Microcystic Macular Edema: Clinical Significance and Pathogenetic Mechanisms

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ABSTRACT

Microcystic macular edema represents a specific type of intraretinal cystic changes, localizing predominantly in the inner nuclear layer and detectable using the optical coherence tomography. Contrary to the classic concepts on the macular edema as a result of vascular permeability, microcystic macular edema is not accompanied by exudation and it is perceived as the manifestation of neuroglial dysfunction, often associated with the damaging of the optic nerve. Initially described in patients with multiple sclerosis, microcystic macular edema was subsequently detected in the wide spectrum of diseases, including glaucoma, neuromyelitis optica spectrum disorders, diabetic retinopathy, occlusion of the retinal veins, senile macular degeneration and epiretinal membranes. The key pathogenetic mechanisms are considered the retrograde transsynaptic degeneration of the ganglionic cells in the retina and the functional/structural damage of the Muller's cells, in particular, the impaired operation of the AQP4 aquaporin channels. The morphological features of the microcystic macular edema, its location and clinical significance vary depending on the main disease and in a number of cases can act as the early biomarker of the neurodegenerative process. The article contains the pathophysiological models, the clinical correlates and the modern methods of the diagnostics of microcystic macular edema with special emphasis on the role of multimodal visualization and artificial intelligence technologies. Taking into consideration the rates of accidental detection and the potential relation to the systemic diseases, microcystic macular edema should be considered not as an isolated ophthalmology condition, but as the component of wider neuroretinal disorder requiring interdisciplinary approach to the diagnostics and follow-up.

Keywords: *microcystic macular edema; Muller's cells; retinal neurodegeneration; optical coherence tomography; retrograde degeneration.*

For citation:

Danilova EA, Plokhikh IV, Djanbekova LM, Tyan AE, Nafikova GI, Antipina GI, Bikbulatova AI, Rybina YuA, Khulagov MS, Batdyeva MI, Gaifullina KM, Vasilyeva IV, Krivosheeva AE, Usmanov IA. Microcystic Macular Edema: Clinical Significance and Pathogenetic Mechanisms. *Journal of Clinical Practice*. 2025;16(3):58–70. doi: 10.17816/clinpract680846 EDN: QAEGZM

Submitted 28.05.2025 Accepted 29.06.2025 Published online 09.07.2025

List of abbreviations

IR — infrared visualization
MME — microcystic macular edema
OCT — optical coherence tomography
AQP4 (Aquaporin-4) — aquaporin-4 (the protein of water channels encoded by the *AQP4* gene)
GCL — ganglion cell layer
INL — inner nuclear layer
RNFL — Retinal Nerve Fiber Layer
SCP — Superficial Capillary Plexus

https://doi.org/10.17816/clinpract680846

клиническая практика 2025 Том 16 №3

Микрокистозный макулярный отёк: клиническое значение и патогенетические механизмы

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АННОТАЦИЯ

Микрокистозный макулярный отёк представляет собой специфический тип интраретинальных кистозных изменений, локализующихся преимущественно во внутреннем ядерном слое и выявляемых с помощью оптической когерентной томографии. Вопреки классическим представлениям о макулярном отёке как следствии сосудистой проницаемости, микрокистозный макулярный отёк не сопровождается экссудацией и рассматривается как проявление нейроглиальной дисфункции, часто ассоциированной с поражением зрительного нерва. Первоначально описанный у пациентов с рассеянным склерозом микрокистозный макулярный отёк впоследствии был обнаружен при широком спектре патологий, включая глаукому, нейромиелит спектра AQP4, диабетическую ретинопатию, окклюзию вен сетчатки, возрастную макулярную дегенерацию и эпиретинальные мембраны. Ключевыми патогенетическими механизмами считают ретроградную транссинаптическую дегенерацию ганглиозных клеток сетчатки и функциональное/структурное нарушение клеток Мюллера, в частности нарушение работы аквапориновых каналов AQP4. Морфологические особенности микрокистозного макулярного отёка, его локализация и клиническое значение варьируют в зависимости от основного заболевания, а в ряде случаев могут служить ранним биомаркером нейродегенеративного процесса. В статье рассматриваются патофизиологические модели, клинические корреляты и современные методы диагностики микрокистозного макулярного отёка с особым акцентом на роль мультимодальной визуализации и технологий искусственного интеллекта. Учитывая частоту случайного выявления и потенциальную связь с системными заболеваниями, микрокистозный макулярный отёк следует рассматривать не как изолированное офтальмологическое состояние, а как компонент более широкой нейроретинальной патологии, требующей междисциплинарного подхода к диагностике и наблюдению.

