Graefe's Archive for Clinical and Experimental Ophthalmology (2021) 259:1685–1694
https://doi.org/10.1007/s00417-020-04995-z

REVIEW ARTICLE

Macular microhole and foveal red spot syndrome: a critical review of the literature

James H. Garcia[1] · Mark Johnson[2] · Gaurav Shah[3] · Carsten H. Meyer[4] · Gustavo B. Melo[5] · Eduardo B. Rodrigues[6]

Received: 28 July 2020 / Revised: 11 October 2020 / Accepted: 23 October 2020 / Published online: 2 November 2020

Abstract

Purpose The purpose of this article is to review the literature on nomenclature, natural history, clinical features, diagnosis, management, and prognosis of both macular microhole (MMH) and foveal red spot syndrome (FRS).

Methods A PubMed primary literature search (February 1, 2020) utilizing the terms macular microhole, foveal red spot syndrome, and outer retinal hole was conducted. All chosen articles were case reports or case series. Articles qualified for inclusion if they documented symptoms, imaging findings, or followed patients longitudinally.

Results A total of 14 studies from 1988 to 2019 that evaluated either MMH, FRS, or both were included in the review. No comparative study between the two defects was found. Studies often used the terms FRS and MMH interchangeably to reference both partial- and full-thickness lesions of the macula. Spectral-domain optical coherence tomography (SD-OCT) was most frequently able to identify these lesions and revealed an absence of all neural retinal layers from the inner limiting membrane (ILM) to the retinal pigment epithelium (RPE) in the full-thickness lesions while the partial-thickness lesions most often involved the photoreceptor layer (PRL) and less frequently the external limiting membrane (ELM). OCT revealed that vitreomacular traction (VMT) was involved in the natural history of both FRS and MMH for a significant subset of patients.

Conclusion The terms MMH and FRS have been used interchangeably in the literature. Advances in OCT have revealed that MMHs and FRSs are distinct but sometimes overlapping entities. We suggest that MMH and FRS are similar entities defined as one or more sharply defined lesions in the fovea of the eye < 150 μm in size. MMHs are a *full-thickness* defect of the entire neuroretina at the center of the foveola while FRSs are *partial-thickness* lesions. Current literature suggests that there may be subtle differences in the pathogenesis, clinical features, and diagnosis between MMH and FRS; however, prognosis and management for both are favorable. Lastly, we suggest that the terms outer lamellar macular microholes and full-thickness macular microholes may be the more appropriate terminologies to refer to FRS and MMH, respectively.

Keywords Foveal red spot syndrome · Macular microhole · Foveal red spot · Macular hole · Outer foveal defect · Outer lamellar macular microhole · Full thickness macular microhole

This article is part of a topical collection on Macular Hole

The primary literature search was conducted at St. Louis University Hospital in the department of ophthalmology.

✉ James H. Garcia
james.garcia@health.slu.edu

[1] Saint Louis University School of Medicine, 1755 S. Grand Blvd., St. Louis, MO 63104, USA

[2] Kellogg Eye Center, Department of Ophthalmology and Visual Sciences, University of Michigan Medical School, Ann Arbor, MI, USA

[3] Department of Ophthalmology, The Retina Institute, St. Louis, MO, USA

[4] Department of Ophthalmology, Augenärzte Kammanneye, Davos, Switzerland

[5] Department of Ophthalmology, Federal University of Sao Paulo, São Paulo, Brazil

[6] Department of Ophthalmology, Saint Louis University School of Medicine, St. Louis, MO, USA

Key messages

- Macular microhole and foveal red spot syndrome have historically referred to a foveal defect presenting as a minute red spot on fundus exam with symptoms including decreased visual acuity and central scotoma.
- However,the terms macular microhole and foveal red spot syndrome have been used inter-changeably in the literature to refer to separate entities.
- Advances in OCT have revealed that MMHs and FRSs are distinct but sometimes overlapping entities.
- With the wide spread use of OCT, the terms outer lamellar macular microholes and full-thickness macular microholes may be more appropriate terminology to refer to FRS and MMH, respectively.

Introduction

Macular microhole was originally coined by Cairns and McCombe in 1988 following a series of prior reports describing small holes in the macula of soldiers suspected of prolonged sungazing [1–3]. The term macular microhole (MMH) has since been used to refer to retinal defects < 150 μm with evidence of a partial- or full-thickness hole. They were considered a distinct entity from macular holes due to their small size, non-progressive nature, and minimal symptoms [4]. In 2003, foveal red spots (FRS) was identified as a separate entity from macular holes, defined as small, well-defined apparent intraretinal lesions with an associated red spot on slit-lamp exam [5]. The terms MMH and FRS were developed prior to the widespread use of optical coherence tomography (OCT) [4].

