studies [49–53].

Several stem-cell types can differentiate into photoreceptors in preclinical models of human retinal degenerative disease, including bone marrow-derived hematopoietic stem cells, bone marrow-derived MSCs, neural progenitor cells (NPCs), and forebrain-derived progenitor cells [54]. Carr et al. [55] evaluated the injection of human iPSC-derived RPE transplants (iPSC-RPE) in murine models of retinal degeneration, with protective effects on photoreceptors and better optokinetic responses in treated rats when compared with the control group. Finally, photoreceptor rescue effects of RPE derived from iPSC have been observed in retinal degeneration in mice [56].

3. Mesenchymal Stem Cells for Retinal Diseases

Mesenchymal stem cells possess the ability of self-renewal and unlimited differentiation. Moreover, it is possible to retrieve MSCs from several human tissues (bone marrow, dental pulp, adipose tissue, etc.). Given their well-known properties and the possibility to isolate MSCs with ease, this cell type represents a promising candidate for the treatment of retinal degenerative diseases [57]. In fact, MSCs feature a good proliferative potential with proven neuroprotective effects and reduced immunogenicity [58]. Furthermore, MSCs and MSC-derived exosomes (MSC-Exos) have been successfully tested for the treatment of retinal inflammation [59–62], injury [63], and degeneration [64, 65].

MSCs derived from both bone marrow and adipose tissue have been injected into the subretinal space of animal models of retinal degeneration with significant improvements in terms of visual function and RGC density, although for a short period [66–68]. Other studies indicated that bone marrow-derived MSCs (BMMSCs) might differentiate into photoreceptors cells after their introduction in the subretinal cavity, as observed in rats with hereditary retinal degeneration [69]. Moreover, transplantation of BMMSCs in animal models of retinitis pigmentosa led to preservation of outer nuclear layer cells, with prolonged photoreceptor survival [70]. Our group had performed preliminary evaluations of MSCs intravitreal injections in rat models, highlighting the ability of MSCs to survive, migrate, and integrate at the level of the ganglion cell layer, which improved in case of retinal ischemia (Figure 1) [71].

(a) (b)

Figure 1: Histological findings revealing integration of mesenchymal stem cells at the level of the ganglion cell layer in the ischemic rat retina. Mesenchymal stem cells were not able to migrate to the ganglion cell layer of nonischemic retina. VB = vitreous body; GCL = ganglion cell layer; IPL = internal plexiform layer; INL = internal nuclear layer; EPL = external plexiform layer; ENL = external nuclear layer; PRL = photoreceptor layer; RPE = retinal pigment epithelium; MSCs = mesenchymal stem cells.

It is indicated that MSCs can express a variety of factors which could protect the injured retina, such as NGF, CNTF, BDNF, bFGF, NTFs, and IGF1 [67, 72, 73]. The mechanisms which these effects are based on have been extensively described in the literature [74, 75]. Moreover, it has been reported that MSCs secrete also factors modulating perfusion and neovascularization in ischemic retina [76, 77].

The intravitreal use of CD34 + BMMSCs in patients with age-related macular degeneration has been evaluated in three phase I clinical trials, with improved visual acuity over a 12-month follow-up (NCT01518127, NCT01068561, and NCT01518842) [78, 79]. In a phase II clinical trial (NCT01560715), a quality-of-life improvement in patients affected by retinitis pigmentosa was observed, although not sustained at 12 months after MSCs injection [80–82].

However, in a study employing CD34 + BMSCs intravitreal injections (with 3.4 × 106 cells in a 0.1 ml suspension), no improvement in visual function was observed in 6 patients affected by AMD, even if no complications occurred [79, 82]. In a study by Weiss et al., patients with different retinal diseases received varied BMMSCs administration methods (retrobulbar, subtenonian, intravitreal, intraoptic nerve, subretinal, and intravenous) in accordance with different ocular diseases (NCT01920867), with improvements in terms of visual acuity and visual field parameters [83–86].

Severe complications and vision loss, related probably to stem-cell preparation, have been observed in a clinical trial adopting adipose-derived MSCs (NCT02024269), leading to the withdrawal of the study [87]. This discrepancy in outcomes between BMMSCs and adipose-derived MSCs may be due to different quantity and preparation of injectable solution, given the significant differences among the conducted trials.

