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The morphology of epiretinal membranes in SS-OCT and SS-OCT angiography and its impact on surgical outcomes

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HIGHLIGHTS

Swept source-OCT (SS-OCT), compared to older spectral domain OCT, enables faster examination and provides information about the area beneath the retinal pigment epithelium (RPE) with reduced number of artifacts. Swept-source OCT angiography (SS-OCT A) is a useful instrument for examining changes in retinal and choroidal vasculature associated with ERM formation.
An accurate and detailed description of morphological retinal features observed during SS-OCT and SS-OCT A examinations helps to assess the grade of ERM and to establish a moment for the surgical intervention.

ABSTRACT

The aim of this review is to revisit the current state of knowledge regarding epiretinal membranes, explore current methods of medical diagnosis, and assess the impact of Swept-source OCT (SS-OCT) and SS-OCT angiography (SS-OCT A) on therapeutic procedures. Several attempts have been made to establish a staging classification system for this well-known retinal pathology, yet not all of them proved to be clinically useful. This work intends to improve understanding of the pathophysiology of the disease, selecting the most important symptoms to aid classification according to the stage of advancement and correct recognition of the appropriate moment of surgical intervention to achieve a better postoperative effect. This article demonstrates the benefits of using SS-OCT and SS-OCT A in the treatment of epiretinal membrane, describing the morphological changes of the retina that can be observed.

Key words: epiretinal membranes, SS-OCT, SS-OCT angiography, SS-OCT A

INTRODUCTION

The development of modern technologies, such as swept--source optical coherent tomography (SS-OCT) and swept-source OCT angiography (SS-OCT A), enables a more accurate diagnosis and more careful observation of the natural progression of many retinal diseases, including epiretinal membranes. In this case, which is the subject of the article, it seems particularly important to identify the right moment for surgical intervention. Pars plana vitrectomy with epiretinal membrane (ERM) removal is the treatment of choice. The recurrence of the disease is reduced by internal limiting membrane (ILM) peeling. However, it is stated that performing surgery in the early stages will not lead to visual improvement but will expose the patient to postoperative complications [1]. Many authors have attempted to create and establish an objective ERM classification system that would indicate the point of initiation of treatment. The use of new technologies and equipment allows for a more accurate description of the disease and the search for parameters indicating progression. This review will navigate through the key milestones in the evolution of ERM classification systems, shedding light on the advantages of SS-OCT and the possible application of SS-OCT A in the therapeutic process.

DEFINITION

An epiretinal membrane (ERM) is defined as an avascular, fibrocellular structure that proliferates on the surface of inner retina along an internal limiting membrane. It is constructed of extracellular matrix, glial cells, retinal pigment epithelium cells, fibrocytes, hyalocytes and collagen fibers in different proportions, depending on membrane's etiology [2–5].

When ERM is not accompanied by any others eye diseases, the idiopathic retinal membrane (IRM) is diagnosed. In case if a patient is diabetic, had previous intraocular surgery, photocoagulation of the retina, uveitis, or experienced ocular trauma a secondary epiretinal membrane is identified [4, 6].

Iwanoff was the first to describe ERM in 1865 [7]. According to publications prevalence is estimated from 7% to 11,6% [6, 8]. The incidence of ERM in the fellow eye of affected patients is evaluated to be between 19.5% and 31% [6, 8].

DEVELOPMENT

Microdamage of the internal limiting membrane (ILM), enables glial cells migration to the surface of the retina, which is one of the factors responsible for ERM formation. Further induction of hyalocytes, macrophages dislocation and production of extracellular matrix follows. It is estimated that among patients with ERM around 73% to 95% experienced posterior vitreous detachment (PVD) prior to ERM formation. It is propounded that PVD is one of the main factors contributing to local microdamage of the ILM. Other factors leading to ischemia of inner retinal layers may also induce ERM formation. Prevalence of ERM is significantly higher after retinal vein occlusion incidents, in sickle cell retinopathy and diabetic retinopathy [9]. Increasing concentration of the inflammatory mediators after cataract surgery, uveitis, after ocular trauma, after laser treatment also promotes secondary ERM development [10, 11]. During this process increase concentration of cytokines, growth factors, activation C3 and C3a cell surface receptors, Notch1 receptor expression is mentioned [11].

The age of the patient is a factor which strongly increases probability of developing ERM [10, 12]. The *Melbourne Collaborative Cohort Study* (MCCS) estimated the prevalence of IRM among patients over 80 years as high as 17% [13].