Since the first publication of OCT in the 90s, different generations of OCT, time domain (TD), spectral-domain (SD) OCT, swept-source OCT, advanced optics OCT, and OCT angiography have been developed [6]. Several studies utilizing newer generation OCT to evaluate both MMHs and FRS have revealed previously undetected microdefects [7]. This article attempts to provide a review of our current understanding of MMHs and FRS and to clarify the nomenclature utilized between the two.

Review of the literature: Nomenclature

In the literature, the terms MMH and FRS have both been used to refer to foveal or juxtafoveal single red lesions < 150 μm in size with varying involvement of retinal layers. The original study that identified MMHs hypothesized that the lesion was likely confined to the internal limiting membrane (ILM) and neuroepithelium located near the center of the capillary free zone of the fovea centralis [1]. Retinal pigment epithelium (RPE) was believed to be uninvolved given the absence of pigment changes on fundoscopic exam [1]. Wolf and Wolf-Schnurrbusch evaluated 14 patients with MMH and confirmed with an argon laser aiming beam that all patients had a full-thickness hole [7]. Both Cairns and Reddy's studies were prior to the advent of OCT, and therefore, the extent of retinal involvement was not able to be confirmed [1, 8].

In 2005, Zambarakji et al. utilized two generations of OCT to evaluate MMHs. Five patients were examined using both OCT 2 and OCT 3, with 80% of those patients demonstrating a microdefect in the outer retina and/or RPE on OCT 3 but not on OCT 2 [9]. In total, 15 out of 18 eyes (83%) showed similar defects when evaluated by OCT 3. In contrast to Reddy et al., none of the patients in this study were found to have a full-thickness hole [8]. This was further supported by Emerson et al. who utilized OCT 3 to evaluate suspected MMHs and demonstrated a partial-thickness defect involving the posterior retina or RPE in 4 of 5 cases [4]. It is important to note that of the 27 patients that did not undergo OCT 3, varying involvement of the retina ranging from partial- to full-thickness were suspected based on biomicroscopy. All subsequent studies have incorporated OCT.

In 2003, Douglas et al. reported on 13 patients with foveal or juxtafoveal crimson red lesions approximately 100 μm in size or smaller [5]. Several OCT scans were conducted on 7 eyes with foveal lesions and were unrevealing. Absence of a lesion on OCT led the authors to conclude that foveal red spots were not associated with any abnormality in the retinal architecture [5]. Since then, several authors have suggested that the term FRS may have been used to refer to MMHs [4, 9]. This confusion likely stems from the use of TD-OCT, which is often unable to detect these minute lesions, in contrast to SD-OCT.

In a review of posterior vitreous detachment (PVD) sequelae, Johnson suggests a more precise definition of MMH and FRS: MMH is defined as a *full-thickness* macular defect (< 150 μm) with sharp, flat edges associated with a stage 2 PVD and no residual vitreomacular traction, while FRS is defined as a tiny (< 100 μm) red lesion in the central or paracentral fovea that is not a full-thickness defect [10]. Johnson et al. further notes that FRS may be associated with small breaks

in the photoreceptor layer, and therefore, prior studies evaluating MMHs were often describing FRS [5, 9, 10]. Various reports continue to refer to MMHs with partial-thickness involvement or include patients with both partial- and full-thickness defects [11–13] . On the other hand, others utilize separate terminology such as "outer retinal hole," "outer retinal cyst," or "macular cavitation" in order to clearly describe the defect they refer to [14, 15].

It is imperative to have precise definitions of both MMH and FRS to prevent conflating these terms. Accurate and consistent terminology will facilitate future studies to better uncover differences in prognosis, management, and clinical features if any truly exist. We suggest that terms MMH and FRS refer to similar entities, defined as one or more sharply defined lesions in the fovea of the eye < 150 μm in size. MMH is a *full-thickness* defect of the entire neuroretina at the foveola, while FRS is a *partial-thickness* defect involving the outer retina (Figs. 1, 2, and 3a). The rest of this article will provide a review of our current understanding of both MMH and FRS, utilizing the above definition regardless of the terminology used by the original article.

Epidemiology

To date, there have been no studies that have been robust enough to draw valid conclusions on the epidemiology of either MMH or FRS. This is likely a result of their infrequency and relatively recent discovery. Several older reports prior to the widespread use of OCT likely include both MMH and FRS. This variance across studies prevents accurate statistical analysis. Based on current data, neither MMH nor FRS appears to show a gender preponderance (Table 1). The mean age of affected patients ranges from 34.6 to 60.7 years after excluding single-patient reports (Table 1). The incidence rate and racial predispositions remain largely unknown. Subsequent studies will benefit from the inclusion of racial demographics in order to determine if any predispositions do exist.