4. Mesenchymal Stem Cells for Macular Holes: Current Evidence

Currently, little evidence is present in the literature regarding the application of mesenchymal stem cells for the treatment of macular holes, in both animal models and humans. In order to assess the feasibility of cell therapy in the treatment of macular holes, Hara et al. and Yamana et al. first applied human adipose-derived MSCs in rabbit models of retinal hole [88, 89], with restoration of anatomic integrity.

Encouraged by these positive findings, Xuqian et al. injected in vitro adipose-derived MSC cultures into rabbits with retinal holes undergoing vitrectomy, evaluating the effects with optical coherence tomography and immunohistochemical analysis. OCT images of treated eyes day showed reattachment of the everted hole edges at the second day after surgery with onset of healing tissue at the 4th postoperative day, in contrast with control eyes in which healing was delayed till the 32nd postoperative day. In addition, final retinal thickness was significantly greater in treated eyes (with values similar to normal retina) in comparison with control eyes ($p = 0.001$), with more evident differences at early postoperative time [90].

To confirm the effects of adipose-derived MSCs, additional cell injections were performed in refractory retinal holes after surgery in the control group, with clear observation of a healing process similar to the one occurred in the treatment group.

The histological analysis by Xuqian et al. confirmed that healing tissue cells were different in the retinal holes of the treated group compared to the control group. In fact, control eyes presented a proliferation of collagenous fibrotic tissue, while the retina of treated eyes featured mesenchymal tissue with photoreceptor- and bipolar-like cells. However, it was observed that these cells were not originated from injected MSCs since the transplanted donor cells did not survive abundantly in the healing tissue. Xuqian assumed that the healing process in the transplantation group was promoted by MSCs expression of cytokines with antiapoptotic functions and related to extracellular matrix development, such as intercellular adhesive factors, with better adhesion of the retina to the RPE.

A recent case series of 7 human patients affected by refractory and late-stage macular holes evaluated effects on visual function and safety of MSC suspension and MSC-Exos in combination with pars plana vitrectomy and gas tamponade (SF6 or air in patients receiving exosomes) or heavy silicon oil (in patients receiving cell suspension). Silicon oil was employed in order to limit the dispersion of the cell suspension, and patients were instructed to remain

in supine position for 1 day. Silicon oil was then removed with surgery in the two patients receiving the cell suspension [91].

BCVA improvements were observed in five patients presenting hole closure after surgery, with a mean postoperative visual acuity of 20/110 (ranging from 20/160 to 20/50). The complete hole closure was observed at 19 days after surgery, by average (ranging from 3 days in a case receiving MSCs suspension to 30 days in patients receiving intravitreal MSC-Exos). The only patient who did not experience improvements in visual acuity was a woman with a 4-year history of macular hole, which was already treated with previous unsuccessful surgery. Nevertheless, she presented hole closure at 1 month after pars plana vitrectomy with intravitreal MSC-Exos, even if her BCVA remained unchanged. Only one of the treated eyes did not presented a macular hole closure after pars plana vitrectomy in combination with phacoemulsification and intravitreal injection of MSC-Exos, but its BCVA improved slightly (from 20/200 to 20/160) probably due to cataract removal. Among all the patients included in the case series, reduction in central scotoma was observed, with significant improvements in one patient receiving 20 μg of MSC-Exos via intravitreal injection in association with an air tamponade (in accordance with an improvement in BCVA from 20/200 to 20/50).

In regard to adverse reactions, formation of fibrotic epiretinal membrane due to proliferation of injected cells occurred in one patient receiving MSCs in association with pars plana vitrectomy and heavy silicon oil endotamponade. This fibrotic membrane was then removed through an additional surgical procedure, and the pathological analysis revealed the proliferation of fibroblast-like cells. In the following 6 months, no recurrence of fibrotic membrane was observed, and a decrease in central scotoma was reported. Moreover, the first patient who underwent treatment with 50 μg of MSC-Exos presented signs of inflammation in the anterior chamber, which was resolved 3 days after application of steroid eyedrops. Thereafter, MSC-Exos dose was reduced to 20 μg without observation of other cases of significant inflammation. All patients were subjected to a follow-up period lasting between 0.5 and 3 years, without evidence of side effects related to MSCs and MSC-Exos and risk of teratoma development. However, limitations of this preliminary study lie in the small number of patients and the absence of a comparison with a control group, preventing the assessment of the real therapeutic effects of MSCs and MSC-Exos.