Ключевые слова: *микрокистозный макулярный отёк; клетки Мюллера; ретинальная нейродегенерация; оптическая когерентная томография; ретроградная дегенерация.*

Для цитирования:

Данилова Е.А., Плохих И.В., Джанбекова Л.М., Тян А.Е., Нафикова Г.И., Антипина Г.И., Бикбулатова А.И., Рыбина Ю.А., Хулагов М.С., Батдыева М.И., Гайфуллина К.М., Васильева И.В., Кривошеева А.Е., Усманов И.А. Микрокистозный макулярный отёк: клиническое значение и патогенетические механизмы. *Клиническая практика.* 2025;16(3):58–70. doi: 10.17816/clinpract680846 EDN: QAEGZM

Поступила 28.05.2025 Принята 29.06.2025 Опубликована online 09.07.2025

INTRODUCTION

Microcystic macular edema (MME) represents a specific form of retinal disorder, characterized by the formation of clearly delimited cystous cavities, predominantly in the inner nuclear layer (INL) and detectable by means of optical coherence tomography (OCT) [1, 2]. Initially described by J.M. Gelfand et al. [3] in patients with multiple sclerosis and optic neuritis, MME was subsequently revealed in a number of ophthalmological and systemic diseases, including the optic neuropathies, the diabetic retinopathy, the epiretinal membranes and the neurodegenerative processes in the central nervous system [4–7].

Unlike the diabetic macular edema and the senile macular degeneration, MME is not associated with significant vascular or inflammatory disorders,

which allows for considering it an independent clinical-pathogenetic entity [8]. The most probable mechanisms of its development are considered the retrograde transsynaptic degeneration of the ganglionic cells and the dysfunction of the Muller's cells, however, their interrelation and the contribution in the clinical signs require further research [8].

MICROCYSTIC MACULAR EDEMA: GENERAL PROVISIONS

Pathogenetic mechanisms

The development of MME is related to several key pathogenetic mechanisms, the basic of which is believed to be the retrograde transsynaptic degeneration (table 1) [9–17]. Unlike the classical forms of macular edema, related to vascular permeability, in cases of MME, there is no exudation present, which is confirmed by the results of OCT and angiography [9–11].

Retrograde degeneration developing after the death of ganglionic cells and their axons is accompanied by the damage of the structure of bipolar neurons in the INL, which results in the development of intraretinal cavities [12–14]. A clear correlation is observed between the zones of visual field loss and the topography of cystous changes, which emphasizes the secondary (neurodegenerative) origin of MME.

The dysfunction of the Muller's cells is another significant factor of pathogenesis. These glial cells support the water-ion homeostasis of retina, including the use of aquaporin channels (Aquaporin-4, AQP4). The impairment of their functions, including the one developing under the effects of autoantibodies (for example, in cases of the neuromyelitis of the optic nerve), can lead to the intraretinal accumulation of fluid with no signs of vascular leak [11, 12, 15].

Mechanical impact — the vitreomacular traction — is perceived as an additional but not universal mechanism. Though the tension in the vitreous body can enhance the formation of cysts, it is not the obligatory condition for their development [16].

The possible additional link is the inflammatory component, especially in cases of multiple sclerosis, in which the internal retina can be involved into the subclinical inflammatory process [3, 17], however, the clear relation between the presence of MME and the activity of multiple sclerosis is not determined as of today.

Thus, MME represents a multifactorial phenomenon occurring with a background of axonal loss, glial dysfunction and possible participation of inflammation. The role of each of these components may vary depending on the main disease.