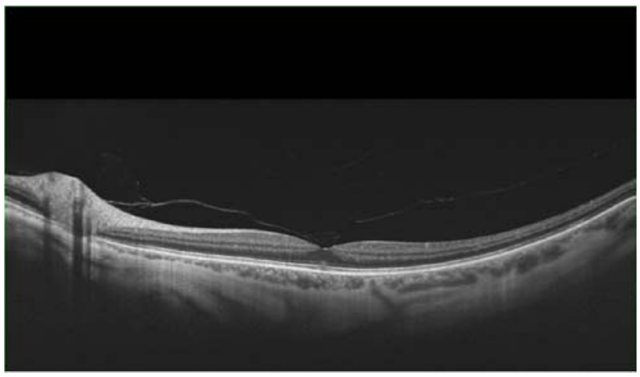

Fig. 1 OCT imaging of a 62-year-old-male with a partial-thickness outer foveal defect associated with vitreofoveal traction from a stage 1 PVD

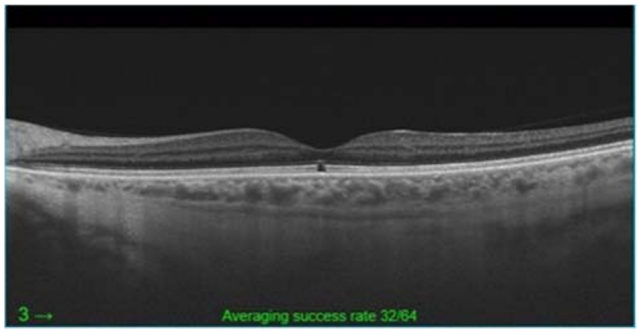

Fig. 2 OCT imaging of a 49-year-old-female with a unilateral partial-thickness outer foveal defect in the absence of ongoing vitreofoveal traction. No history of trauma or sungazing was reported. The defect may be the result of an undetected macular hole undergoing closure after complete PVD

Pathogenesis

Many theories have been proposed regarding the pathophysiology of MMH and FRS. Initial reports of MMH were in association with sungazing but it was later revealed that these were self-inflicted solar burns [2, 3, 22]. In the original article by Cairns and McCombe, a history of sungazing was absent in all cases of microholes [1]. Several studies since then have found no association with sungazing and some have completely excluded patients with any history of sungazing in their studies [4, 8, 9].

Improvements in OCT imaging have provided strong evidence suggesting that most FRSs are caused by vitreofoveal traction. Yildirim et al. and Ooto et al. each found that a significant portion of patients with FRS had either a concomitant PVD or recent spontaneous release of vitreomacular traction (VMT) [12, 21]. Both authors suggest that a subset of FRS is due to VMT. Further evidence for a vitreous traction patho-mechanism comes from the largest case series to date, which evaluated 46 FRS with SD-OCT [10]. A statistically significant correlation between the size of the defect as measured by the horizontal diameter and volume, and the presence of vitreomacular interface abnormality (VMIA) was noted. Further individual case studies have also posited vitreous traction as the etiology of FRS, with two cases in association with PVD and one with focal choroidal excavation [17, 20, 23].

Similarly, in eyes with full-thickness MMH, macular PVD is a nearly universal finding and points to vitreous traction as the etiology in most patients [8, 17, 18]. Johnson et al. suggests that MMH develops as a result of high anteroposterior tractional stress during stage 1 PVD [10, 24]. The unusually high traction stress results from a tiny vitreofoveal adhesion size and results in the sudden development of a full-thickness defect as a small piece of foveal tissue (operculum) are avulsed during vitreofoveal separation. Because the defect is

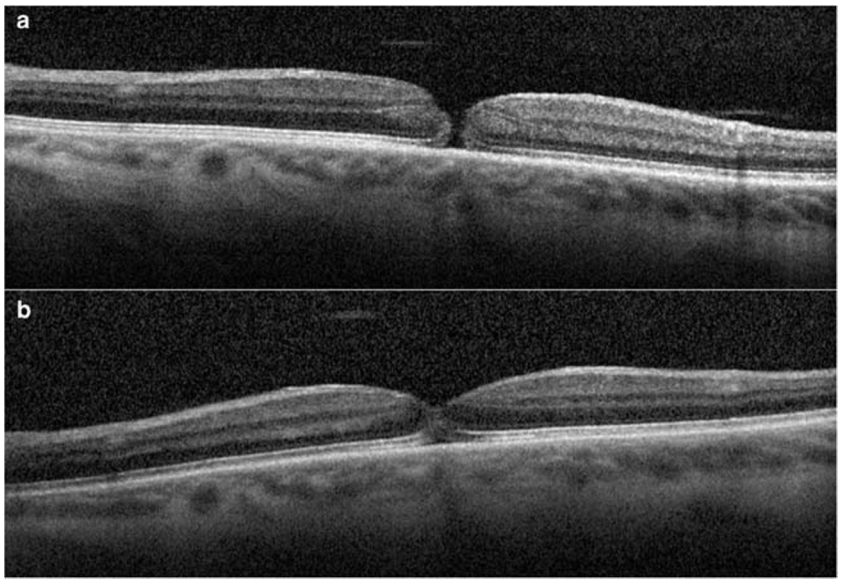

Fig. 3 OCT imaging of a 49-year-old man with a MMH induced by blunt trauma (**a**). The posterior hyaloid remains attached throughout the macular area. Two months later, OCT imaging shows that the MMH is spontaneously healing (**b**)

