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Macular edema in ocular inflammation

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ABSTRACT

Aim of this paper is to present the pathophysiological processes and the ultrastructure of the retina, important for the formation and development of macular edema. Macular edema is defined as an abnormal leakage and fluid and/ protein accumulation in the external plexiform layer and inner nuclear layer (on/under the macula), as well as swelling of Muller cells that lead to its thickening and swelling. It occurs as consequence of increased leakage from the retinal perifoveal capillaries and consequential macular thickening that, if it lasts longer than 6 months, is seen as chronic in nature. Based on clinical and imaging techniques, macular edema is classified as ischemic and non-ischemic (cystoid or diffuse). Macular edema is not an isolated ocular disease but is rather a complication of an isolated ocular inflammation or of an ocular inflammation that's associated with systemic non-infectious (autoimmune) or infectious diseases. This paper, in addition to the pathogenesis and clinical manifestations of macular edema, also briefly covers imaging and treatment procedures and emphasizes the importance of treating the underlying inflammatory diseases that has led to the formation of the macular edema.

Methods: This was a retrospective and observational study.

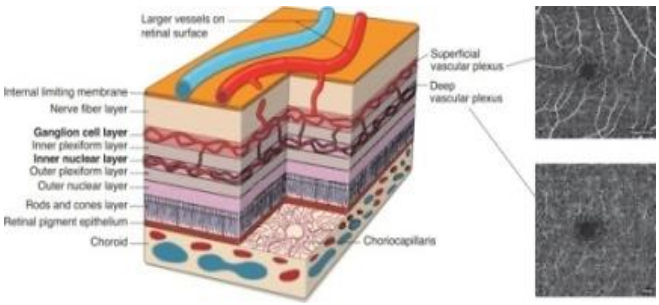
Keywords: blood retinal barrier; Muller cells; retinal pigment epithelium; cytokine; inner blood retinal barrier; outer blood retinal barrier; optical coherence tomography; angiography; ocular inflammation; macular edema.

Introduction

Understanding the basic anatomy of the eye and the ultrastructure of the retina is of the utmost importance for our understanding of, amongst some, the blood retinal barrier (BRB), and the pathological processes that occur such as macular edema (ME).

Neurosensory retina is a thin transparent structure that develops from the inner layer of the optic cup and is made up of neuronal; glial; and vascular elements i.e. of 13 retinal layers: internal limiting membrane (ILM); nerve fiber layer (NFL); ganglion cell layer (GCL); inner plexiform layer (IPL); inner nuclear layer (INL); middle limiting membrane (MLM); external plexiform layer (OPL); outer nuclear layer (ONL); external limiting membrane (ELM); rod and cone inner segments (IS); rod and cone outer segments (OS). [Fig.1]

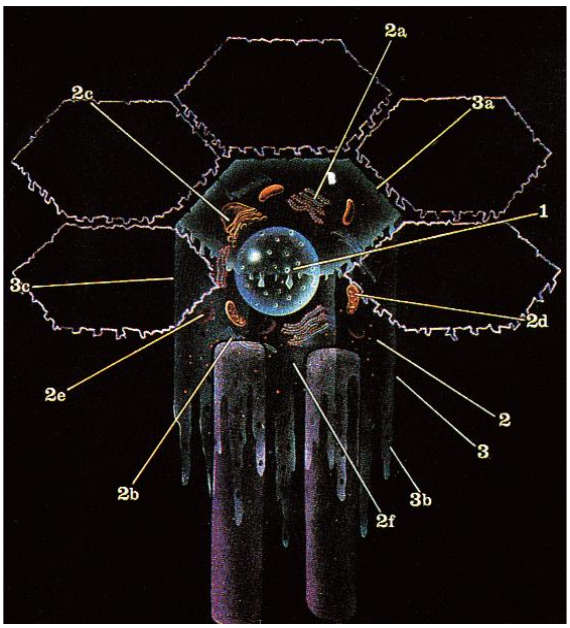
Fig.1 Anatomy and ultrastructure of the retina



Angiograms by Brar MD, Vikram S and schematic by Mark Miller

Photoreceptor layer of the **neurosensory retina** is made up of: **outer** (OS)(site of phototransduction that contains highly specialized neuroepithelial cells called rods and cones whose OS is made up of parallel stacked membranes that contain visual pigment such as opsin that's charged with retinal and is surrounded by a mucopolysaccharide matrix which makes contact with the apical processes of the retinal pigment epithelium (RPE)) and **inner segment** (IS)(one of the most metabolically active sites in the body with regards to oxygen consumption and protein production; cytoplasmic component of the photoreceptor cell packed with mitochondria and rough endoplasmic reticulum). As central retina, superiorly and temporally to the optic nerve, is a relatively cone-rich zone, rod and cone photoreceptors can be distinguished by the shape of their IS.[1] [Fig.2]

Fig.2 Retinal pigment epithelium cell



1. nucleus; 2. cytoplasm; 2a. rough reticulum; 2b. smooth reticulum; 2c. Golgi body; 2d. mitochondria; 2e. lysosomes; 2f. pigment granules; 3. cell membrane; 3a. basal region; 3b. apical region; 3c. lateral region

Outer segment (OS) of the photoreceptor represents the outermost layer and interacts with the apical processes of the RPE. OS of the photoreceptor cell and the RPE **have no tight junctions or other intercellular connections** between them.