Specific features of visualization

MME manifests with hyporeflexive cystous structures, predominantly of parafoveal location, more often in the lower part of the INL, showing the shape of an arch or a crescent. These changes are well visualized upon the spectral OCT as the zones of local decrease in the reflectivity, corresponding to the intraretinal cavities [11]. According to the data from B. Wolf et al. [11], in the lower third of the cysts, hyperreflective inclusions can be found, especially in cases of optic nerve atrophy. OCT-tomography of the macular profile (face map) has shown the predominant location of cysts in the upper and nasal quadrants (72%), while in cases of multiple sclerosis, even distribution was observed [3, 11]. In the

Table 1

Pathogenetic mechanisms of microcystic changes in the macula in cases of optic nerve damage

Mechanism	Backbone of the mechanism	Sources	Note
Neurodegeneration	Atrophy of the axons and ganglionic cells in the retina, leading to secondary degeneration of INL	[9–11]	Main background mechanism
Vitreomacular traction	Mechanical effects on the vitreous body with the thinned retina after the death of ganglionic cells; leading to microschisis	[16]	Cause-and-effect relation not proven
Retrograde transsynaptic degeneration	Secondary degeneration of post-synaptic bipolar neurons in the INL after the death of ganglionic cells	[12–14]	The most probable main mechanism
Dysfunction of the Muller's cells	Impaired homeostasis of fluid and ions in the retina due to the damage or dysfunctions of the gliocytes (including AQP4)	[11, 12, 14]	Confirmed for ONM and hereditary opticopathies
Inflammatory mechanism (including the multiple sclerosis)	INL as a target for inflammation, especially in multiple sclerosis; MME may correlate with the neurological deficit	[3, 13, 17]	No univocal relation to the activity of inflammation

Note. ONM — neuromyelitis optica; MME — microcystic macular changes; INL — inner nuclear layer of retina; AQP4 — aquaporin-4.

https://doi.org/10.17816/clinpract680846

glaucoma-affected eyes, MME is more often detected in the lower hemisphere of the retina [18], which can reflect the topographic features of neurodegeneration in various forms of optic neuropathy.

Infrared (IR) visualization and red-free images allow for visualizing the characteristic arch- or ring-shaped obscuring caused by the diffraction with a background of cysts [14, 19]. Adaptive optics also reveals the oval hyporeflexive structures that indicate the degeneration of the INL cells [19].

Fluorescent angiography in the majority of cases does not reveal exudation, which confirms the non-vasogenic nature of MME [11], however, separate cases describe the diffuse leakage of fluorescein into the INL, indicating the probable partial impairment of the hematoretinal barrier [20].

Data from OCT-angiography supplement the pathophysiological findings: a correlation was found between MME and the disorders in the superficial capillary plexus (SCP), which can indicate the microvascular component of the pathogenesis [21].

Thus, the combined set of imaging methods (OCT, OCT-angiography, infrared visualization, adaptive optics) ensures the accurate diagnostics of MME and promotes to its differentiation from other forms of maculopathy (table 2) [3, 11, 18–21].

MICROCYSTIC MACULAR EDEMA IN CASE OF THE OPTIC NERVE DISORDERS

The MME is associated with a broad spectrum of optical neuropathies, both acquired and hereditary, including multiple sclerosis, optic neuritis, glaucoma, compression-related and ischemic forms, as well as the Leber's disease and the autosomal dominant optic atrophy (table 3) [1, 3, 6, 11–13, 17, 18, 20–36].

Multiple sclerosis

First described by J.M. Gelfand et al. [3], MME in multiple sclerosis occurs in 4.7–6.1% of the cases and is more associated with the preceding optic neuritis [3, 13]. Its presence correlates with the worse neurological parameters defined when using the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Severity Score (MSSS), as well as with the decrease of vision acuity and thickening of INL [13, 20, 22]. The main pathogenetic hypotheses include the inflammatory damage of INL, the retrograde transsynaptic degeneration and the glial dysfunction related to the autoantibodies to KIR4.1 (inwardly rectifying potassium channel) and AQP4 [17, 20]. With the progression of the disease, thinning is observed in the inner layers of retina along with the worsening of visual functions [23–25].

