MACULAR EDEMA IN UVEITIS

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ABSTRACT
In the present study we have made a review of the relevant literature on pathogenesis and modern diagnostic methods for macular edema (ME) in uveitis.

Macular edema is a typical non-specific complication of uveitis, one of the common causes of visual impairment. ME can be found in all types of uveitis. In 85% of cases of intermediate uveitis, the visual impairment is due to the development of cystoid macular edema. The macula is more rarely affected in panuveitis (35%), anterior (20-26%) and posterior (20%) uveitis. The etiological agent is of great importance for the course and treatment of inflammatory diseases.

Among the imaging diagnostic methods that are capable of detecting macular edema with fluid accumulation in the retina (either diffuse or distributed in cysts) are the fluorescein angiography (FA) and the optical coherence tomography (OCT). OCT allows a quantitative assessment of retinal thickening and how it changes throughout therapy. FA can be used to determine very precisely the site of a vascular leakage and assess how badly the vascular wall has been affected by the inflammatory process.

CONCLUSION: Macular edema occurring during an inflammatory process is one of the causes for visual acuity loss in uveitis. OCT and FA are useful complementary imaging methods for investigation of structural changes in retinal architecture in uveitis patients.

Key words: macular edema, uveitis, optical coherence tomography, fluorescein angiography

INTRODUCTION
In ophthalmologic literature macular edema (ME) is considered one of the leading causes of impaired vision in eye diseases such as inflammatory diseases, vascular disorders of the retina and of the chorioidia, traction maculopathies, retinal detachment, intraocular tumours, etc. It is an abnormal thickening of the macula as a result of fluid and lipoprotein accumulation in the extra- and/or intracellular neurosensory spaces.1,2

ME and cataract as well as their combination are believed to be the most common cause of decreased visual acuity in patients with uveitis.3 Diseases of the uvea are one of the five leading causes of blindness in the developed countries along with diabetes, tapetoretinal degenerations, congenital anomalies and traumas, causing complete blindness in 10-15% of the cases.3-8 Diabetes and uveitis are potentially curable which justifies the research to find as good a diagnostic and therapeutic approach as possible.

AIM
The aim of this literature review was to clarify the pathogenesis, frequency and type of macular engagement in different types of uveitis depending on their anatomic localization and etiology and to assess the significance of the imaging diagnostic methods of fluorescein angiography (FA) and optical coherence tomography (OCT) for a diagnosis of macular edema in uveitis patients.

PATHOGENESIS
Studies have shown that ME, depending on the specific etiology, develops along different pathophysiological mechanisms: knowing them well is of much importance for the adoption of one or another therapeutic approach.9

Macular edema is thought to develop as a result of disruption of the blood-ocular or blood-retinal barrier: it can be external if the integrity of the retinal pigment epithelium (RPE) is destroyed and internal when the endothelial cells of the retinal...
vessels are affected.9,10 The contacts between the endothelial cells and the RPE cells are in the zona-lae ocludentes. The retinal vessels walls, including the capillaries, are non-fenestrated. This functional unit maintains the volume and composition of the extracellular space of the neurosensory retina and of the subretinal space. RPE has other functions besides being a barrier. Its functions include also the fluid exchange balance between the vitreous cavity and the choroid. The enzyme carboanhydrase in the cellular membranes of RPE act as a pump that evacuates the fluid from the vitreous cavity and the retina into the choroid vessels.9,10 Müller cells are thought to play an important role in acting as metabolic pumps which keep the macula dehydrated.10 Müller’s cells extend across the entire retina, from the external limiting membrane to the internal limiting membrane. They response to disruption of homeostasis by intracellular edema that causes the retina to thicken. The persistence of the edema leads to liquefactive necrosis of Müller cells and the formation of intraretinal cysts, predominantly in the outer neurosensory retina.11,12 The edema may also cause abnormalities in RPE enabling fluid to increase from choroidal capillaries to the retina.12,13