External limiting membrane (ELM) that separates the photoreceptor nuclei from its OS and IS **isn't a true membrane** but is formed by the attachment sites of the adjacent photoreceptors and the Muller cells and, as it is highly permeable, it allows oxygen and macromolecules to pass from the choroid into the outer retina.

Outer nuclear layer (ONL) contains nuclei of cone and rod photoreceptors.

Outer / external plexiform layer (OPL) is made up of synapses between the photoreceptors and the bipolar cells and is the region into which horizontal cell fibers descend and regulate synaptic transmission. Radial fibers in this portion of the OPL are known as the **Henle's fiber layer** (HFL).

Middle limiting membrane (MLM) is **not a true membrane** but a **junctional system** in the inner third of the OPL where synaptic and desmosomal

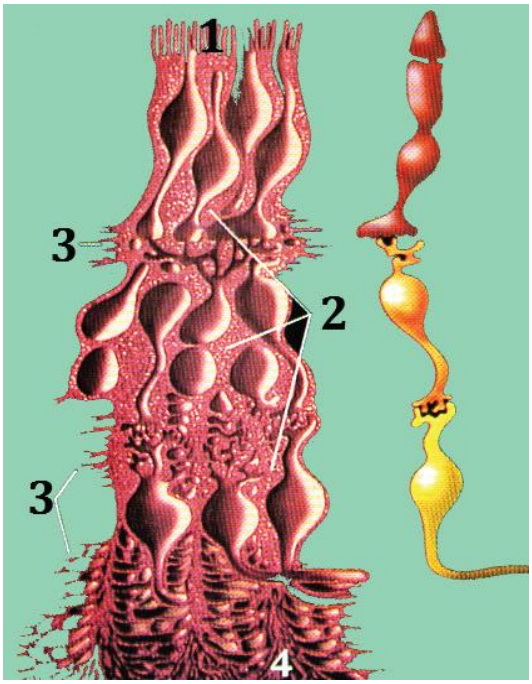
connection (mechanical cell-to-cell adhesion that allows for some flow between cells) occurs between inner fibers of the photoreceptors and processes of bipolar cells.

Internal limiting membrane (ILM) is **not a true membrane** as it is formed once Muller cells' footplates attach to the basal lamina. Basal lamina of the retina has different thicknesses and appears wavy on the retinal side (where it follows the contour of Muller cells) and smooth on the side of the vitreous. ILM; the posterior vitreous cortex; and an intervening extracellular matrix make up **vitreoretinal interface** (VRI).[2]

Macula lies between the temporal vascular arcades and has fovea in its center which in turn has a specialized region known as the foveola in its center. On the edge of the foveola HFL lies almost parallel to the ILM so that once these extracellular spaces are filled with fluid or exudates there is formation of petaloid or star-shaped patterns.

Special part in the pathophysiological processes in the retina is attributed to the **Muller** and RPE cells.[Fig.3]

Fig.3 Muller cells



1. fibers in a shape of an inverted cone; 2. honeycomb network; 3. horizontal fibers; 4. radial expansion

Muller cells were first proposed as a specific subtype of cells in 1969 by Yamada (and interpreted by Gass as a central "plug") and it was stated that they exist in the central fovea and provide structural support to the foveal cones (Gass referred to as specialized Muller cell cones i.e. look like inverted cones).[3,4,5] Muller cells are **glial cells**, that extend (vertically) from the ELM (inward) to the ILM, whose nuclei are located in the INL where they provide structural support and nutrition to the retina, are thus of vital importance for normal physiology.[2] Muller cell processes, along with unmyelinated cone and rod photoreceptors axons, make up the HFL between the ONL and OPL, thus making the Muller cell component of the HFL of particular relevance in the parafoveal region where they may even be equal in number to the cones.[3,6,7] Subsequently, as Muller cells in the parafoveal region (unlike the central inverted plug) have a z-shaped anatomical configuration in the HFL, they may guarantee structural stability of the parafovea by increasing retinal compliance and resistance to mechanical stress and in so doing protect the parafoveal photoreceptors from tractional forces. On the other hand, as Muller cell processes run together with axons of the cone and rod cells structural damage at this level may compromise the capacity of photoreceptor to synapse in the OPL, which would lead to a decrease in visual acuity (VA). Presynaptic damage to the photoreceptors' axons and the mechanical stretching of the HFL could interrupt or degrade photoreceptors' signaling and potentially contribute to vision loss in schitic disorders.[3]