Neuromyelitis optica

The rate of developing MME in cases of optic neuritis reach 20–40% and, generally, it is limited to the eyes with past history of optic neuritis [3, 21, 26–29]. The pathogenesis includes autoimmune impairment of the Muller's cells via the AQP4-IgG and further glial dysfunction increasing the retrograde degeneration [28]. According to "two-hit" hypothesis [12],

Table 2

Specific visualization features in cases of microcystic macular changes

Visualization method	Characteristic findings	Source	Note
Spectral OCT	Hyporeflexive arch-shaped microcysts, predominantly in the lower part of INL	[11]	Reflecting the intraretinal cavities
OCT, face map profile	Predominant location in the upper and nasal quadrants (72%)	[11]	Variability of distribution in various diseases
OCT in multiple sclerosis	Even distribution of microcysts in the macula	[3]	Specific features in multiple sclerosis
OCT in glaucoma	Microcysts in the lower hemisphere of the retina	[18]	Possible locational susceptibility
IR-visualization, red-free filter	Obscuring, arch-shaped and ring-shaped structure	[14, 19]	Relate to the diffraction of IR-radiation
Adaptive optics	Oval-shaped hyporeflexive structures	[19]	Degeneration of the INL-cells
Fluorescent angiography	Absence of exudation, in some cases — moderate leakage	[11, 20]	Supporting the non-inflammatory nature of the MME
OCT-angiography	Impairment of SCP, correlation with MME	[21]	Role of microvascular changes

Note. OCT — optical coherence tomography; IR — infrared visualization; MME — microcystic macular changes; INL — inner nuclear layer or retina; SCP — superficial capillary plexus.

Table 3

Microcystic changes in the macular in various forms of optic neuropathy

Neuropathy type	Specific features of the MME	Proposed	Sources
Multiple sclerosis	MME in 4.7–6.1% of the patients were associated with episodes of ON, thickening of INL, impaired visual functions	Neuroinflammation, dysfunction of the Muller's cells, autoantibodies to KIR4.1 and AQP4	[3, 6, 13, 17, 20, 22–30]
Neuromyelitis optica	MME in 20–40% of the patients, specifically in the eyes with past optic neuritis, more expressed thinning of the RNFL and GCL	Antibodies to AQP4, glial dysfunction, retrograde degeneration, vascular impairments of the SCP	[3, 12, 21, 26–28]
Non-inflammatory optical neuropathy (ischemic, compression-related etc.)	MME in 8.8–20.4% of the eyes correspond to the zones of lost nerve fibers	Retrograde transsynaptic degeneration, vitreomacular traction	[12, 19, 30–32]
Hereditary optical neuropathy (ADOA, LHON)	Ring-shaped perifoveal distribution of cysts, matching with the zones of RNFL and GCL loss	Mitochondrial dysfunction, glial instability, vitreal traction	[19, 33, 34]
Non-arteritis anterior ischemic optical neuropathy	Transitory MME during the INL acute phase; in some cases — stable changes in several months	Impaired blood-brain barrier, dysfunction of the Muller's cells, glymphatic insufficiency	[12, 30, 35, 36]

Note. MME — microcystic macular edema; ON — optic neuritis; INL — inner nuclear layer; KIR4.1 — potassium channel, associated with Muller' cells; AQP4 — aquaporin-4; RNFL — retinal nerve fiber layer; GCL — ganglion cell layer; SCP — superficial capillary plexus; ADOA — autosomal dominant optical atrophy; LHON — Leber's disease.

the development of MME requires a combination of axonal loss and glial damage. Data from OCT-angiography show the presence of microvascular disorders in the SCP, which can reflect the additional vascular component of pathogenesis [21].

Other neuropathies

MME is also observed in cases of non-inflammatory optical neuropathies — ischemic, traumatic, compression-related or hereditary [6, 12, 30]. Histologically they are accompanied by degenerative INL cavitations with no signs of inflammation [31]. The spatial location of the cysts detected using the infrared visualization and adaptive optics corresponds to the zones of ganglionic cells density [32].

In cases of autosomal dominant optic atrophy and Leber's disease, MME is detected in 5–20% of the cases, predominantly in the perifoveal zone [19, 33]. It is suggested that vitreoretinal adhesion can enhance the cavitation of the retina with a background of mitochondrial insufficiency [12, 34].

In case of non-arteritic anterior ischemic optic neuropathy (NAION), transient "peripapillary MME" was described, resolving within one month, probably, due to the impaired hematoretinal barrier and glial dysfunction [30, 35, 36]. In a number of cases, classic MME was developing months after an acute episode, which corresponds to the pattern of transsynaptic degeneration [12].

Glaucoma

MME was first described in glaucoma patients as the manifestation of severe axonal loss [11]. According to the data from T. Hasegawa et al. [18], microcysts were detected in 6% of the patients with primary open-angle glaucoma, predominantly at the later stages of the disease. Their presence correlated with the localized defects of the retinal nerve fiber layer (RNFL) and with the thinning of the ganglion cell layer (GCL), while in cases of severe total decompensation (average deviation <15 dB) MME was not registered.