Blood-retinal barrier disruption in uveitis patients is a result of endogenous secretion of inflammation mediators which are a defensive immune mechanism in vertebrates.9,14 The source of these mediators is the arachidonic acid in the membrane phospholipids. Under the action of phospholipase A2 and phospholipase C, by cyclooxygenase and lipoxygenase pathways, respectively, prostaglandins, thromboxan A2 and leukotriens are formed, leading to vasodilation and increased vascular permeability (indirectly – via potentiation of other mediators).9,14 Other proinflammatory cytokines (small peptides regulating inflammation) like TNFα and IL-1β lead to damage (ruptures) of the blood-ocular barrier.9 Elevated levels of vascular endothelial growth factor (VEGF) in the ocular fluid have been found in patients with macular edema of uveitis origin. VEGF is a known pathogenetic factor, increasing the permeability of the endothelial cells.14,15 The disruption of the blood-ocular barrier leads to fluid accumulation predominantly in the outer neurosensory layers (outer plexiform layer).16

INCIDENCE

In the relevant literature the average annual incidence of uveitis has been reported as 17-52 per 100 000 population5,6 and depends on geographic, genetic, ethnic and environmental factors4,6. It has increased three-fold over the last decade as compared with the incidence 40 years ago. It affects predominantly people in the working age between 20 and 50 years, half of these patients being in the age range of 30-40 years.7,17 This age range of high prevalence defines uveitis as a disease with a considerable socioeconomic impact. Uveal disorders in people under 20 years occur 7 times as rare but run a more severe course.17

Uveitis has been reported to subside in many of the cases, but a considerable number of the affected patients develop a chronic persistent disease that damages the ocular structures and impairs the vision.7-9,17 Cystoid macular edema (CME), cataract and glaucoma are the major complications resulting from uveitis that causes reduction of the visual acuity. The onset of ME during the inflammatory process is one of the causes for vision impairment.9,17

The literature is quite ambiguous about a correlation existing between foveal thickness and visual acuity (for the different ocular disorders). Whereas Reinthal et al. (2004) did not find any correlation between foveal thickness and visual acuity, Ant-cliff et al. (2000) observed a weak correlation. In a recent study Sivaprasad et al. (2007) reported an inverse correlation between foveal thickness and visual acuity.34 Okada and Vujosevic (2007) published a study in which they demonstrate the correlation between retinal thickness, visual acuity and retinal sensitivity. Visual acuity is more often affected in patients with chronic and/or panuveitis than in patients with acute and/or anterior uveitis.8,19 Studies have shown that visual acuity in uveitis depends not only on macular thickness, but also on the duration of edema, small capillaries perfusion, photoreceptors damage, dysfunction of retinal pigment epithelium and ocular medium transparency.20

Macular edema is presented in literature as a typical yet non-specific complication which can occur in all types of uveitis but is predominantly observed in disorders of the vitreous body (in 85% of the cases of intermediate uveitis the vision impairment is caused by CME)21, but can occur also in anterior (20-26%), posterior (20%) uveitides and panuveitides (35%).22 Involvement of the posterior segment in the inflammatory process leads to macular edema, sometimes to papillary edema, to posterior vitreitis that causes loss of visual acuity and is hard to treat.23,24

The prevalent opinion is that endogenous uveitis
MACULAR EDEMA

The review of literature shows that priority is given in research to finding the most accurate method to diagnose macular edema. Fluorescein angiography and optical coherence tomography are two of the imaging modalities that can detect fluid in the retina. OCT can not only detect presence of fluid in the retina, but also show how it is distributed; and it also can quantitatively assess retinal thickness. Using FA we can identify the precise area of vascular leakage - hence the imaging modalities that are used in diagnosing secondary macular edema in uveitic patients are optical coherence tomography and fluorescein angiography.