small and all vitreous traction has been relieved, spontaneous healing of the microhole typically occurs. Johnson further observed that an outer foveal defect characteristic of FRS can be seen during healing of a MMH but can also be seen in association with traction from a stage 1 PVD in which no full-thickness defect develops [10, 24]. Moreover, vitreous traction associated with blunt trauma or whiplash has been previously reported to produce similar-appearing lesions [25–27]. Both Cairnes and McCombe and Emerson and colleagues state that a history of trauma was noted in several patients included in their studies [1, 4]. In summary, current evidence and our clinical observations suggest that both MMH and FRS are typically caused by vitreofoveal traction prior to or coincident with vitreofoveal separation, either as part of age-related PVD evolution or associated with trauma. It appears that the stability of symptoms and good prognosis of most patients with MMH and FRS are in part due to the spontaneous healing of these small defects that typically occurs following the relief of vitreous traction.

With respect to both MMH and FRS, mechanical stress of Muller cells may be involved in their pathophysiology. The fovea has a unique composition with stabilization of tissue structure coming solely through microtubules and intermediate filaments of Muller cells that span through Henle's fiber layer (HFL) and outer nuclear layer (ONL) [28]. This stabilization provides resistance to both anteroposterior and tangential tractional forces. Tractional disruption of the inner Muller cell layer of the fovea is believed to result in the formation of macular holes [29]. A similar mechanism may play a role in the formation of both MMH and FRS.

Although most cases of FRS and MMH appear to be caused by anteroposterior vitreous traction, other factors may be responsible in a subset of cases (Fig. 2). For example, outer foveal defects are commonly observed during the healing of prior idiopathic macular hole or MMH. Tangential traction forces associated with epiretinal membrane also occasionally induce outer foveal dehiscences or small full-thickness holes (Table 2). Moreover, cases of FRS have been confused with other pathologies, such as solar maculopathy, that may produce an outer foveal facet [14]. These will be discussed more extensively below.

Clinical features

MMH and FRS present similarly with patients most frequently noting a tiny scotoma or a change in visual acuity (VA), typically without metamorphopsia (Table 1). Less frequently, patients may report new floaters, micropsia or macropsia, or no symptoms. The symptoms usually affect one eye but bilateral involvement may occur as well (Table 1). Lesions may be discovered incidentally, with a minute red or yellow lesion noted on a biomicroscopic examination of the macula. In these cases, further evaluation may reveal a scotoma that the patient may not have noticed [9]. If symptomatic, many reports state that the onset appears to be acute in nature. The mean duration of symptoms prior to presentation ranges from several weeks to several years and symptoms are generally non-progressive (Table 1).

Early reports of MMH and FRS stated that all patients presented with a small red lesion on fundus examination. In 2014, Vasishnavi et al. found that only 24 out of 46 eyes (52%) with confirmed FRS on OCT had a red spot on initial examination [11]. In a series of 3 patients with FRS, Yildirim et al. found that 1 of 3 patients had a characteristic red defect on color fundoscopy [21]. These recent findings are likely the result of the growing awareness of the clinical presentation of