5. Discussion and Clinical Perspectives

Adjuvant surgical strategies, such as ILM inverted flap and ILM insertion, have been adopted to improve outcomes in refractory and large macular holes with successful anatomical and visual outcomes [42, 92, 93].

However, these techniques are not without potential problems, such the risk of direct damage to RPE. Moreover, the heterogeneous characteristics of late stages and refractory macular holes may prevent the actual assessment of the effects of adjuvant procedures on postoperative results. Among the few studies comparing different adjuvant techniques, the analysis by Park et al. concluded that the inverted flap technique resulted in better recovery of photoreceptor layers with better functional outcomes, when compared with ILM insertion [94].

Stem-cell therapy has emerged as a novel candidate approach for the treatment of retinal degenerative diseases, given their proven effects of neurogenesis, cell replacement, reduced apoptosis, and modulation of inflammation and immune responses [95, 96]. MSCs can be easily retrieved from numerous adult tissues and can potentially differentiate into RPE cells and photoreceptors, providing the possibility of a retinal cell replacement therapy. Moreover, protective effects of MSCs towards RGCs have been demonstrated in an animal model of glaucoma [72].

In case of a macular hole, it is advisable to achieve the contact between the retinal neural epithelium and the RPE, in order to obtain hole closure [89]. Thereafter, adherence of the detached retinal edges to the RPE layer promotes cell migration and proliferation of the overlying retina.

Xuqian et al. in their analysis on animal models concluded that MSCs promote hole closure rate with accelerated healing. Morphological histochemical and OCT observations showed significant differences between repair tissues in eyes receiving MSCs and the reference group, which presented a typical fibrotic scarring [90].

Previous studies have demonstrated that MSCs promote the expression of adhesive factors [97] and extracellular matrix development [98]. In addition, several studies demonstrated the antiapoptotic and protective effects of MSCs, even at the gene level [99, 100]. In addition, MSCs may exert their reparative effects on the retina through material transfer, with improvement in visual function [101, 102].

According to these findings, a possible rationale for future stem-cell therapy may be developed, and failure of macular hole surgery may be explained by long-term detachment of neuroretina from the RPE layer.

In comparison to gene therapy, MSCs provide multiple rescue pathways with a plurality of combined effects. Moreover, in a previous paper published by our group, we observed that the presence of a human retinal pigment epithelial cell-line supernatant helped cells preserve the typical MSC morphology [103]. Therefore, we can hypothesize that RPE can represent an ideal environment in which MSCs can exert their function of cytokines and neurotrophic factors release.

It has been reported that up to 44% of large macular holes remain open after vitrectomy with ILM removal [26] and repeated surgeries in case of failure are associated with a lower closure rate compared with primary surgery [104].

In the only available pilot study, macular hole closure was achieved in six of seven patients who underwent MSC or MSC-Exo therapy, with five patients showing improvements in BCVA. These results suggest that MSCs and MSC-Exos may contribute to hole closure and visual function recovery [91]. MSCs and MSC-Exos can therefore be dedicated to cases of refractory macular holes after first surgery, in which satisfactory results are more difficult to achieve.

Compared with cell suspensions, exosomes are easier to employ, presenting lower immunogenicity and risk of proliferation. It was reported that MSC-Exos have similar protective effects towards the retina after laser-induced lesions and experimental model of uveitis [64, 105].

Since MSC-Exos do not tend to disperse in the vitreal cavity after injection, heavy silicon tamponades and patient positioning may not be relevant to promote their effects. However, the mechanism of MSC-Exo therapy is still not fully understood. It has been suggested that miRNAs carried by MSC-Exos promote neurogenesis and functional recovery [106].

Another issue that must be addressed in larger trials is toxicity of MSCs or MSC-Exo in the treatment of retinal diseases. Among the existing clinical trials, three patients were affected by severe bilateral vision loss after receiving intravitreal injections of autologous adipose tissue derived stem cells, due to severe vitreoretinal proliferation [87] (probably occurred as a result of transformation of injected cells in myofibroblasts-like cells). According to these findings, MSC-Exo therapy may be safer than cell suspension, since cell proliferation is less likely to occur.