Optical coherence tomography is a novel non-invasive, non-contact imaging modality for assessment of retinal and optic nerve diseases. Its principle of operation is similar to the one used in B-echography, but instead of sound waves it uses light waves emitted from a low-frequency laser with wavelength of 840 nm thus providing much greater resolution than in B-echography. The difference is in the different speed of penetration of light and ultrasound in the eye. The velocity of light is approximately a billion times greater than that of ultrasound. The wavelength of the light source used in the OCT units is close to that of the infrared light making it insignificantly visible to patients. This reduces the patients’ discomfort during the investigation as much as possible. Tissue light absorption and dispersion are detected based on the low frequency interferometry phenomenon.

There are two main categories of OCT instrumentation: Time-Domain OCT (TD-OCT) and Spectral-Domain OCT (SD-OCT). SD-OCT devices have many advantages over the TD-OCT devices: higher speed, greater resolution, more precise differentiation of retinal layers (resulting in “thicker” retina when measured by spectral OCT), capability of 3-dimensional reconstruction of the retina, etc.

When measuring the retinal thickness, which is the border between the internal limiting membrane (ILM) and the retinal pigment epithelium (RPE), all OCT devices define the internal limiting membrane as an internal border. The difference in retinal thickness measured by different OCT devices is a result of the different manner of determining the external border. Stratus (Time-domain) OCT determines the external retinal border above the connection between the internal and the external photoreceptor segment (OS/IS). Cirrus HD (Spectral-domain)-OCT and RTVue 100 (Spectral-domain) OCT include additionally the external segment and perform measurements closer to the RPE. 3D OCT-1000 (Spectral-domain) measures even closer to the RPE. The distance between RPE/ Bruch’s membrane and IS/OS is 60 μm to 80 μm, which explains the difference in measurement results of one and the same retinal thickness by different OCT devices.

The B-scan obtained with OCT has been shown to be a longitudinal cut through the retina displaying the separate layers according to their reflectivity. The highly reflective layers are depicted in red in colour scanograms or white in black-and-white ones, while low-reflective layers are blue or black, respectively. A normal retinal OCT scanogram in the macular area shows the foveal depression and layer structure. The choriocapillaris and RPE are highly reflective and are seen as a red band. Above them there is another red band corresponding to IS/OS border and the blue band of the low-reflective neural sensorium. With spectral OCT besides the two red bands (registered with time-domain OCT) corresponding to the choriocapillaris/RPE and IS/OS border, there is a third one corresponding to the most distal part of the outer neurosensorium segments which are highly reflective. The other highly reflective innermost red band corresponds to the layer of nerve fibers. Under it, there are the inner plexiform and nuclear layers, followed by the outer nuclear and plexiform layers, the plexiform layers being more reflective (they are perpendicular to the light) than the nuclear layers (cell bodies are parallel to the light). When using spectral OCT and good quality of the scanograms, another moderately reflective thin layer may be differentiated: it corresponds to the outer limiting membrane and is situated in front of the IS/OS segment layer.
There is consensus among researchers about the importance of measuring the retinal thickness in the foveal area, in which an edema can cause reduction of visual acuity. This determines one of the main applications of OCT in clinical practice – diagnosis and follow-up of ME. OCT diagnostic criteria for macular edema are: increase in retinal thickness, flattening of the foveal depression and decrease in retinal reflectiveness due to fluid accumulation, obliterating its layer structure with or without presence of cystic spaces. There are three OCT patterns of macular edema:

1. Diffuse macular edema (DME, sponge-like): diffuse, vaguely differentiated, hypo-reflective zone, characterized with thickening predominantly of the outer retinal layers, flattening of the foveal depression, and disruption of the layer structure of the retina. Histologically, it is an intercytoplasmic edema of Müller cells (Fig. 2).13

2. Cystoid macular edema (CME) – presents with cystic, hyporeflective spaces, separated by hyper-reflective bridges (septi) (Fig. 3). It is further subclassified as:
   2.1. External CME – the cysts are localized in the external retinal layers (more common).
   2.2. Internal CME – the cysts are localized in the internal retinal layers.
   2.3. Combined CME – presence of cysts throughout the entire retinal thickness.