Table 1 Current FRS and MMH studies

Author name	Year	Defect	Size (μm)	Patient (n)	Eyes (n)	Avg age (years)	Sex	Symptoms	Sx duration (mo.)	Mean initial VA	Mean final VA	Follow-up (months)	PVD	OCT
Cairns et al. [1]	1988	MMH and FRS	50–150	17	18	39.9	8 M, 9 F	9 Sc, 7 VA, 4 Mm, 2 Asx	8.8	20/35	20/40	18	1 Inc	N
Reddy et al. [8]	1996	MMH	50–133	14	14	54.7	6 M, 8 F	12 Sc, 5 Mm, 1 floaters	NR	20/30	20/25	23.4	14 Inc, 5 Comp	N
Douglas et al. [5]	2003	FRS	< 100	13	18	34.6	6 M, 7 F	7 blurry vision, 1 monocular diplopia, 2 distorted vision, 1 VA, 1 Asx, 1 Asthenopia	NR	20/24	20/25	58	NR	Y (4)
Zambarakji et al. [9]	2005	FRS	50–100	22	24	50	11 M, 11F	14 Sc, 8 Mm, 2 Asx, 2 micro/macropsia	36	20/34	20/33	48	7 Inc	Y (18)
Johnson [16]	2005	MMH	~50	3	4	55	1 M, 2F	NR	NR	20/20	NR	34.75	4 Inc → 3 Comp	Y (2)
Lai et al. [17]	2006	MMH	137	1	1	62	2 F	VA, floater	0.5	20/40	20/30	0.75	1*	Y
Emerson et al. [4]	2007	MMH and FRS	35–150 (88 ± 4)	31	35	44 ± 3	17 M, 14 F	13 Sc, 14 VA, 3 distortion, 1 floaters, 3 Asx	16 ± 4	20/30	20/32	41 ± 10	9 of 27*	Y (18)
Camaroy et al. [18]	2011	MMH	< 150	1	1	72	1 M	VA	NR	20/40	20/40	2	1 Comp	Y
Gella et al. [13]	2012	FRS†	48–385 (163 ± 99)	11	12	56.1 (± 15.4)	5 M, 7 F	2 VA, 1 Mm, 7 Asx	NR	0.15 ± 0.17 logMAR	NR	NR	4 of 12*	Y
Vasishnavi et al. [11]	2013	FRS	79.33 ± 15.29	39	46	50.25	21 M, 8 F	NR	19.44	0.117 (0.21) log MAR	Unchanged	11.67 ± 3.63	26 Inc	Y
Yu et al. [19]	2015	FRS	38	1	1	57	1 M	Sc	2	20/25	NR	NR	1 Inc	Y
Fukumoto et al. [20]	2015	FRS		1	1	38	1 F	Mm	3	20/25	NR	NR	1 Inc	Y
Ooto et al. [12]	2014	FRS	NR	12	14	59.4 ± 11.5	5 M, 7 F	NR	NR	0.082 ± 0.087 log MAR	−0.041 ± 0.081	26.9 ± 11.4	3 Comp, 6 Inc	Y
Yildrim et al. [21]	2019	FRS	122–156 (139.3)	3 169	3 192	60.7	1 M, 2F 83 M 77F	1 VA, 2 Mm, 1Sc		20/30		32	3 Inc	Y

Studies currently available in the literature that have examined FRS and MMH. The defects listed in the table were identified utilizing the definition provided in this review, regardless of the original article's listing. Visual acuity is based on far distance. * Extent of PVD not specified; † study included patients with defect > 150 μm

Sc scotoma, *Mm* metamorphopsia, *Asx* asymptomatic, *NR* not reported, *VA Visual Acuity*, *Inc* incomplete, *Comp* complete

Table 2 Proposed pathogenic mechanisms of MMH and FRS

1. Mechanical forces
   a. Anteroposterior traction
      i. Vitreomacular traction
         1. During incomplete (stage 1) PVD
         2. During vitreofoveal separation
         3. Associated with trauma
   b. Tangential traction (e.g., ERM)
2. Healing/closure of prior macular hole*

* Closure of prior macular hole or MMH may result in FRS

these lesions and use of OCT regardless of findings on slit-lamp exam (SLE). It is important to reiterate that both of these reports only examined patients with partial-thickness FRS, and therefore, the absence of a red spot cannot confidently be extended to MMH.

Diagnostic tools: imaging and OCT findings

Proper imaging is crucial in the evaluation of both FRS and MMH. The lesions are often detected on slit-lamp biomicropscopy as small (< 150 μm horizontal width at the narrowest point), well-defined red lesions at the fovea [8, 30]. Some reports of MMH state that the lesion was identified as a 'small yellow spot' on fundoscopic exam [17]. More recently, only 24 out of 46 eyes (52%) with confirmed FRS on OCT had a red spot on examination. In these cases, multicolor or infrared reflectance imaging may be helpful to detect the lesion; however, diagnosis should ultimately rely on OCT. (Fig. 4) [19].

Fluorescein angiography (FA) has been utilized to evaluate MMH and FRS and was frequently unable to detect any defect. Reddy et al. found corresponding window defects in only 3 out of 7 patients with full-thickness MMH [8]. Emerson et al. showed that 19/19 eyes with suspected FRS and MMH had no foveal transmission defect on FA [4]. Similarly, Douglas et al. found no defect on FA in 18 eyes evaluated for suspected FRS [5]. Fluorescein angiography appears to yield inconsistent findings in both MMH and FRS.

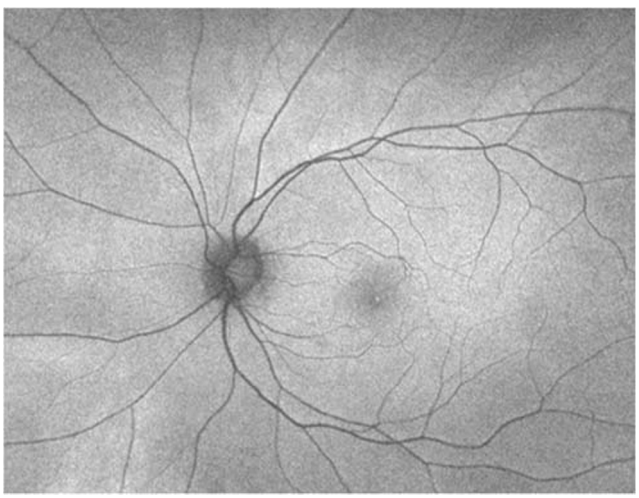

Fig. 4 Infrared reflectance imaging detected a microlesion later confirmed to be FRS on OCT. Initial SLE imaging was unable to detect lesion