Early stages might have subclinical course [4, 9]. As ERM develops, visual acuity decreases and metamorphopsia may occur [4, 9, 14].

DIAGNOSIS

Initially, only the slit lamp examination with fundus photography was used for scientific research and clinical practice to distinguish and classify the pathology. Eventually the optical coherent tomography (OCT) was introduced for diagnostic purposes. This non-invasive technique enabled in vivo imaging of biological tissue in cross-section. Firstly, spectral domain OCT was applied. Nowadays SS-OCT, with the ability to visualize not only the retina, but also the vitreous and choroid, is implemented. SS-OCT has allowed scanning the area below retinal pigment epithelium (RPE) and improved quality of acquiring results among patients with high refractive errors or with nontransparent optical structures. Increased scanning speed from 50,000 to 100,000 scans per second not only accelerates the examination, but also reduces number of artefacts caused by involuntary eye movements [15].

Obtaining wider scans in swept source technique (12 mm vs 9 mm in spectral domain OCT [SD-OCT]) might be especially favorable in case of extrafoveal ERMs. Some apparatus has a function of autofluorescence imaging, what highlights tortuosity of the retinal vessels since macular pucker stage.

CLASSIFICATION SYSTEMS AND PROGNOSTIC FACTORS

Many attempts have been made to classify ERM according to its morphological structure. Proper and accurate staging system enables assessment of influence on vision acuity, choice of most appropriate treatment [9, 16] including qualification to surgical intervention and anticipating possible postoperative effect [10, 17].

First significant classification was introduced by Gass in "Stereoscopic atlas of macular diseases" [18]. He listed 3 stages, including:

1. Cellophane maculopathy (first stage) – translucent membrane without distortion of the inner retina.
2. Crinkled cellophane maculopathy – translucent membrane with distortion of the inner retina.
3. Macular pucker – non-translucent membrane with distortion of the inner retina with concomitant retinal folds.

The next staging system was proposed by Hwang in 2012. It was focusing on distinguishing epiretinal membranes covering and sparing the foveal area. Multifocal electroretinography showed decreased retinal sensitivity in fovea attached to ERM. Moreover, the relation between central subfield thickness (CST) and increased thickness of internal retinal layers and decreased retinal function was found. Hwang proved that pseudoholes and pseudoholes with splitting have a similar retinal response to eyes without ERMs. Authors linked this with relatively anatomically correct outer retinal layers [19].

In 2013 Itoh et al. examined the correlation between defect of interdigitation zone, defect of ellipsoid zone, defect of external limiting membrane – ELM ("Nomenclature for Optical coherence Tomography" 2016) and best corrected visual acuity (BCVA) in 1st, 3rd, 6th, 9th, and 12th month after vitrectomy with ERM removal. The authors found a significant link between the preoperative length of the interdigitation zone and BCVA 12 months after surgery. Preoperative length of ellipsoid zone defect and ELM defect showed no correlation with postoperative BCVA [20].

In 2014, Konidaris et al. presented a division of the ERM into 9 categories, which emphasized the presence or absence of PVD [21]. Authors focused on the role of PVD in the pathophysiology of IRM, highlighting that PVD was observed in 81% patients [21]. Due to its descriptive character of anatomical changes, it was never implemented in clinical practice.

In 2016 systematic review "Prognostic factors of epiretinal membranes" was published. Defects in interdigitation zone and RPE, defects in ellipsoid zone, cystoid macular edema, increased central foveal thickness (CFT), central macular thickness (CMT) and increased thickness of inner nuclear layer were pointed as unfavorable prognostic factors. Parameters such as CFT, and defects in ellipsoid zone were associated with coexisting metamorphopsia. Common length of outer segments of photoreceptors, smooth ILM profile, proper thickness of ganglion cell-inner plexiform layer were mentioned as good prognostic factors liked with better postoperative BCVA [22]. In the same year, Rouvas et al. demonstrated that over a long-term observation (38 months) there were no significant changes in BCVA or CFT among patients with nontractional ERM. Conclusion was formed that patients with intact ellipsoid zone may remain stable without the necessity of surgical intervention [23]. Similar results were obtained by Theodossiadis et al. In his research over 3 years macular thickness increased by an average of 12.29%. Slow progression of ERM was accompanied by a modest decrease of BCVA, with a mean loss of 4 letters on *Early Treatment Diabetic Retinopathy Study* chart [24].