Research has shown that all cystic areas visible on OCT result from a prolonged edema, and loss of Müller cells and retinal neurons. The fact that Müller cells are radially oriented explains why retinal edema and the cysts are not localized in a single layer.35 Large cystic areas visible on OCT are situated predominantly in the macular area. Smaller cysts can be detected in the parafoveal and extrafoveal areas. This coexistence of cysts with different sizes and localization is due to the macular structure. The initial cystoid changes can be found in the outer plexiform layer.34,35,36

The edema type is used for evaluation of consequent visual acuity. In cases of concomitant presence of both DME and CME type of edema, it is classified as CME. CME is more refractory to treatment compared to DME. In eyes with both types of edema, DME subsides faster. In some cases the edema that is found initially is DME which later becomes CME.34 The retinal thickness in CME is much greater than that in DME. External CME resorbs faster than internal CME the latter having a worse prognosis. A correlation has been found between the internal retinal cysts and the presence of epiretinal membrane (ERM – hyper-reflective membrane on the internal retinal surface), which explains why the resorption of internal retinal cysts is delayed. Clinically undetermined epiretinal membrane must be suspected in cases of persistent internal retinal cysts.34

3. Serious detachment of neural sensory layers in the macular area from the RPE/choriocapillaris – it presents with a clear split of the photoreceptor layer from the highly reflective RPE.33 The two layers form an acute angle (20-30°) at the edge of the detachment, and the area under the photoreceptor layer is typically low-reflective (Fig. 4).22 It is
due to a disturbed pump function of RPE and fluid accumulation between RPE and the photoreceptor layers. The serous neurosensorium detachment does not correlate with the duration of uveitis and shows good response to therapy. Pathogenetically, it is unclear; it is associated not only to impaired vascular permeability, but also to impaired pump function of RPE.21,34

OCT is reported in literature as a method capable of making an important qualitative and quantitative assessment of ME.13,34,35 It can determine the edema type and find the localization of the edema, measure retinal thickness, assess the ERM condition, detect serous neuroepithelium detachments and follow-up and assess its development during the course of the disease and the response to therapy.34

Fluorescein angiography is an imaging diagnostic method which has been used for more than 50 years in ophthalmology; it can provide “in vivo” information about the retinal vascular circulation and about the pathophysiology of retinal arterioles, capillaries and venules. Water solution of fluorescein sodium salt injected intravenously is used in FA. Fluorescein angiography utilises the fluorescence emitted by fluorescein which is excited by exposure to blue light at a wavelength of 465–490 nm, and glows in the yellow-green section of the spectrum (520–530 nm).38

This procedure should be performed with the following relative contraindication taken into consideration: first trimester of pregnancy, allergy, renal failure (dose adjustment is needed), severe heart or pulmonary failure. Possible side-effects include: yellow colouring of the skin, mucous surfaces and urine; nausea; transient headache; allergic reactions; provocation of severe acute glaucoma due to maximal midriasis.38

The central part of the macula, fovea centralis, is 1.5 mm in diameter, with the foveola in the centre of the fovea (0.35 mm), which normally lacks capillaries – a foveolar avascular zone. This area has a clinical and diagnostic significance; it usually overlaps with the size of the fovea, but is characterized with great variability of FA: from 250 to 600 μm in healthy people. It is usually round or oval in shape and is surrounded by a single layer of capillaries forming the perifoveolar vascular circle, whose disruption is detected by FA.36-38

FA presents the possibility of assessing blood-retinal barrier integrity as a whole. If damaged, fluorescein diffusion in the extravascular space of the neurosensorium is observed. Edemas are categorised in three groups depending on the degree of blood-retinal barrier damage:
1. Focal edema – focal hyperfluorescence as a result of a leakage in an area in which there are microaneurisms and/or locally dilated capillaries. The intact section of the macula has good macular perfusion.1,2
2. Diffuse edema – diffuse leakage in the macula which is seen in FA as widespread leakage of fluorescein involving the whole circumference of the fovea and delayed diffuse hyperfluorescence. The retinal morphology remains unchanged in diffuse edema.1,2
3. Cystoid edema – the dye pools in the outer plexiform layer in the newly formed cystoid spaces of the macula shown in FA as a petalloid (Fig. 5) or honeycombed pattern (Fig. 6) of hyperfluorescence in the late phase.1,35