The mechanism of MME in glaucoma, besides retrograde degeneration, can include mechanical instability in the inner retinal layers with a background of RNFL/GCL thinning and INL tension [18]. According to N. Murata et al. [37], the occurrence rate of MME was 1.6%, with this, the surface area of the microcystic changes was related to the impaired central field of vision. J. Brazerol et al. [38] have also found the rate of 3% of the cases, supposing that the thinning of the ganglion layers is accompanied by compensatory thickening of the internal nuclear/external plexiform layers and the development of cysts designated as the manifestation of "retrograde maculopathy".

The research by K.I. Jung [39] has shown that the thickening of the INL can precede the formation of MME, acting as the early marker of glaucoma progression. Additionally, the variations of intraocular pressure can induce reactive gliosis of the Muller's

https://doi.org/10.17816/clinpract680846

cells, increasing their functional load and facilitating the development of cystous changes [39–42]. Despite this, G. Mahmoudinezhad et al. [43] did not confirm the presence of statistically significant association between MME and the rate of glaucoma progression, estimated by the mean deviation (MD) and by the visual field index (VFI). Nevertheless, the authors have noted the clear location of the retinal microcysts predominantly in the lower hemisphere of the retina (84%), which corresponds to the zone of typical glaucoma-related damage of the upper vision field [3, 44]. It was also noted that MME is not related to the epiretinal membranes, which rules out the vitreomacular traction as the leading mechanism [18, 44].

Thus, MME in glaucoma can be considered as the potential morphological marker of progressive central damaging of the optic tract, related to the glial dysfunction, to the local neurodegeneration and to the instability of inner retinal layers.

MICROCYSTIC MACULAR EDEMA IN CASES OF NEUROLOGICAL DISEASES

Microcystic changes in the retina are considered as the potential manifestation of transsynaptic retrograde degeneration in cases of disorders in the central nervous system. The research works confirm the degeneration of RNFL and GCL in patients with congenital abnormalities in the brain, with ischemic strokes and craniocerebral injuries, which is being associated with the loss of trophic support from the cortical neurons [45–47]. However, in single lesions of the posterior segments of the optic tract (for example, after hemispherectomy), MME was not found [48], which encouraged W.A. de Vries-Knoppert et al. [49] to differentiate the direct axonal and the transsynaptic degeneration. Only in cases of anterior impairment (chiasm, retrobulbar compression) the thinning of the retinal nerve fiber layer / ganglionic cell layer is registered with the inner plexiform layer and INL thickening along with the development of MME. The authors have isolated three types of degeneration [49] — the direct retrograde (the aggressive one with the development of MME), the local transsynaptic (restricted and slowly progressing) and the widespread transsynaptic (in cases of massive lesions, accompanied by axonal instability).

M.L. Monteiro et al. [50] have investigated 26 patients with chiasmal compression and found that MME is detected upon using the OCT in 35.3% of the eyes, while the hyporeflexive zones at the IR-image — in 64.7% of the cases. In total, signs of retrograde maculopathy were found in 58.8% of the eyes. Hyporeflexive foci were especially often detected in cases of striated atrophy, even in the absence of cysts in the OCT data, which emphasizes their diagnostic value in chronic disorders.

Thus, in cases of neurological disorders, no MME can be detected at the later phases, however, IR-visualization allows for revealing signs of retinal degeneration. This emphasizes the significance of the combined approach with using OCT and multispectral visualization for the evaluation of various stages of transsynaptic degeneration.

MICROCYSTIC MACULAR EDEMA IN CASES OF EPIRETINAL MEMBRANES

Epiretinal membranes may cause the development of intraretinal cysts, morphologically similar to MME, even in the absence of fluorescein leakage [51–54]. This calls into question their relation to the classical cystoid edema and allows for considering such changes as the manifestation of traction-related or retrograde maculopathy.

The research by A. Govetto et al. [16] has revealed MME in 55% of the patients with epiretinal membranes and glaucoma versus 11.3% of the patients without glaucoma. After vitrectomy, cysts were disappearing only in patients without glaucoma, which shows the role of retrograde component in the optic neuropathy. Mechanical tension of the epiretinal membranes can disrupt the functioning of the Muller's cells, blocking the reabsorption of fluid and stimulating the formation of cysts [55, 56].