Finally, as of today, there is no standardized number and volume for cell injection into the retina. Current clinical trials have injected from 1.68×104 to 3.4×106 cells in a 100–150 μl suspension, but the exact quantity needed still remains to be discovered.

6. Conclusions

The application of mesenchymal stem cells as an adjuvant treatment for refractory and late-stage macular holes can be considered as a promising perspective, in the light of the recent functional and anatomic outcomes in both animal and human trials. Combination of pars plana vitrectomy and MSCs injections or MSCs exosomes application seems feasible, but the evidence regarding their safety needs to be expanded. Nevertheless, autologous mesenchymal stem cells can be extracted from the same patient, which can act both as the donor and the receiving subject, lowering rejection rates and immunological reactions. Furthermore, repeated injections can be performed, if needed. The beneficial effects of MSCs suspensions and exosomes lie in their neuroprotective properties and in the facilitation of macular hole adhesion to the RPE, which promotes healing and closure. These aspects can lead to an effective visual rehabilitation in cases destined to poor results with simple surgery (even if hole closure is achieved). However, MSCs application at the retinal level can lead to unwanted differentiation of transplanted cells with onset of vitreoretinal proliferation, and the presence of preexisting tumors whose growth may be promoted by immunosuppression provided by MSCs represents an important contraindication [107]. Autologous MSCs can be considered safe in terms of immunogenicity and de-novo malignancy development [108]. Finally, long-term clinical trials featuring control groups are still required in order to compare the efficacy of MSCs applications with pars plana vitrectomy and other adjuvant techniques.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Review Article

Fundus Autofluorescence in Lamellar Macular Holes and Pseudoholes: A Review

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Macular pseudoholes (MPHs) and lamellar macular holes (LMHs) have been recently defined according to spectral domain optical coherence tomography (SD-OCT) criteria. A major feature for differentiating an MPH from an LMH remains the loss of foveal tissue. The anatomy of the foveola is peculiar with the macular pigment (MP) embedded in a very thin layer of tissue underlying the internal limiting membrane and mainly constituted of a specialized group of Müller cells and Henle's fibers. Despite the near microscopic resolution (≈5–7 μm) and the capability to visualize the outer retina in detail, SD-OCT may fail to ascertain whether a very small loss of this foveolar tissue has occurred. Blue-fundus autofluorescence (B-FAF) imaging is useful in this respect because even very small loss of MP can be identified, suggesting a corresponding localized loss of the innermost layers of the foveola. A definition of MP loss would help differentiating an LMH from an MPH where B-FAF imaging will be negative.

1. Introduction

Macular pseudoholes (MPHs) and lamellar macular holes (LMHs) have been defined in many different ways [1, 2], but the common denominator has always been whether or not a loss of foveal tissue is present. Even in the last classification by the International Vitreomacular Traction Study Group [3], MPHs are characterized by the absence of foveal tissue loss, whereas in LMHs, a partial defect of the inner fovea should be present.

Clinically, by fundus examination, both MPHs and LMHs have a similar appearance with a round and well-circumscribed reddish lesion at the center of the fovea [1, 4–11]. Functional tests, such as the Watzke-Allen test [12] and microperimetry [13], in which no scotoma is detected in either MPH and LMH, are not useful for differentiating between these conditions, and both clinical entities can lead to similarly impaired vision (median 20/40) [1–4].

Time domain (TD) [1, 7–11, 14] and spectral domain (SD) [2, 3, 15, 16] optical coherence tomography (OCT) have expanded our knowledge about pathogenesis, morphology, and progression of these clinical entities. However, despite their near-microscopic resolution (≈5–7 μm) and the capability to visualize the outer retina in detail, SD-OCT may fail to ascertain whether a very small loss of foveal tissue has occurred. Blue-fundus autofluorescence (B-FAF) imaging is useful in this respect, especially in early LMHs when there is a lack of evident break in the inner fovea and dehiscence of the retina [2, 14], and the diagnosis of MPHs or LMHs remains a matter of speculation.