Retinal pigment epithelium (RPE) consists of a single row of mononuclear, hexagonal cells that are connected to each other by occludent bonds (junctions) that are equivalent to the **blood-retinal barrier** (BRB) and thus prevent the passage of water and ions. RPE is the first tissue to be pigmented (melanin is the basic pigment of the RPE and it's found in cytoplasmic granules i.e. melanosomes) and, whilst melanogenesis continues throughout ones life, as we get older, melanin granules fuse with lysosomes and disintegrate so that the fundus becomes less pigmented. Besides melanin, which is important for

both its role in the absorption of light (reduces light scattering in the eye) and in stabilizing free radicals that bind retinotoxic drugs, there is another important brownish pigment called lipofuscin that accumulates with time and that is present both in the **central nervous system** (CNS) and in the RPE. Lipofuscin originates from lipids found as part of photoreceptor OS, so that RPE takes it up and degrades and it can then subsequently be deposited together with other membrane fragments on the basement membrane (Bruch's membrane or *lamina vitrea*). So, RPE is important not only as its cells are rich in mitochondria and actively participate in oxidative metabolism, i.e. they contain antioxidant enzymes (superoxide dismutase and catalase) thus reducing the production of free radicals that can damage lipid membranes, but also as it plays a role in formation and maintenance of the photoreceptor matrix that is important for retinal adhesion.[8]

Additionally, RPE plays a role in production of growth factors (i.e. **platelet-derived growth factor** (PDGF), **pigment epithelium-derived growth factor** (PEDF), **vascular endothelial growth factor** (VEGF), **fibroblast growth factor** (FGF); etc.) through which RPE controls the vascular endothelium, its permeability, recovery and proliferation (reparative processes).

Due to the fact that RPE releases proinflammatory mediators (such as cytokines: interferon β (IFN β); interleukin 1 (IL-1); interleukin 6 (IL-6); interleukin 8 (IL-8); monocyte chemoattractant protein 1 (MCP-1)) and that it is able to present itself as an antigen presenting cell to the immune system, it can participate in amplification of the inflammatory pathway (e.g. IFN β balances expression of pro- and anti-inflammatory mediators).

Barriers and transport systems

Retina is a highly metabolic structure that has dual circulation in which its' innermost layer is supplied by the branch of ophthalmic artery (i.e. central retinal artery) and its' outer layer is supplied by the choroid. Retinal blood vessels are akin to the cerebral blood vessels and maintain the inner BRB.[1]

In order for a dry medium to be maintained (i.e. that the hyaloid membrane remain attached to the retina) there must be an equilibrium between the vitreous body; retina; and the choroid (a steady flow of fluid from the subretinal space to the choroid in which inner and outer BRB play an essential role). A process that is guaranteed both by the integrity of the structures that form the inner and outer BRB and by the osmotic forces that exist across them.

BRB not only separates blood from the surrounding retinal tissue and regulates flow of blood and proteins from the surrounding tissue but it also regulates efflux of leukocytes from blood into the surrounding tissue (in case of inflammation).

Inner blood retinal barrier (on the capillary level) is a result of close association between neurons; glia; pericytes; and the vascular endothelium and is located in the inner retinal microvasculature whilst the **outer blood retinal barrier** consists of junctions **between** RPE **cells** (tight; adherent; and gap). The most important function of inner BRB is to regulate transport of fluid and various molecules across retinal capillaries. Alteration in transport (paracellular and/ transcellular) across vascular bed can result in an increased permeability and thus changed flow.

Interendothelial cell transport (paracellular transport) occurs between endothelial cells. This transport is regulated by molecular complexes that are located in the intercellular spaces (made up of three types of junctions: tight; adherent; and gap).[9]

Tight junctions form a "watertight seal" that blocks water and ions and consist of transmembrane proteins (occludins; claudins; and **junctional adhesion molecules** (JAM)) that are linked to the actin cytoskeleton (by cytoplasmic-scaffolding proteins that are necessary for formation of tight junctions).

Adherent junctions are made up of vascular endothelial cadherins and, as they are crucial for VEGF-R interaction, play a key part in both development of the retinal barriers and regulation of paracellular permeability.[9,10,11]

Gap junctions are chiefly part of cells that propagate electrical signals. They are aggregates of intercellular channels that act like tunnels and allow for direct cell to cell transfer of water, ions and small molecules and are vital for passing rod-mediated signals throughout the retina.

Transendothelial cell transport (transcellular transport) involves migration of plasma membrane vesicles (containing receptors for transferrin; albumin; immunoglobulins; lipoproteins; insulin; and various growth factors such as: PDGF; VEGF; and transforming growth factor β (TGF β)) from one side of the cell to another.[9]

As caveolae-mediated transcytosis regulates entry of plasma macromolecules into the retinal tissue (transcellular transport) it has an important role in upholding retinal protein gradients and thus in adjusting movement of fluid.[9,10,11]

Neurovascular unit (so called), through interaction of macroglia (Muller cells and astrocytes) with mural cells, i.e. pericytes (specialized cells involved in regulation of expression of tight junction proteins and in modulating the inner BRB in physiologic and pathologic conditions) and smooth muscle cells, provides, and aids in, selective and well regulated setting for the proper functioning of retinal cells.[9,12,13] So, for example as, retinal capillaries have pericytes on the luminal surface they directly contribute to the endothelial barrier function (ratio of density of pericytes to endothelial cells being 1:1).