The combination of epiretinal membranes and glaucoma increases the risk of MME [57]. Research works demonstrate both the regress of cysts after surgery and their repeated occurrence [56, 58, 59]. A number of authors relate these changes to the retrograde maculopathy triad — thinning of GCL, thickening of INL and formation of cysts [56]. However, the effect of MME on the vision prognosis remains disputable: some data show the absence of correlation, others show the worsening of outcomes in patients with significant MME and with an ectopy of the foveal layer [60].

Histologically, MME in case of epiretinal membranes is resulting predominantly from the mechanical damage of the Muller's cells, not from the neurodegeneration. MME is often detected with mature (stage III–IV) epiretinal membranes, but extremely rarely — in cases of macular holes [61], which confirms the role of chronic traction.

Thus, MME in cases of epiretinal membranes forms due to the mechanical destruction of glial cells, especially with a background of glaucoma, which requires taking it into consideration in the surgical tactics and when predicting the functional outcome.

Macular diseases

Water homeostasis of the retina is provided by a number of mechanisms, not depending on the hematoretinal barrier [8]. Excessive fluid may be produced even in the absence of inflammation or vascular leakage, which is caused by the absence of lymphatic system, by high metabolism in the photoreceptors and by the constant osmotic gradient between the vitreous body and the vascular membrane.

The removal of fluid is carried out by means of the activity of pigmented epithelium (retinal pigment epithelium, RPE), by the osmotic pressure of the choroid and by the functioning of the Muller's cells, which regulate the ion transport, absorb water and promote to its relocation to the choroid. These cells also affect the functioning of the retinal pigmented epithelium, including the regulation of the synthesis of vascular endothelial growth factor (VEGF) [62–64].

The macular zone is especially affected by the accumulation of fluid due to its high metabolic activity and the anatomic features, namely, the dense architecture, the adjacency to the premacular space and the fragile regulatory system relocating the fluid [65, 66].

In cases of abnormalities impairing the functioning of the Muller's cells (neurodegeneration, hypoxia, traction) or the pigmented epithelium (for example, in senile macular degeneration), non-exudative accumulation of fluid may develop, which form the basis of developing microcystic changes and other non-vasogenic forms of macular edema (table 4) [1, 8, 66–80].

Senile macular degeneration

Microcystoid lesions, morphologically similar to MME, may be detected at the later stages of both the atrophic and the exudative form of senile macular degeneration [8]. Among them, there are external retinal canaliculi, the subretinal transitory hyporeflexia and pseudocysts, developing mostly due to the degeneration of the Muller's cells. Such lesions do not show any leak upon fluorescent angiography and they are characterized by chronic course with a background of metabolic decompensation of neuroretina.

External retinal canaliculi represent the stable hyperreflexive structures in the external layers, unlike the regressing MME [66]. The subretinal transitory hyporeflexia, on the contrary, has a transient course and does not involve the internal layers [67]. Pseudocysts in geographic atrophy are registered in ~27% of the cases [68], with this, they are not associated with a risk

Table 4

Microcystic changes in the macula in cases of macular diseases and retinopathies

Disease	Type of changes	Characteristics and pathogenesis	Sources
Senile macular degeneration	Pseudocyst, ERC, STH	Degenerative non-vasogenic changes, not accompanied by exudation, related to the impaired functions of the RPE and the Muller's cells. Differ from the MME by the location and stability	[8, 66–70]
Diabetic retinopathy	PMC, thickening of INL	Early glial dysfunction, changes without exudation, more in the nasal and temporal quadrants. Precedes the classical DME	[1, 71, 72]
Retinal vein occlusion	MME	Often combined with glaucoma, associated with unfavorable prognosis. Resistant to therapy in cases of concomitant glaucoma	[73, 74]
Macular telangiectasis of type 2	Cystous changes	Early loss of the Muller's cells, degenerative mechanism, absence of response to anti-VEGF, possible development of secondary macular holes	[75–77]
Central serous chorioretinopathy	Degenerative cysts	Chronic form, no exudation, in the external layers of retina, often with pachychoroid changes	[78, 79]
Hereditary retinal dystrophies	Cystic changes	Reported in cases of various hereditary abnormalities, predominantly of degenerative nature, up to 30% without exudation	[80]

Note. ERC — external retinal canaliculi; STH — subretinal transitory hyporeflexia; PMC — pseudomicrocystic changes; DME — diabetic macular edema; MME — microcystic macular changes; RPE — retinal pigment epithelium; INL — inner nuclear layer; VEGF — vascular endothelial growth factor.

https://doi.org/10.17816/clinpract680846

of secondary exudation [69]. Degenerative cysts in cases of exudative senile macular degeneration can persist with a background of anti-VEGF therapy [70], however, they differ by the pathogenesis and they are not associated with neuroglial mechanisms.