Govetto et al. introduced another classification scale in 2017. It was based on morphological structure of fovea in OCT scans. Term EIFL – ectopic inner foveal layers – was propagated. Authors defined it as the presence of continuous hypo- or hyperreflective band, extending from the inner nuclear layer (INL) and inner plexiform layer (IPL) across the foveal region and visible in all OCT scans centered in the fovea [25]. Created division included: stage one with presence of foveal pit and well-defined retinal layers. Second stage without presence of the foveal pit, but with well-defined retinal layers. Increased thickness of outer nuclear layer (ONL). Stage three is characterized by presence of EIFL with preserved structure of retinal layers and foveola. In last most advanced stadium, no foveal pit is present, EIFL is noted, and retinal layers are distorted [25]. The cotton ball symptom was the subject of Govetto's study. It was described as a round or diffuse hyperreflective area between ellipsoid zone and the interdigitation zone at the center of the fovea. Cotton ball sign was firstly described by Tsunoda and was linked to active tractional forces in the central foveal area. The correlation between persistent postoperative presence of Cotton ball sign and decreased postoperative BCVA was noted. Tsunoda posited that long-standing traction contributed to photoreceptor functional damage and visual acuity reduction [26].

In 2020 Karasavvidou et al. investigated correlation between outer and inner retina OCT biomarkers, such as: central foveal thickness, maximal retinal thickness (MRT) ganglion cell-inner plexiform layer complex thickening, inner retinal thickness, inner retinal layer irregularity index and visual acuity with IRM. Multivariate analysis documented MRT and disorganization of the retinal inner layers (DRIL) as negative prognostic factors [27].

Further research proved factors such as age, interdigitation zone (IZ) layer defects, EIFL presence, increased thickness of ONL layer is linked with BCVA only in short period of time after surgery [14]. Two years postoperatively, BCVA is correlated with the preoperative presence of DRIL and strong adhesion between the ERM and the retina [14]. Authors managed to portrait changes occurring 2 years after surgery. A decrease of CRT and normalization of retina structure were observed. The incidence of DRIL before vitrectomy was estimated to be around 16.53 % and after surgery around 4.13%. EILF incidence decreased from

28.93% to 10.92%. Stretched ONL was noted only in 19.83% patients compared to 52% before intervention [14]. The decrease of these factors is a sign of proper healing process.

ADVANTAGES OF SS-OCT

SS-OCT is exceptionally useful for diagnosing under RPE. It has been documented that in eyes after vitrectomy with ILM peeling undergo choroid structural changes resulting in decrease of choroidal vascularity index and choroidal thickness (CT) [28, 29]. In 2016 it was observed that eyes with an irregular outer choroidoscleral boundary (CSB) recover visual acuity faster after pars plana vitrectomy (PPV) than patients with regular CSB [30]. In 2021 Zobor et al. postulated that choroidal changes did not influence BCVA [31]. Further research to evaluate significance of this parameters is needed [28–31].

The demand for better high-resolution imaging resulted in introduction of intraoperative OCT (iOCT). As mentioned above, SS-OCT provides many advantages over SD-OCT, such as reduced sensitivity to roll-off, increased examination speed, and wider examination area which are crucial during surgery. Near-real time visualization may be beneficial during surgical maneuvers intervening into micro-architectural alterations of retina. iOCT may be valuable tool in establishing the starting point for the peel, observing retinal formation after peeling and confirming the completeness of the ILM peeling [32]. Unexpected micro-complications, invisible under the microscope, might be detected and successfully repaired. iOCT is a novel technique that requires development of proven effectiveness.

SS-OCT A IMPLEMENTATION

OCT angiography (OCT A) is widely applied in diagnostics of retinal diseases. Govetto in his publications observed progressive reduction of foveal avascular zone (FAZ area) among patients with ERM in OCT-A examination. In the first stage – according to staging system proposed by author – only mild disturbance of vessel architecture may be observed, with asymmetry with the unaffected fellow eye. In stage two and three deformations reach significant state. Reduction of FAZ area is advancing, displacement of the vessels towards foveal center is remarkable. In stage four epiretinal membrane foveal avascular zone is almost absent and displacement of bigger vessels towards foveola may be noticed. Authors noted deformations in both deep and superficial capillary plexus supposedly due to tractional forces displacing course of the vessels. Those observations seem to prove lack of macular-foveal capillaries [25]. Research was taken to determine if FAZ changes after vitrectomy with ERM removal. Kitagawa noticed enlargement of FAZ 6 month after surgery, but still not as extensive as in the other healthy eye [33]. In 2019, Mastropasqua et al. documented changes in perfusion density (PD), vessel diameter index (VDI), and vessel tortuosity (VT) of the superficial capillary plexus in the para- and perifoveal regions of healthy eyes and eyes with ERM. Vessel length density (VLD) differ only in parafoveal region. Six months after the surgery parameters such as: PD, VLD and VT of parafoveal region significantly improved. Authors claim that no statistically significant difference was observed in terms of PD, VLD and VT in perifoveal region before and after surgery for whole 6-month follow up. Finally, no significant correlations were found between anatomical and functional parameters, except for the vessel tortuosity that was significantly positively associated with central macular thickness at 6 months [34].