An essential role in the neurovascular unit is played by a type of macroglia (i.e. the Muller cells) that are the **barriers' functional link** (i.e. directly connected with the blood vessels and responsible for the formation and maintenance of the retinal barrier) and are supported by microglia that are involved in retinal immunological surveillance as they are able to influence Muller cells to regulate extracellular homeostasis.[9,14]

Outer nuclear layer and remaining layers of the outer retina are perfused by the choroid. In terms of perfusion, the OPL represents a "watershed zone". Perfusion by the two circulations can differ, not only depending on location or on retinal thickness, but also depending on exposure to light.[1,2]

Outer BRB is made up of RPE and intercellular junctions (including tight; adherens; and gap junctions) and regulates transport **between** the choriocapillaris and the retina and via osmosis maintains the adhesion between the photoreceptors and the RPE. On the other hand, transport **across** retinal capillaries is regulated by the inner BRB.

Important role of RPE in the transport of water and electrolytes is in that fluid is pumped against strong hydrostatic or osmotic pressure from the retina to the choroid. Its membranes contain selective ion channels and transport systems for the transport of ions; metabolites; glucose; and amino acids.

These channels differ from each other and are located in the basal and apical part of the cell. While sodium-potassium pump is active at the apical part, chlorine-bicarbonate exchange takes place at the level of the basal membrane of the pigment cells. It is due to these pumps that water and ions move **transcellularly**. Movement of water and electrolytes in the apical-basal direction of the RPE generates current. Water transport can be reduced by blocking the transfer of ions in the basal direction or by stimulating transfer in the apical direction.

Disorders of the barrier (such as its disruption) can cause fluid to leave the subretinal space faster due to intraocular pressure (IOP) and osmotic "suction" (originating from the choroid). Junctions between RPE cells play an important role in preserving the dryness of the subretinal space e.g. disruption of the RPE intercellular junctions can allow fluid to enter from the choroidal space. Unlike retinal vessel, choroidal capillaris are characterized by extensive attenuation of the endothelium and numerous fenestrae.[9]

Macular edema

Macular edema (ME) is defined as an abnormal leakage and fluid and/ protein accumulation in the

OPL and INL (on/under the macula), as well as swelling of Muller cells that lead to its thickening and swelling. It occurs as consequence of increased leakage from retinal perifoveal capillaries and consequential macular thickening that, if it lasts for longer than 6 months, is seen as chronic in nature.

Macula is a region of the retina that is rich in highly metabolic cells, and is a primary site for inflammatory; vascular; and metabolic processes. Horizontal orientation of Henle fibers in relation to ILM facilitates fluid accumulation and cyst formation (cystoid cavities surrounded by Muller cells). Although fluid can accumulate in all of the retinal layers it does so less frequently between OPL and ELM.[15] ME is seen on the OCT as retinal layering that's followed by presence of intraretinal cavities in the absence of back-reflection.[15]

According to the mechanism of occurrence, ME can be **ischemic** (associated with ischemic maculopathy); **nonischemic** (focal and diffuse) and **tractional**.

Ischemic macular edema can occur due to relative macular ischemia, as consequence of capillary nonperfusion on the macular border which results in increased avascular region (>500μm), and cell damage which occurs once it is >1000μm. On the other hand, vascular occlusion results in protein leakage from blood vessels and the formation of the edema.[16]

Focal or cystoid macular edema (CME) occurs when perifoveal liquid accumulates in the OPL. Cysts that occur are of radial orientation and look like a sunflower.

In 1975 Gass was first to describe an opening of a cystic roof (an abortive process) of a **lamellar macular hole** (LMH) as persistent CME.[17]

It is possible that the tissue that covers the base of the LMH, (that's formed as a result of spontaneous closure of **full thickness macular hole** (FTMH)), originates from Muller cells that have spread and proliferated from the ELM to the ILM. Anatomical recovery that follows also leads to functional visual recovery.[17]

Diffuse macular edema is diffuse fluid accumulation in the macula that leads to macular swelling and thickening.

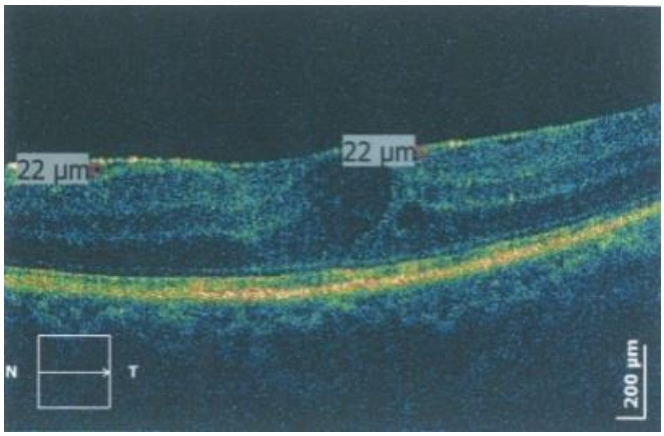
Tractional macular edema is caused by retinal wrinkling and contraction of the **epiretinal membrane** (ERM) i.e. upon tractional ERM retina is disrupted (in layers) which allows for fluid accumulation that can, due to the absence of reflectance, on an OCT image be seen as small cysts. Loss of normal foveal contours is considered to be one of the early signs of retinal deformation and can be attributed to development of ERM and subsequent formation of ME.[15]

Epiretinal membrane (ERM) (macular pucker) is an avascular fibrocellular membrane that develops on the inner surface of the retina and can result in various stages of macular dysfunction.[18] Complex pathophysiological mechanisms are involved in membrane formation and they are based on tissue damage and reparation of the same.[18]