Upon the development of diabetic retinopathy, MME with pseudomicrocystic changes occurs already at the early stages, before the development of vasculopathy. According to the data from R. Forte et al. [71], pseudomicrocystic changes were observed in 14% of the eyes with intact vision acuity, but with decreased photosensitivity. These changes are accompanied by thickening of the INL, which indicates the glial dysfunction before the development of macular edema [72].

The morphology of pseudomicrocystic changes in cases of diabetic retinopathy differs: the cysts are elongated, with blurred margins, localizing at the nasal and temporal quadrants of the macula. It is suggested that they reflect the hypoxia-induced impairment of the Muller's cells, enhanced by the impaired chorio-capillary perfusion [1].

Thus, in cases of senile macular degeneration, just like in the diabetic retinopathy, microcystic changes represent a result of various pathogenetic mechanisms — degenerative, hypoxic or glial. Their detection has a differential-diagnostic and prognostic value, especially at the early stages of the disease.

Retinal vein occlusion

MME often occurs after the retinal vein occlusion, especially in the untreated cases. According to the data from the retrospective research by A. Francone et al. [73], MME was detected approximately in 70% of the eyes with retinal vein occlusion. Notably, the concomitant glaucoma was a significant risk factor of developing MME in cases of retinal vein occlusion. In the eyes with combined disease (retinal vein occlusion + glaucoma), there was a larger number of cystoid cavities and a more significant decrease of the best corrected vision acuity comparing to the isolated retinal vein occlusion. After the anti-VEGF therapy, MME persisted in 44% of the cases when combined with glaucoma, while in the isolated retinal vein occlusion — only in 15%. However, even in the latter group, the presence of MME was associated with increased risk of edema recurrence, of the shortening inter-interval period between the injections and the necessity of longer supportive therapy [74].

The obtained data emphasize that MME in cases of retinal vein occlusion can be considered a marker of unfavorable functional prognosis, especially in the settings of glaucoma-related optic neuropathy, where the glial mechanisms of compensating the hydration balance are initially abnormal.

Other diseases

Macular telangiectasis type 2 is characterized by early cystous changes in the inner layers of retina and by whitening of the parafovea. Histologically confirmed reduction of the Muller's cells indicates their central role in the pathogenesis. The progression is accompanied by the degeneration of the external layers and of the photoreceptors, as well as by the risk of developing the secondary lamellar macular hole [75, 76]. Anti-VEGF therapy is ineffective and it can aggravate the atrophic changes [77].

Central serous chorioretinopathy in its chronic form may be accompanied by cystoid lesions with no signs of leakage, predominantly in the external layers of retina. Such changes are often resistant to the therapy and are associated with pachychoroid morphology [78, 79].

Hereditary retinal dystrophy, including the S-cone syndrome, the Best disease and the pigmented retinitis, are also accompanied by microcystic changes. In part of the patients (up to 30%), the cysts are not detectable when using the fluorescent angiography, which confirms their degenerative nature [80].

Thus, MME can be found in a wide spectrum of diseases — from vascular to hereditary, reflecting the universal mechanisms of glial dysfunction or of the structural depletion of neuroretina.

DISCUSSION

MME represents a phenotypically recognizable but pathogenetically heterogeneous condition occurring during multiple ophthalmology and systemic diseases. Modern data indicate that the development of MME is the result of several interacting pathophysiological mechanisms, including the neurodegeneration, the glial dysfunction and the impairment of water homeostasis. Though most commonly MME is associated with chronic disease of the optic nerve, its presence was also documented in cases of senile macular degeneration, diabetic retinopathy and retinal vein occlusion.