Mao et al. proved decrease of vessel density in in superficial capillary plexus and increase of density in deep perifoveal capillary plexus after vitrectomy. Authors proved correlation between smaller FAZ area, smaller FAZ perimeter and bigger vision acuity improvement after vitrectomy with ERM removal, suggesting greater BCVA gain among patients with advanced stages of the epiretinal membrane. This conclusion may imply late surgical intervention as more beneficial [35].

DISCUSSION

The morphology of ERM is one of the most important factors based on which the patient is qualified for surgery. Enabling a non-invasive in-depth resolved imaging of the retina is crucial for proper diagnosis, establishing the moment of surgery and anticipating the results. Many classification systems of ERM have been developed, yet not all of them have proved to be clinically useful. The problem is that many factors seem to be of great importance in univariate analysis, while their significance is less pronounced in proper, sophisticated multivariate analysis. According to current, reviewed literature, in 2 years observation time only DRIL and strong adhesion of ERM is correlated with BCVA. In a short observation time, factors such as IZ layer defects, age, EIFL presence, DRIL, and increased thickness of the ONL layer were evaluated as unfavorable prognostic factors linked with BCVA post-surgery. CFT, and defects in ellipsoid zone were associated with coexisting metamorphopsia. The cotton ball sign was described as a marker of tractional forces in the foveal region. Pathomorphological features such as EIFL and DRIL were noted as determinants of advanced ERM.

Eyes with ERM undergo choroid thickness changes [36], which have also been observed after vitrectomy with ILM peeling [28, 29]. ERM is not only ILM surface disease, but also induces structural alterations in the retina and choroid.

Combined cataract surgery and vitrectomy with ILM peeling cause longer recovery in CRT and CT [31].

SS-OCT angiography is a novel non-invasive approach that enables the examination of retinal and choroidal vasculature. It has been reported that the FAZ area decreases with the development of the epiretinal membrane. It is not clear why such a difference in vascularization is observed; nevertheless, an increase in the FAZ area after surgery has been described as a sign of proper healing. Changes in FAZ area are occurring in many retinal diseases. In diabetic retinopathy increased FAZ indicates progression of the disease, but not always is associated with decrease of vision. In 2020, it was documented that the FAZ area increased more prominently after vitrectomy with optic pit stuffing among patients without subretinal fluid than among patients with subretinal fluid. However, no difference in visual acuity was observed [37]. On the other hand, it has been proven that postoperative FAZ area is a prognostic factor for BCVA and central retinal thickness 1 month after macular hole surgery [38]. The role and cause of changes in FAZ area after ERM removal have yet to be established, but further research on this parameter is warranted.

Through the implementation of angio-OCT, we possess the capability to systematically evaluate alterations in vessel density within both the superficial and deep vascular plexus, both in the parafoveal and perifoveal regions. A decrease of vessel density in superficial capillary plexus after surgery may be linked with mechanical trauma during peeling. An increase in density in the deep perifoveal capillary plexus, along with improvement in parameters such as PD, VLT, and VT in the parafoveal region, was noted.

The introduction of intraoperative SS-OCT may prove to be a revolution in the future. High-resolution imaging will be beneficial during surgical maneuvers on many levels. Nowadays, this technology has certain limitations.

CONCLUSION

SS-OCT and SS-OCT A already have significant impact on assessment of ERM, qualification and post-surgical follow up. Several ERM classification systems have been designed with the aid of OCT; however, no exact moment for surgical intervention has been established yet. OCT is essential not only for identifying unfavorable architecture and localization of the membrane, but also it is an indispensable tool for estimating if disease is progressing over time. Qualification for surgery should be based on symptoms such as a decrease of BCVA and metamorphopsia presence. Stable cases may be successfully monitored without imperative to operate. Patients with advanced ERM benefit the most from intervention strategies – stable improvement may occur up to 2 years after the surgery [14].

Additional parameters may be evaluated by supplementing the examination with OCT Angiography. Implementation of innovative solutions requires confirmation of their effectiveness through scientific research and continuous knowledge updating by clinicians.

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