In cases in which there is residual in the form of posterior vitreal capsule, ERM occurs subsequently to **posterior vitreous detachment** (PVD) and in turn to ILM detachment and hyalocyte proliferation on its inner surface, which in turn causes inner retinal surface contractions that are themselves followed by contractions of the ILM. Small break on ILM occurs during PVD and allows macro- and micro- glial cells to proliferate along the inner retinal surface thus forming ERM.[15,19,20]

Usually, ME is caused by distortion and traction of ERM on the intraretinal blood vessels that results in disturbed retinal microcirculation and decreased capillary flow in conjunction with the loss of apposition between the retina and the RPE. [Fig.4] Thickening and stratification of the retina and intraretinal fluid accumulation (cystoid or diffuse ME) together with withdrawal of central foveal layers can be a result of **persistent macular traction**.

Fig.4 Tractional epiretinal membrane and CME



As it is actually the preservation of the photoreceptor layer that is of the utmost importance for good visual function the fact that ERM (that does or doesn't bridge the fovea) sustains tractional ME and that good VA is associated with low **central macular thickness** (CMT) on its own is of little consideration.[18,21]

Pathophysiology

Many factors are responsible for sustaining an equilibrium that is essential for proper functioning of the body. Understanding pathogenesis allows for better understanding and thus management of the underlying disease.

Macula i.e. the fovea has three capillary networks that form anastomotic rings so that there exists a high density of blood vessels. On the other hand macular OPL with its' interconnected fibers can act as great basins for fluid accumulation which can lead to decreased reabsorption of extracellular fluid.

Passive forces (intraocular pressure (IOP)) push fluid into the retina, while **osmotic pressure** and **active forces** provide active transport of matter on the level of RPE, thus drawing fluid and molecules from the retina into the choroidea.

Development of intra and extra cellular ME can be explained through Starlings' law and occur as consequence of a disbalance of inflow and outflow of fluid (any amount of fluid entering the retina also has to leave the retina in order for it to remain dry) and retinal hydraulic conductivity that results in breakdown of BRB and intraretinal and subretinal fluid accumulation (changed equilibrium).[9]

Intracellular macular edema occurs if BRB is intact but, as ionic arrangement between intra and extracellular spaces has changed (i.e. there is higher Na concentration in the cells thus forming cytotoxic edema), retinal cells swell.

Extracellular edema occurs when both inner and outer BRB are disrupted (state of which is best confirmed by **fluorescein angiography** (FA). Increase of inner and outer BRB permeability results from numerous mechanisms that act synergistically to cause passage of extracellular fluid into the retina (most often in the OPL and INL or in the subretinal space i.e. subretinal fluid) and subsequent accumulation of the same in cavities (cysts).

There are numerous factors that are of importance for the pathogenesis of **inflammatory ME** such as: capillary endothelial damage caused by breakdown of BRB; vascular incompetence; RPE dysfunction; changes in membrane conductance as consequence of acting osmotic forces and increased permeability (leakage and accumulation of fluid and protein in the extracellular space); production of proinflammatory mediators e.g.: leukocyte adhesion molecules and nitrogen monoxide (NO) prostaglandins; leukotrienes and cytokines (IL-6; IL-10; IL-1; IL-8; INF α; INF β; INF γ; tumor necrosis factor α (TNF α)). Cycloxygenase as an enzyme that participates in cascade of arachidonic acid and production of prostaglandins is responsible for the increased permeability of blood vessels and formation of the ME.[9,22] Activation of **glial cells** (**microglia and macroglia**) i.e. of Muller cells (**macroglia** that regulate homeostasis of the extracellular space) and of **microglia** (that are involved in retinal immunological surveillance) through VEGF and proinflammatory cytokine production contributes to changes in permeability of the vessels. Elevated levels of VEGF (that are produced by activated glial cells) upregulate intercellular adhesion molecule 1 (ICAM-1) and lead to increase in permeability, dysfunctional retinal barrier and leukocyte extravasation.[9,10]

Several inflammatory mediators, including cytokines and VEGF, and activation of matrix metalloproteinase

can alter the proteins constituting intercellular junctions.[9,10,14] Adhesion and expression of **tight junction proteins** is regulated by VEGF that will, through interaction with its receptor, induce a cascade of intracellular phosphorylations of vascular endothelial cadherins and occludins that will together with the production of metalloproteinase, that is stimulated by other inflammatory mediators, lead to degradation of tight junction proteins thus resulting in a loss of integrity of the BRB and consequential increase of capillary permeability (disruption of RPE intercellular junctions favors fluid accumulation in the subretinal space).[9,23,24]

It has been shown that **Glial fibrillary acidic protein** (GFAP), expressed in the OPL and HFL, may contribute to the biomechanical properties of Muller cells via upregulation of intermediate filaments after mechanical stimulation. GFAP expression in Muller cells is a very sensitive indicator of stress. GFAP distribution may support the assumption that Muller cell processes in the HFL underlie the structural stability of the parafovea.[3,25,26]

Important role in the pathogenesis of inflammatory ME, besides glial cells, is played by mastocytes.