Microperimetry has also been used to evaluate FRS. In a study involving 12 patients, a statistically significant negative correlation between the diameter of the defect and the retinal sensitivity of the area was discovered [13]. It is important to note that 4 of the 12 patients included in this study had a defect > 150 μm, and no clear distinction was made between full- and partial-thickness involvement. A report of a single patient with FRS found a 3- to 4-dB decrease in retinal threshold in the corresponding lesion when compared to the surrounding normal macula [19]. Microperimetry may therefore be useful in detecting FRS if others are inconclusive. Its utility in MMH has not been evaluated but is likely similar.

More recent articles have focused on the specific layers and extent of the retina involved in FRS and MMH by OCT assessment (Figs. 1, 2, and 3a). MMH is by definition a full-thickness foveal break with an absence of all neural retinal layers from the ILM to the RPE [24]. Often, these are rectangular in shape and well defined. The status of the vitreoretinal interface in these eyes is important to note [8, 17, 18].

In contrast, FRS has been found to involve primarily the PRL with potential involvement of the ELM. In a report on 12 patients with FRS, a series of SD-OCT scans were conducted on each patient which revealed involvement of the IS/OS and COST line with an intact RPE in all patients [12]. Gella et al. found 100% PRL involvement and 33% ELM involvement in 12 eyes [13]. However, the latter study utilized one SD-OCT scan to evaluate the patients. RPE involvement was reported in some patients but this is likely the result of secondary atrophic effects. As in MMH, varying vitreoretinal interface abnormalities can be seen and should be noted [4, 9, 11, 19].

Studies have consistently revealed that newer generation OCT machines have a higher rate of detecting retinal defects in both MMH and FRS [4, 9, 19]. The increasing evidence suggests that OCT is likely the most important modality for evaluating these defects. A 2015 report of a single FRS case suggests that high-density B-scans of 11 μm may better detect these lesions in the retina when compared to low-density scans on regular SD-OCT [19]. Further, swept-source OCT may better detect vitreous abnormalities compared to standard SD-OCT [19]. While other modes of imaging, including advanced optics and microperimetry, were also able to detect the lesions, the use of these modalities did not offer any additional diagnostic insight [11, 19]. Regular SD-OCT imaging using the entire macular cube scan and 3D imaging appears to be sufficient to detect the majority of FRS and MMH lesions. Further work-up may only be necessary if initial imaging is unremarkable.

Differential diagnosis

MMH, FRS, and macular holes (MH) have many similar features and may be confused by clinicians. Stage 1 MH presents as a yellow spot or ring on a biomicroscope and is always associated with VMT with either inner or outer retinal changes, and affected individuals are typically asymptomatic [31, 32]. Stage 1 MH is most similar to FRS; however, FRS typically presents as a red lesion on fundus exam, may or may not have evidence of vitreofoveal involvement, involves only the outer retina, may be the result of a healing larger MH or MMH, and typically presents with symptoms. Stage 2 MHs, which are most similar to MMHs are full-thickness defects ≥ 250 μm, always have VFT, and present with metamorphopsia and loss of central vision [31, 32]. Both stage 1 and 2 MHs have a less favorable prognosis when compared to MMH, with progression noted in 40% of stage 1 and over 75% of stage 2 holes [31, 32] In summary, FRS and MMHs are typically distinguished from stage 1 and 2 macular holes, respectively, by their abrupt onset, small size (< 150 μm), tiny red lesion, outer partial-thickness (FRS) or full-thickness (MMH) involvement on OCT, varying involvement of the vitreofoveal interface and spontaneous healing in most cases.

Solar maculopathy has historically been reported to produce similar-appearing lesions to MMH and FRS [1, 2]. OCT evaluation has revealed that solar maculopathy is a partial-thickness defect localized to the PRL that characteristically appears as a hyporeflective rectangle with straight edges [14]. More recently, focal choriocapillary circulation disturbances corresponding to areas of retinal loss have been reported when photic maculopathy lesions were evaluated by OCT angiography and en face OCT [33, 34]. In addition to this, bilateral involvement, absence of vitreous abnormality, and history of sungazing are helpful in making the diagnosis of solar maculopathy.

FRS has a larger differential diagnosis due to various reports of outer foveal defects or cavitations seen in association with several pathologies and toxins. Comander et al. provide an extensive differential diagnosis for partial-thickness outer foveal defects that includes the following: Welder's maculopathy, tamoxifen retinopathy, juxtafoveal macular telangiectasia, achromatopsia, alkyl nitrite abuse, acute retinal pigment epitheliitis, and Stargardt disease [14, 35–38]. A careful history and use of other diagnostic tools, such as FA, are imperative in ruling out these pathologies, as OCT alone may be insufficient.