Retrograde transsynaptic degeneration is traditionally concerned as a central pathogenetic mechanism, especially during the neurodegenerative diseases of the optic tract, however, mounting evidence underlines the key role of the dysfunction of the Muller's cells, the glial elements of retina, responsible for water-ion balance and the structural support of

the inner retina [31, 81]. Specifically — in recent years, the participation of AQP4 channels, expressed by the Muller's cells, gains more attention. Their functional incompetence, mediated by the autoantibodies in cases of optic neuromyelitis, results in the impaired transcellular water transport and the development of MME. At the same time, there are data that indicate the more multi-purpose role of AQP4 in the development of MME, including cases of multiple sclerosis. The interaction of AQP4 with Kir4.1 Potassium channels, also expressed by the Muller's cells, maintain the osmotic balance in the retina. The impairment of the combined regulation of these channels lead to the decreased resorption of fluid and to the development of the intra-retinal cysts [1, 16].

The additional role in the impaired functions of the Muller's cells can be played by the mechanical damage, especially in cases of epiretinal membranes. Research works have demonstrated that delamination of INL during the surgery for epiretinal membranes can aggravate the damage of glial cells, resulting in the increased rates of postoperative MME [61]. Thus, the unifying link for the multitude of various diseases is the impairment of the functional or structural integrity of the Muller's cells, which results in the dysregulation of AQP4 and water homeostasis.

Separate attention deserves the topography of microcystic changes, which are in many cases localized predominantly at the nasal and temporal quadrants of the perimacular area. Such selectivity can be resulting from the specific anatomical features of the vascular system of the choroid, in particular, the watershed areas between the basins of posterior ciliary arteries located between the central fovea and the optic nerve disc. These zones can be more vulnerable to hypoxic or ischemic effects [82].

Interesting observation is the registration of hyperreflexive inclusions in the macular zone in patients with senile macular degeneration and diabetic retinopathy, which can represent the activated microglial cells. This indicates the probable involvement of the inflammatory cascades at the early stages of degenerative and vascular retinal diseases, predisposing to the development of MME [83].

Despite the clearly defined morphological characteristics, clinical significance of MME remains a matter of discussion. The MME is not always accompanied by impaired vision acuity, especially at the early stages, however, in patients with multiple sclerosis and senile macular degeneration, the presence of MME was associated with the worsening of the functional parameters and with the decreased sensitivity of the retina [3, 13, 28]. At the same time, in cases of myelitis, such associations are less clearly trackable, while the intensity of MME does not correlate with the total level of neurological incapacitation.

Thus, MME should be estimated not as an independent nosological entity, but as a morphological marker of neuroglial balance destabilization at the macular zone. Its detection can act as an alarm signal both for the ophthalmologists and for the neurologists, pointing out the necessity of deeper structural and systemic examination arranged for the patient.

CONCLUSION

Microcystic macular edema represents a non-specific manifestation of impaired water homeostasis in the retina, associated predominantly with the dysfunction of the Muller's cells and retrograde neurodegeneration, observed in a wide spectrum of diseases — from the damage of the optic tract to the vascular, degenerative and hereditary retinopathies, which requires accurate differential diagnostics. Due to the presence of modern visualization methods, MME gains the value as an important morphological marker, capable of indicating an occult disorder, which emphasizes the clinical-diagnostic value of MME and the necessity of further cross-disciplinary research.

ADDITIONAL INFORMATION

Author contribution: *E.A. Danilova,* conceptualization, literature search and analysis, data processing, manuscript writing; *I.V. Plokhikh*, *L.M. Dzhanbekova,* conceptualization, literature analysis, data processing, manuscript editing; *A.E. Tyan*, *G.I. Nafikova*, *G.I. Antipina,* discussion and interpretation of data, manuscript editing; *A.I. Bikbulatova*, *Yu.A. Rybina*, *M.S. Khulagov*, *M.I. Batdyeva,* data discussion; *K.M. Gaifullina*, *I.V. Vasilieva*, *A.E. Krivosheeva*, *I.A. Usmanov,* participation in manuscript preparation and approval of the final version. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding sources: The article was prepared out without attracting external funding.

Disclosure of interests: The authors declare no conflict of interests.

Statement of originality: The authors did not use previously published information (text, illustrations, data) while conducting this work.

Data availability statement: The editorial policy regarding data sharing does not apply to this work.

Generative AI: Generative AI technologies were not used for this article creation.

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