Mastocyte (/mast cell) are granulocytes derived from myeloid stem cells that are part of both the immune and neuroimmune systems, not only release various proinflammatory factors (including cytokines; chemokines; prostaglandins; growth factors; and proteases) but are also rich in heparin and histamine (vasodilator). Release of histamine from the mastocytes can seriously affect the integrity of retinal barriers through the control of transcription of VEGF-regulated genes (including genes for proteins that are important for the structure of the tight junctions).[9]

Degranulation of mastocytes plays an essential role in ocular inflammation (first activated cells in **experimental autoimmune uveitis** (EAU)) and is involved in outer retinal barrier dysfunction.

Muller cells participate in the local immune response and surveillance (release of immunomodulatory mediators) and regulate extracellular homeostasis through aquaporins and transmembrane potassium channels (Kir) where reduction of potassium (K) conductance is involved in development of cytotoxic edema (characterized by cell swelling and death of the Muller cells).[9,27]

In physiologic condition neural activity requires that there be rapid intake of sodium (Na) and calcium (Ca) into the nerve cell and this is directly associated with excretion of K from the extracellular space where Muller cells potassium channel (Kir 4.1 and Kir 2.1) ensures that there is rapid transfer of K from the extracellular environment into its intracellular space (as to avoid accumulation and neuronal hyper excitability). Kir 4.1 channels work simultaneously with integral membrane proteins that conduct water through the cell membrane (aquaporin 4 (AQP-4) that's encoded by the AQP-4 gene) in the extrusion of K and water via ATP-dependent active transport into the retinal capillaries.

In case of inflammation there will be an overall decrease in synthesis and/ a mislocation of Kir 4.1 channels that will result in anomaly polarized cell; intracellular edema; and subsequent accumulation of subretinal fluid.[9]

Results of experiments preformed on normal and inflamed rat eyes suggest that in both endogenous and therapeutical corticosteroids control the expression and localization of Kir and AQP-4 channels.[9,10,27] Increased vascular permeability can occur (under condition of stress) due to the fact that cells can produce both proinflammatory cytokines and vast amounts of VEGF.[9] So, in physiological conditions, besides macroglia, microglia are directed towards immunosuppression as well, and can, turn to a proinflammatory state and in so doing influence the Muller cells' capability to regulate extracellular homeostasis.[9]

Prevalence and incidence of ME, depend both on chronicity of the inflammation and on how persistent traction ERM is, and can lead to disruption of the photoreceptor layer and thus substantially affect visual outcome (whilst permeability and size of ME don't have to correlate with it).[16,28]

Partial reabsorption of ME can be under the influence of both TNF α blockers and anti-VEGF that are thus part of the treatment plan.[16,29]

Intraocular inflammation is a well-known cause of ERM and those ERM which are specifically associated with uveitis differ from idiopathic ones in their cellular composition and appear characterized by inflammatory cells such as macrophages; microglia; and Muller cell extensions, suggesting that the etiology stems from diverse pathogenic mechanisms[9] Intraocular inflammation can hence lead to formation and exacerbation of epimacular membrane as proinflammatory mediators are identified (i.e. in the vitreous) and they include: TNF α; activated complements; fibrinogen; and other innate immune response factors.[9,30] Proliferation of cellular components and contraction of the membrane can result in **vitreomacular traction** (VMT) and localized elevation with ME.

Retinal stress can initiate an innate immune response which is programmed to neutralize "negative" stimuli and restore homeostasis which then leads to activation of immune competent retinal resident cells (i.e. Muller cells; microglia; and RPE) that are associated with the production of proinflammatory mediators (i.e. VEGF; cytokines; histamine; prostaglandins; chemokines; and other factors) that influence permeability resulting in BRB breakdown and ME. Activation of various inflammatory pathways will lead to UME (further demonstrated by the effectiveness of treatment with corticosteroids).[9,31]

Etiology of inflammatory macular edema

According to Standardization of Uveitis Nomenclature (SUN), UME is considered to be a structural complication of uveitis that can occur both as part of the disease course or as a post-op complication and at the same time isn't associated with any particular anatomical location.[32]

ME can develop in intermediate; posterior; panuveitis; anterior uveitis (most often cyclitis); and retinal vasculitis (caused by different autoimmune and infectious etiologies i.e. Behcet's disease; sarcoidosis; systemic lupus erythematosus; etc.).

Vasculitis belongs to a heterogeneous group of diseases in which some or all blood vessels, i.e. only arteries; only veins (more frequently); arteries and veins; or capillaries (capillaritis), are target of an abnormal immune response. **Systemic vasculitis,** that can be primary or secondary, is defined as an inflammation of the blood vessels localized in the eye and in various other systems and organs.