FRS may also occasionally need to be differentiated from intraretinal cysts that are produced by diabetic macular edema (DME). Characteristically, patients with DME produce several patterns on OCT [39, 40]. Of the patterns, cystoid macular edema (CME) may appear most similar to FRS. However, SD-OCT CME often shows several cystoid spaces in the outer plexiform layer (OPL) spanning vertically with retinal elevation and subretinal fluid [40]. A past medical history of diabetes and SLE findings in addition to fluid leakage seen on FA may help distinguish these lesions from FRS [39–41].

Management and prognosis

Changes in vision are often reported as a presenting symptom in both MMH and FRS. However, it appears that VA is often well preserved (Table 1). All studies that followed up on patients with these defects have reported either stable or improved VA (Table 1). Despite the frequent PRL involvement, no direct association has been found between the size of defect and VA [9]. However, worse VA was associated with an increase in cone disruption area as measured by adaptive optics scanning laser ophthalmoscopy (AO-SLO) [12]. To our knowledge, no study has evaluated differences in mean VA between FRS and MMH.

MMH and FRS were initially believed to have a favorable prognosis due to reports of stable or improved symptoms and VA without any intervention [1, 8]. These findings have been further supported by OCT (Figs. 3a, b). Forty-six eyes with FRS (average size = 79.33 μm) were found to remain within 10 μm of measurements taken at first visit in all patients after a mean follow-up of 11.67 months [11]. Another report of three eyes found that the mean size of FRS decreased from 139.3 to 93.3 μm after an average of 32 months [21]. Lai et al. reported a full-thickness MMH that underwent spontaneous closure and transitioned to FRS on 3-week follow-up examination [17].

The favorable 7prognosis seen in the vast majority of patients may be partially related to vitreofoveal separation (VFS). Of the 5 patients with FRS that were found to have a decrease in cone disruption area during follow-up, 3 were found to have a VFS and two had a complete PVD [12]. Similar findings were reported by Johnson with 3 of 4 patients with OCT-confirmed MMH progressing from incomplete to complete PVD [16]. This finding suggests that relief of anteroposterior vitreofoveal traction may result in stability and healing of these defects in most patients.

Very few reports exist of intervention or progression in the context of MMH or FRS. Ooto et al. refers to a single patient that required the administration of oral 40 mg/d prednisone 16 weeks after initial visit when an increase in size of lesion and scotoma was noted [12]. Cone disruption area and VA improved following systemic steroid use. Another report found evolution of a full-thickness MMH to a lamellar macular hole in association with the epiretinal membrane [18]. No intervention was mentioned in the report. Additionally, we provide a case of a single patient with symptoms of blurry vision and central scotoma secondary to MMH and was treated with 0.35 ml injection of sulfur hexafluoride twice (Fig. 5). OCT 5 days after initial injection revealed a minute partial-

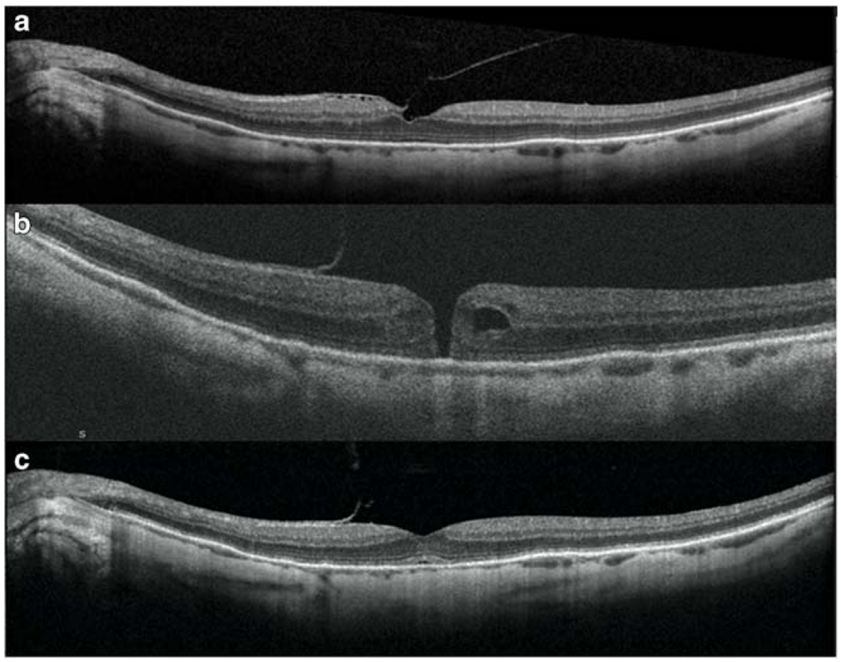

Fig. 5 Sequential OCT imaging of 72-year-old patient that developed a MMH. (**a**) OCT 4 years prior to MMH development shows evidence of an incomplete PVD beginning temporally. There continues to be juxtafoveal attachment at the epimacular surface. (**b**) Patient presented with symptoms of blurry vision and showed evidence of central scotoma. OCT revealed a full-thickness MMH (narrowest width 90 μm), perifoveal cyst, and progression to a release of vitreous cortex from the fovea. (**c**) OCT imaging 5 days after initial 0.35 ml injection and 2 days after, second 0.35 ml injection of sulfur hexafluoride revealed closure of the hole with evidence of a small, partial-thickness lesion in the outer retina

thickness lesion in the outer retina. Examination several months later shows resolution of lesion and associated symptoms. Given the current literature, it appears that there is no major difference in the management and prognosis between FRS and MMH. Future prospective studies will be needed to further evaluate this.