2. Pathogenesis

The pathogenesis of MPHs and LMHs is not fully understood. It has been hypothesized that an MPH is attributable to the centripetal contraction of an epiretinal membrane [4]. In contrast, an LMHs is thought to be the result of an abortive process in the formation of an FTMH. Posterior vitreous detachment is the main initiating process of the latter, but epiretinal membrane contraction has been suggested as a likely secondary factor [2, 16, 17]. This mechanism is also supported by two findings: (i) 62% to 89% of LMHs may present with an epiretinal membrane [1, 2]; and (ii) pseudo-opercula, suggestive of an aborted macular hole, have been reported in only 24% of patients with LMH [1]. Therefore, it seems that the pathogenesis of LMH cannot

simply be attributed to an abortive anteroposterior traction, the classic process in FTMH formation.

3. Anatomy

In a normal fundus, the distribution of fundus autofluorescence (AF) is diffuse, with decreased intensity at the optic nerve head, the retinal blood vessels, and the macula [18, 19]. Macular AF is attenuated by the presence of luteal pigment, which has a very high density in the fovea (Figure 1(a)). Originally, the foveolar macular pigment was thought to be located in the Henle fiber layer (Figure 1(b)) [20]. It has been recently demonstrated that (in addition to the typical "z-shape" Müller cells of the fovea) there are 25–35 unique Müller cells in the foveola [21]. These Müller cells are suggested to form the "Müller cell cone," i.e., the inverted cone-like structure that overlies the area of high photoreceptor density in the primate foveola [22]. Inner processes and nuclei of these specialized Müller cells together with the axons of the highly packed foveal cones constitute the very thin layer of tissue immediately below the foveolar internal limiting membrane (ILM) (Figure 1(c)); that is, the place where the foveolar macular pigment is located at high density [21]. The density of the macular pigment decreases continuously from the center to the periphery of the foveola. The stalk of the "Müller cell cone" as well as Müller cell processes in the nerve fiber layer, inner plexiform layer (IPL), outer plexiform layer (OPL), and Henle fiber layer (HFL) in the central fovea walls also contain the macular pigment, albeit at lower density [20, 21]. Any foveal defect, including an LMH that spares the photoreceptors [2], may alter the degree of foveal AF by decreasing the amount of masking luteal pigment and thus increasing the foveal AF.

4. Imaging Techniques

4.1. Slit-Lamp Biomicroscopy. Slit-lamp biomicroscopy in patients with MPHs and LMHs may simply show the common feature of a round, reddish lesion at the center of the macula, but it is not sensitive enough to detect a small loss of foveal tissue, which is present in LMHs with preserved visual acuity. Additionally, the presence of an epiretinal membrane is not definitive in the differential diagnosis of LMH and MPH; as mentioned above, 62% to 89% of patients with LMH may have an associated epiretinal membrane [1, 2], which will always be present in MPH [4].

Haouchine et al. [1] showed that only 28% of LMH cases diagnosed with OCT were diagnosed as LMH on fundus examination. Likewise, Witkin et al. [2] reported that only 37% of LMH cases diagnosed using ultrahigh-resolution OCT were detected clinically on fundus examination. These data show the limitation of slit-lamp biomicroscopy in the diagnosis of LMH.

4.2. Optical Coherence Tomography. The criteria for the OCT diagnosis of MPH and LMH were originally defined by Haouchine et al. [1] and Witkin et al. [2] and subsequently confirmed by the International Vitreomacular Traction Study Group [3].

The four basic criteria for the OCT diagnosis of LMH are an irregular foveal contour, a break in the inner fovea, a dehiscence of the inner foveal retina from the outer retina, and an absence of a full-thickness foveal defect with intact foveal photoreceptors. Further confusion was added to the debate by a later assertion that LMH with lamellar cleavage of their edge remain pseudoholes because there is no loss of foveal tissue as shown by SD-OCT [16]. It is clear that one of the major problems encountered in an OCT diagnosis of a foveal defect is the difficulty of determining with certainty whether there is loss of retinal tissue. Furthermore, if there is loss of foveal tissue, it is difficult to determine its anatomic location. The reason for that became apparent looking at the last SD-OCT classification of posterior ocular layers by the International Nomenclature Panel [23] who took into consideration the findings on Henle's fibers imaging [24, 25]. As already mentioned, the foveal center is made of a thick photoreceptor layer and a specialized group of Müller cells [21]; Henle's fibers are reduced to an extremely thin layer (Figure 2(a)). The entry position of the SD-OCT beam through the pupil must vary to reliably identify Henle's fibers temporal and nasal to the fovea [24, 25] (Figures 2(b) and 2(c)). The acquired images correlate beautifully with histologic specimens (Figures 2(a)–2(d)), but the inner foveolar layers remain difficult to visualize in normal eyes (Figures 2(b)–2(d)). If a LMH is suspected (i.e., loss of foveal tissue), it is even more difficult to determine whether or not this thin layer of tissue under the foveolar ILM containing the macular pigment is missing (Figures 3(a) and 3(c)).