Clinically, it is a pathological process that is (in an acute phase) characterized by inflammation and blood vessel wall necrosis that can (in a chronic phase) due to thickening of the wall, result in ischemia and formation of new blood vessels (neovascularization).[16]

Retinal vasculitis (RV) can occur isolated (only retinal blood vessels are affected by inflammation so that it is deemed to be an autoimmune response, i.e. autoimmune anti-retinal anti-S antigen vasculitis) and/ in conjunction with systemic inflammation of various blood vessels throughout the body.[16] On the other hand, there is an increased risk of ME in the older population as retinal cells decrease their functioning with time and coupled with intraocular inflammation can, due to cellular dysfunction and vascular incompetence, result in increased entry of fluid through the retinal vessels and reduced drainage through the RPE.[9] Additionally, atherosclerotic lesions can lead to cardiovascular diseases which can be affirmed by high blood pressure; hypercholesterolemia; increased BMI; and prolonged heavy smoking to name but a few, which can in turn also modify structure and function of microscopic blood vessels through the activation of a low-grade systemic inflammatory response that involves oxidative stress; leukocytes diapedesis; and endothelial barrier dysfunction which can all lead to systemic microvascular leakage. Microvascular leakage can take part in the development of UME (trace microalbuminuria present).[9]

Other mechanisms that are involved in the **etiology of UME** include: inflammatory choroidal vascularization; severe complication of intraocular

inflammation as a result of pathological process that involve the RPE and Bruch's membrane; papillary edema that diffuses contiguous to macular area and central chorioretinopathy that's exacerbated by chronic use of corticosteroids.[9,31]

Diagnostic procedures and imaging techniques

Diagnostic methods and tests for assessment of macular function are: VA test (Snellen chart); color vision and contrast sensitivity test; electroretinography (ERG); and Amsler grid eye test.

Necessary, reliable methods used for diagnosis of transparent media are: **direct and indirect ophthalmoscopy** (fundoscopic exam); **fluorescein angiography** (FA); and **optical coherence tomography** (OCT).[16]

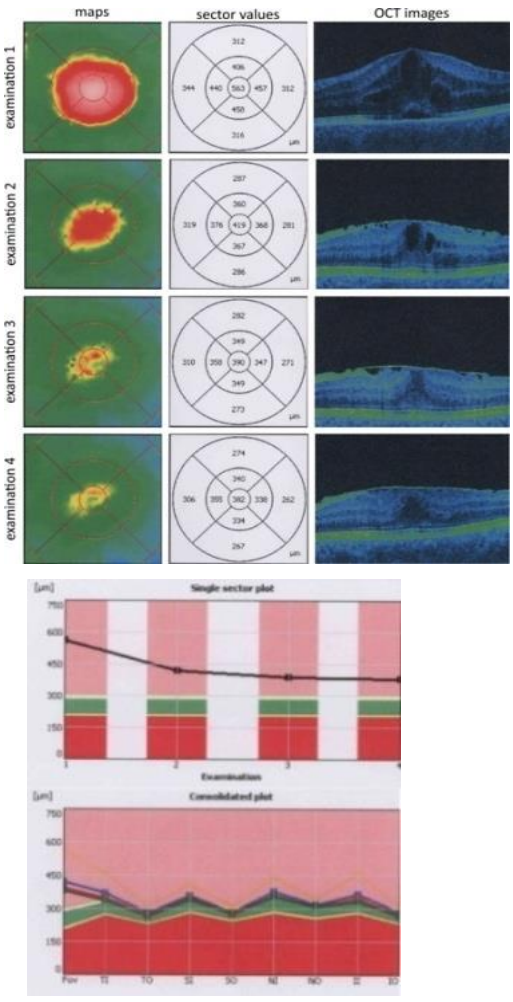
Fluorescein angiography registers fluorescein leakage from the capillaries and RBV and allows for analysis of the **state of the inner BRB** and accurate determination of the areas of capillary leakage and the type of ME. FA provides clear difference between diffuse ME (inadequately defined regions of hyperfluorescence and abnormal capillary leakage) and CME (cystic spaces localized in the OPL that are filled with fluorescein and look like a flower), and in case that any ME persists for an extended period of time cystic spaces can merge and result in an irreversible macular disorder.[16]

If RPE layer is disordered as consequence of inflammatory process in the choroid, outer BRB can be viewed with the aid of **indocyanine green (ICG) angiography** (choroidal blood vessels contain free ICG molecules).[16]

Invasive procedures such as **FA and ICG** are used in evaluation of BRB disruption and evolution of choroidal neovascularization (CNV) but they will not be able to provide data on the extent of these structural changes and as such are not as good in follow-up of intraretinal and subretinal edema and evolution of ERM whereas will OCT provide more in-depth information of the deep tissues and any histological changes that might have occurred.[15]

Optical coherence tomography is a noninvasive, qualitative and quantitative, high resolution imaging technique used to acquire *in vivo* cross sectional images of the retina; measure macular thickness (volume; average; and central macular thickness) and to view changes of the photoreceptor layer (e.g. photoreceptors; pigment epithelium; subretinal space; ILM; and ELM).[16] Thus, as it can be repeated, OCT (Spectral-Domain OCT (SD-OCT); High-Definition OCT (HD-OCT); Swept-Source OCT (SS-OCT); etc.) is especially useful for follow-up and assessment of: treatment and evolution of macular changes; size and localization of vitreoretinal adhesions; size of ERM and its' distance from the "surface".[16] So, OCT is a very useful tool used to determine the difference between diffuse and cystoid ME; measure the size of retinal cysts and amount of subretinal fluid; as well as to analyze changes of the vitreoretinal interface (VRI) and the state of the subretinal neovascular membrane (NVM) (from abortive to developmental stages). [Fig.5]

Fig.5 Sarcoidosis; OCT treatment follow-up



OCT is an only "imaging tool" that allows for acquiring of histopathological data without performing actual invasive histopathological techniques.