In the petalloid pattern of fluorescence we can see clearly demarcated circular hyperfluorescent areas different in size found only in the macular centre. The large cystoid areas of hyperfluorescent are in the outer nuclear and plexiform layers.35
Fluorescence of the honeycomb type is seen predominantly in the parafoveolar area visualised as multiple small circular hyperfluorescent areas of different intensity. Cystic spaces are found in the outer and the inner nuclear and plexiform layers.

Serous detachment of neurosensory layers can be diagnosed only by OCT despite the fact that very late FA phases (30-60 minutes) may reveal edema in some cases. Microaneurisms and neovascularization are visualized solely by FA which however is an invasive method and might cause systemic complications, while OCT is harmless and may be performed repeatedly.

In the presence of adequate retinal compensatory mechanisms, fluorescein leakage would not be widespread and would not lead to fluid accumulation and retinal thickening. In uveitic patients the blood-retinal barrier is damaged early, while the compensatory mechanisms are still preserved and the early vascular injury is visualized with FA. In these cases FA is a more sensitive method for detecting macular edema.

There is a significant correlation between OCT and FA findings, especially when CME is diagnosed. The cystoid macular edema visible on FA is always visualized on OCT, while the diffuse FA leakage may be seen as diffuse or cystoid in OCT which makes OCT a more sensitive method than FA in CME diagnostics.

In some cases, a transitory leak that has already ceased would not show on FA but would be seen in OCT as a fluid space before compensatory mechanisms have removed the extra retinal fluid.

Optical coherence tomography allows morphological assessment of structural changes in different retinal layers, and FA presents qualitative assessment and information about the anatomical sites of the vascular leakage. Although fluorescein leakage indicates where thickening is likely to get increased, it does not give a measure of thickening itself. OCT is a method allowing detection and measurement of changes in retinal thickness. When these two methods are used jointly they present a more comprehensive picture of the pathophysiological mechanisms of ME.

**CONCLUSIONS**

Macular edema occurring in the course of the inflammatory process is one of the causes for vision reduction in uveitis. Knowledge of its pathogenesis and the use of diagnostic methods for its early detection is important for an effective treatment.

OCT and FA are useful complementary imaging methods for investigation of the structural alterations in retinal architecture in uveitis patients. OCT and FA are necessary for the diagnosis, follow-up and prognosis of the sight recovery after retinal diseases treatment.

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OTEK MAKULY PRI UVElITE
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РЕЗЮМЕ
Отек макулы (OM) представляет типичное неспецифическое осложнение в ходе развития увеита. Его появление является одной из причин понижения зрительной функции. OM может наблюдаться при всех типах увеита. В 85% случаев с интермедиарным увеитом повреждение зрения объясняется развитием кистоидного OM. Реже макула затрагивается при панувеитах (35%), за которыми следуют передние (20-26%) и задние (20%) увеиты. Этиологический возбудитель играет существенную роль при ходе и лечении воспалительных заболеваний.

Флюоресцеиновая angiography (FA) и оптическая кохерентная томография (OST) представляют образно диагностиические методы, с помощью которых можно регистрировать OM с наличием флюида в сетчатке (диффузно или распределённо в виде кист). OST позволяет дать количественную оценку толщины сетчатки и ее динамики в ходе лечения. С помощью FA точно можно определить место существующего сосудистого ликвиджа (вытекания) и оценить поражение сосудистой стенки вследствие воспалительного процесса.

ВЫВОДЫ: Появление отека макулы в ходе воспалительного процесса является одной из причин снижения зрения при увеите. OST и FA полезны, взаимно дополняющиеся образные методы исследования структурных изменений в архитектонике сетчатки у пациентов с увеитом.