Therefore, because of the peculiar reflectivity of the innermost retinal layers in the foveola, OCT imaging might not be sensitive enough to detect early loss of foveal tissue, that is, an initial LMH.

4.3. Fundus Autofluorescence. The accuracy of this technique has been reported to be comparable to that of fluorescein angiography [26, 27] for the diagnosis of FTMH.

Fundus autofluorescence (AF) has challenged the current OCT concepts regarding the differentiation between MPH and LMH [1–3, 5, 14, 16]. Thus, foveal lesions with SD-OCT features of MPH (i.e., irregular foveal contour with steep edges and near-normal central foveal thickness with apparent no loss of tissue) often demonstrate increased foveal AF (Figures 4(a) and 4(b)). It was already reported in a study of patients with residual retinal tissue at the bottom of the fovea classified as MPH and LMH according to the OCT profiles established by Haouchine et al. [1] that the foveal AF intensity did not differ between these two conditions [14], where increased foveal AF was found. It could be argued that increased foveal AF could be the result of dislocated macular pigment due to the tangential traction in the fovea exerted by an epiretinal membrane. There are two reasons that seem to oppose this hypothesis: first, the lack of increased AF signal in patients with idiopathic epiretinal membrane and macular pucker (Figures 5(a) and 5(b)). Second, the presence of increased foveal AF signal in eyes with an abnormal foveal

Figure 1: (a) Normal distribution of fundus AF. (b) Frozen section through the fovea of a rhesus monkey. Yellow macular pigment has higher concentration along Henle's fiber layer (courtesy of D. Max Snodderly, PhD, Professor of Neurobiology, College of Natural Sciences, Department of Nutritional Sciences, University of Texas, Austin, USA). (c) Reprinted from Syrbe et al. [21]. Schematic representation of the Müller cell morphology in the peripheral retina (A), foveal slope and parafovea (B), and foveola (C). The somata of Müller cells in the foveola lie in the innermost layer which is composed also by their thin inner processes forming an elaborated plait along and below the internal limiting membrane (ILM).

contour on OCT and no signs of tangential traction in the macula (Figures 6(a) and 6(b)). Lipofuscin-laden RPE generates fundus AF [18], which in the macula is attenuated by the luteal pigment. Most of this pigment in the foveola resides below the ILM, among inner processes/nuclei of specialized Müller cells and axons originating from the foveolar cones [21]. It has been recently demonstrated that in eyes with LMHs, a strong correlation exists between the diameters of the holes measured with B-FAF and those measured at the OPL level with OCT [28]. This may indicate that indeed a loss of foveolar tissue containing the macular pigment at the OPL level in the Müller cell inverted cone is likely.

Thus, even very thin foveal defects, such as those affecting only the innermost part of the foveola sparing the photoreceptors, as in initial LMH, may increase the foveal AF. Therefore, AF findings (i.e., increased AF at the fovea) in patients with MPH and LMH as defined by SD-OCT suggest that in both conditions there could be a loss of foveal tissue.

5. Clinical Implications of AF Findings

The lack of a significant difference in foveal AF between LMH and MPH, as diagnosed by means of OCT imaging, raises questions concerning the validity of this OCT differentiation. If the loss of foveal tissue is considered for the diagnosis of LMH, it must be acknowledge that determining a very thin loss of tissue in the foveola may be difficult using a SD-OCT. There are two options for ascertaining such a type of loss: A direct way would imply a direct visualization of the tissue loss by OCT, with the previous limitations underlined above. An indirect way would be to determine the loss of macular pigment, which is located in the "Müller cell inverted cone" in the foveola, by means of fundus AF. An absence or decrease of the macular pigment would increase foveal AF. The anatomical localization of the macular carotenoid pigments is a complex and controversial subject with evidence suggesting that there is a pigment in both the Müller cells and the cone axons of the fovea. As Snodderly beautifully showed (Figure 1(b)) [20], the macular pigment is present not only under the foveal ILM but also deeper toward the foveal cone fibers and in the outer and inner plexiform layers. Carotenoid pigments have been demonstrated in surgically removed lamellar hole-associated epiretinal proliferation (LHEP) which is supposed to be constituted, at least in part, by Müller cells [29]. Syrbe et al. [21], more recently, could not ascertain with certainty the exact location of the macular pigment if not confirming that