Disorganization of the inner retinal layers (DRIL) is an OCT feature represented by disruption of any one of the two boundaries of INL with the **ganglion cell-inner plexiform layer** (GCIPL) and OPL. Being distinct from other OCT-based biomarkers, DRIL can not only **qualitatively evaluate** the structural disruption in the inner retinal layers but also **quantify their extent.** Transverse diameter of the baseline DRIL is significantly associated with the best corrected visual acuity (BCVA) at different time points and thus can be a reliable biomarker for predicting the BCVA prognosis.[3,6,26]

Due to other underlying factors in case of uveitis and subsequently UME it is imperative that frequent OCT follow-up as well as multimodal imaging be made so that "more information" may be acquired.[33] Histopathologically this correlates to Muller cells in the retinal layers swelling and increasing in volume so that eventually they undergo necrosis and cystoid spaces are formed. **It is for this reason that when it comes to ME there exists a difference between angiograms (FA) and OCT imaging i.e. sometimes cystoid spaces may be degenerative so that there is no accumulation of fluid and the pigment may not cause the cystoid spaces to disappear as they are actually caused by necrosis itself.**[32] Interestingly in **UME there seems to be higher discrepancy** between FA and OCT as compared to other diseases such as retinal vein occlusion (RVO).

OCT angiography (OCTA) is a noninvasive 3D imaging technique that makes use of laser light reflectance of the surface of moving red blood cells to accurately depict vessels through various segmented areas of the eye, thus eliminating the need for intravascular dyes. It is based on the fact that variations in signal caused by moving particles (i.e. red blood cells) allows for the assessment (visualization) of perfused retinal and inner choroidal vasculature so that there is no need of dye injection. OCTA is particularly useful modality for evaluating retinal and choroidal blood flow in patients with inherited retinal diseases.

Treatment

In case of UME visual prognosis depends on the state of retinal layers and duration of the edema i.e. chronic inflammation and longstanding edema inevitably lead to an irreversible disruption of the neural architecture of the retina and subsequent permanent visual loss. It is deemed that ME (with or without uveitis) is one of the most common causes of visual impairment and blindness throughout the world, a high incidence of which can partially be attributed to late detection due to late patient arrival or to either inadequate examination or inadequate applied imaging techniques.[32]

Whilst choosing the appropriate treatment for ME in RV it is important to check: is ME unilateral or bilateral; is ME acute or chronic; is ME ischemic or nonischemic; and what is the etiology of the ME.

Treatment of ME depends on the etiology of the primary disease that has led to the ocular disease as well as on its' chronicity. Even though a consensus has not been reached as to precisely how and when to treat ME there are a number of different options such as for example: ME is only to be treated in the presence of an inflammation; and irrelevant of the absence of inflammation on the eye fundus, if ME is chronic is it to be treated.[16]

Pharmaceutical agents; laser photocoagulation (LFC); and **surgical intervention** can be applied in treatment of ME.

Systemic, autoimmune, noninfectious diseases that have led to the ocular disease and ME should initially be treated with **systemic agents** (e.g. corticosteroids; immunosuppressive; immunomodulatory; biological). Systemic infectious diseases are to be treated with adequate systemic agents.

If systemic therapy is not part of the treatment plan then ME as complication of vasculitis is to be treated with **local medication** and/ surgery.

Local treatment of ME in both, systemic noninfectious as well as infectious cases, consists of drops; subtenonial; parabulbar; and intravitreal corticosteroid agents. Besides locally administered agents nonsteroidal anti-inflammatory drugs (NSAID) and carbonic acid anhydrase inhibitors (in form of drops) are also ordained. In order to stabilize the BRB, besides pharmaceutical agents, treatment of ME requires that **retinal laser photocoagulation** (LFC) be applied as the energy from the laser will coagulate the necrotic RPE cells thus causing proliferation of the adjacent RPE cells and stabilization of tight junction BRB bonds.[16]

Grid LFC is applied in case of uveitic ME as it destroys cells surrounding the affected region, and in so doing decreases their oxygen requirement that thus diffuses from the choroid into the retina only to increase the arteriolar and decrease the hydrostatic pressure in the capillaries and venules.[16] Therefore, better flow of oxygen in the arterioles and reduced hydrostatic pressure in capillaries and venules lead to decreased permeability and to reduced ME.

Surgical intervention is to be performed for e.g. in case of tractional ME caused by contraction of the ERM that leads to retinal layering; decreased pressure within the retinal tissue; and at the same time, increased hydrostatic pressure difference between blood vessels and retinal tissue which leads to ME. Complete release of VMT, i.e. release of ERM, brings about the resolution of macular cysts and ME and subsequent improvement of visual functions. So, surgical intervention (PPV) can be performed in case of intermediate uveitis associated with ME that doesn't respond to pharmaceutical agents.[16]

On the other hand, **vitrectomy** is seen as a method with the aid of which it is possible to remove the vitreous thus increasing the transport of oxygen between the anterior and posterior segments and removing several inflammatory mediators that were located in the vitreous and responsible for development of the ME.

Conflicts of Interest Statement:

The authors have no conflicts of interest to declare.

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