Future directions

Following this review, it is clear that the currently available literature is limited. To date, all 14 studies that have historically examined MMH and FRS have been case reports or case series (Table 1). Furthermore, of the 14 studies, only 4 utilized OCT to confirm diagnosis in a subset of patients, and only 8 utilized OCT to evaluate every patient. It is unclear how many cases classified as MMH in previous studies were FRS because OCT imaging was not provided for every patient. It is also important to note that nearly all studies included in this review utilized far-distance VA (Table 1). Inclusion of near-distance VA may be more meaningful in circumscribed foveal lesions and future studies may benefit from this.

Given the current literature, several questions remain unanswered surrounding FRS and MMHs including (1) the percentage of MMH and FRS that present as definite lesions on fundus exam, respectively; (2) the true incidence of MMH and FRS given that a subset of patients are asymptomatic and, therefore, never diagnosed; (3) the portion of MMH and FRS that occurs in relation to some form of anterior–posterior traction; and (4) if FRS progresses to MMH. Many others remain but these questions are critical in improving our understanding of these pathologies.

Additionally, the current terminology (MMH and FRS) utilized to describe these pathologies may be ambiguous and lead to confusion. MMH may appear as a term based entirely on OCT, while FRS may appear a term used to describe funduscopic findings. This may be inappropriate with the current widespread use of OCT. Therefore, we suggest that the terms outer lamellar macular microholes (OLMMH) and full-thickness macular microholes (FTMMH) may be the more appropriate terminologies to refer to FRS and MMH, respectively. For the purpose of this paper, we have elected to use the historically utilized terms FRS and MMH to refer to these lesions to prevent further confusion. It is our hope that future studies may benefit from the use of the OCT-based terms OLMMH and FTMMH. In turn, this will further uncover the progression of these lesions and determine if additional nomenclature changes or classification by primary and secondary etiologies is required.

Conclusion

MMH and FRS are similar entities defined as one or more sharply defined lesions in the fovea of the eye < 150 μm in size. MMH is a *full-thickness* defect of the fovea while FRS is a *partial-thickness* defect of the outer fovea. The current body of literature suggests that there are subtle differences in the pathogenesis, clinical features, and diagnosis between the two. With regard to pathogenesis, MMH and FRS are largely the result of vitreofoveal traction prior to or concomitantly with vitreofoveal separation. Additionally, healing from a prior idiopathic macular hole may result in MMH or FRS (Table 2).

The clinician should be suspicious of a MMH or FRS in a patient who presents with an acute-onset tiny central scotoma

or disruption in vision. A careful history is needed to rule out other pathologies such as solar maculopathy and stage 1 or 2 macular holes. FRS and MMHs are typically distinguished from stage 1 and 2 macular holes, respectively, by their abrupt onset, small size (< 150 μm), tiny red lesion, outer partial-thickness (FRS) or full-thickness (MMH) involvement on OCT, varying involvement of the vitreofoveal interface, and spontaneous healing in most cases.

Biomicroscopy may reveal a tiny red or yellow defect on the macula, while OCT imaging with multiple line scans frequently detects the lesion. Often, the prognosis is favorable, and intervention is unnecessary due to stability or spontaneously healing. However, careful follow-up is recommended to confirm this.

In the past, ambiguity in definitions has led to multiple studies that unintentionally include both MMH and FRS and is a limitation of our review. OCT has revealed that MMH and FRS are distinct but sometimes overlapping entities, since a healing MMH may appear as a FRS. Lastly, the terms FRS and MMH may be confusing and future studies may benefit from the use of the OCT-dependent terms OLMMH and FTMMH. Prospective comparison of these lesions in conjunction with continued improvement in imaging modalities will continue to enhance our understanding of the similarities and differences of the two.

Acknowledgments Publication of this article was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; Brasília, Brazil) and Pan-American Association of Ophthalmology/Pan-American Ophthalmological Foundation, Paul Kayser/RRF Retina Research Foundation Global Award (PAAO/PAOF; Arlington, Texas).

Author contributions All authors contributed to the study conception and design. The first draft of the manuscript was written by James Garcia, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability All data was obtained and accessed utilizing PubMed.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interests.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Code availability Not applicable.

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