Figure 2: (a) Mammalian foveal histology. Henle's fiber layer continues in the foveal pit as a thin layer (arrows) (courtesy of Roger C. Wagner, PhD, Professor Emeritus of Biological Sciences, University of Delaware, Newark, Delaware, USA). (b, c) Healthy young macula. Enhanced visualization of Henle's fibers shifting the entry position of the SD-OCT beam through the pupil nasal (b) and temporal (c) to the fovea: the thin layer of fibers in the fovea remains undetected on horizontal B-scan. (d) Normal fovea. Acquired images correlate beautifully with histologic specimens (a), but the innermost layers of the retina in the foveola remain difficult to visualize in normal eyes. A less reflective layer opposite to the well-defined hyperreflective layer of Henle's fibers may be seen as continuous in the center (GCL: ganglion cell layer; IPL: inner plexiform layer; INL: inner nuclear layer; OPL: outer plexiform layer (dendritic); HFL: Henle's fiber layer (axonal OPL); ONL: outer nuclear layer).

Figure 3: (a, b) SD-OCT revealing an irregular foveal contour without a break in the inner fovea or a dehiscence of the inner foveal retina from the outer retina. Enhanced visualization of Henle's fiber layer fails to determine whether or not a loss of tissue has occurred in the center. (c) Corresponding fundus AF image showing a lack of macular pigment. A diagnosis of LMH should be made.

(a) (b)

Figure 4: (a) SD-OCT demonstrating an epiretinal membrane, irregular foveal contour with steep edges, no break in the inner fovea or dehiscence of the inner retina from the outer retina. According to OCT criteria, a diagnosis of MPH should be established. Enhanced visualization of Henle's fiber layer fails to determine with the certainty if there is a loss of tissue in the center of the foveola. (b) Corresponding fundus AF image showing a well-defined lack of central macular pigment. A diagnosis of LMH should be made.

(a) (b)

Figure 5: (a) Near infrared SD-OCT horizontal scan and (b) corresponding AF image in a case of epiretinal membrane with tangential tractions but no increased AF at the fovea. A thin layer of residual tissue is visible in the foveolar center (arrow). There is no lack of macular pigment.

(a) (b)

Figure 6: (a) B-FAF OCT image showing increased autofluorescence at the fovea (vertical lines) corresponding to the thinnest part of the foveal pit on structural OCT. (b) Same patient seven years before. A posterior vitreous detachment is visible. To be noted, remnants of foveal tissue attached at the posterior hyaloid.

it is inside the Müller cell inverted cone. That is an important clue for diagnosing tissue loss in the fovea because an increased B-FAF in the fovea would imply the absence of a masking element that should be normally there.

Whether or not this can be used for establishing a differential diagnosis between LMH and MPH remains to be further investigated. However, given the uncertainty encountered in the direct diagnosis of foveal tissue loss with OCT, B-FAF imaging may be of help as to this purpose.

An accurate diagnosis of FTMH, LMH, and MPH is important to determine the proper surgical treatment of these lesions. Different options may be selected according to

the OCT and fundus AF imaging findings. For instance, in the absence of foveal AF, the integrity of the foveal tissue is almost certainly confirmed. Therefore, it is likely that removal of the epiretinal membrane alone is all that is needed in such cases. However, if foveal AF is present, a loss of foveal tissue has very likely occurred, and the decision to operate will depend on many factors, such as the residual visual acuity and progression of signs and symptoms.

Additional Points

Fundus AF imaging is becoming increasingly important in the examination of many macular diseases, including LMH and MPH. In both, a similar degree of functional loss may occur. In such cases, an increased AF signal at the fovea signifies a loss of foveal tissue that is the macular pigment.

Conflicts of Interest

The author declares that there are no conflicts of interest.

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