Macular edema in uveitis

with emphasis on

ocular sarcoidosis

Colofon

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Macular edema in uveitis with emphasis on ocular sarcoidosis

Macula-oedeem in uveïtis met nadruk op oculaire sarcoïdose
(met een samenvatting in het Nederlands)

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1. General description

Macular edema (ME) is an accumulation of fluid in the retinal layers of the macula and is a major reason for loss of visual acuity (VA) in uveitis and other ocular diseases. The macula is the central yellowish area of the retina, which provides sharpest vision and color discrimination. Uveitis is a clinical name for intra-ocular inflammation. Uveitis strictly means inflammation of the uvea, the pigmented vascular middle layer of the eye, comprised of the iris, choroid and ciliary body. In practice, inflammation of the retina or the vitreous is also called uveitis. The intra-ocular inflammation can have an infectious or non-infectious etiology. Non-infectious uveitis is in 25% of the cases associated with systemic diseases.[1] In a recent study of 1076 patients with uveitis, 155 patients (14%) had a systemic inflammatory disease and 116 (11%) had a systemic infection (toxoplasmosis, tuberculosis, HIV, herpes infections).[2] The incidence of uveitis in Western countries is estimated to be 25-52 cases per 100 000 population per year, the prevalence 58-115/ 100 000.[3-5] No accurate estimates are available for developing countries. The peak in the distribution of age at onset of uveitis is in the third and fourth decades. In the United States and Europe, 5-10% of the legal blindness is caused by uveitis,[6] in developing countries approximately 25%.[7] Blindness and/or visual impairment (VA <0.3) develops in at least one eye in 28% of all patients with uveitis, in 41% due to ME.[8] In 35% of the eyes with ME, the VA was less than 0.3.[8] The risk factors for ME include specific uveitis entities (sarcoidosis, birdshot chorioretinopathy and acute retinal necrosis), the anatomical location (panuveitis and intermediate type)[8] and the severity of the uveitis. Increasing age is also an important risk factor for development of ME in uveitis, but is also associated with a decreased ability to recover vision after therapy.[9,10] Smoking was also found to be a risk factor for cystoid ME.[9,11,12]

2. Imaging

a. Optical Coherence Tomography

ME can be diagnosed by slit lamp biomicroscopy, but subtle cases can be missed. Traditionally, fluorescein angiography (FA) has been the diagnostic tool for detecting and documenting ME, but in recent years, Optical Coherence Tomography (OCT) has become the routine diagnostic tool to diagnose and monitor ME. This technique was introduced commercially in 1996 and is analogous to ultrasound imaging. Instead of using sound, light is used to acquire high resolution retinal images. A beam of light (laser) is directed onto the retina. The magnitude of the reflected or backscattered light is measured using low-coherence interferometry.[13] First, the time domain (TD-) OCT technique became available. In 2006, a large improvement was obtained by the introduction of the spectral domain OCT (SD-OCT), by mainly a higher scan resolution (axial scan resolution SD-OCT 5 μm vs TD-OCT 10 μm) and reduction of motion artifacts (SD-OCT 18000 vs. TD-OCT 400 axial measurements/sec).

Spectral domain is a type of Fourier domain detection that measures light echoes from all time delays simultaneously. Especially on the RPE-level, new reflection lines can be distinguished with SD-OCT.[13-15] Moreover, in patients with poor media clarity (as often occurs in uveitis), SD-OCT is better than TD-OCT.[15] There are substantial differences in measured retinal thickness between TD- and SD-OCT and between different SD-OCT devices, due to different definitions of the outer retinal border. The retinal thickness measured with a Cirrus OCT is 43 µm greater than measured with a Stratus OCT, which is probably caused by the Cirrus OCT detection of the outer band of the retinal pigment epithelium (RPE) versus the Stratus OCT detection of the inner/outer segment photoreceptor junction (IS/OS junction). Moreover, correlation of measurements of the (peri/para)foveal zones is variable.[16] The retinal layers visible on the SD-OCT images are shown in Figure 1:

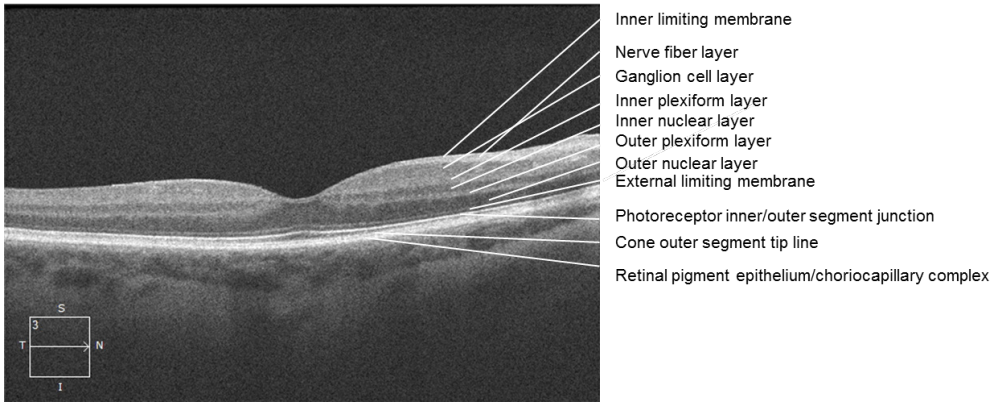

Figure 1. SD-OCT image of a normal retina

Spaide and Curcio showed that the IS/OS junction line in fact aligns at the level of the ellipsoid portion of the inner segments,[17] but for simplicity, the term IS/OS junction line will be used in this thesis.

b. Fluorescein angiography

Fluorescein ($C_{20}H_{12}O_5$) is a diagnostic marker with a molecular weight of 332 g/mol that is injected in the antecubital vein and reaches the eye in 10-15 seconds. With excitation light having a wavelength of approximately 494 nm (blue), green fluorescent light is emitted at a peak wavelength of 521 nm that is captured by the fundus camera. The retinal circulation is usually visible 1-3 seconds after the onset of choroidal filling. At 30 seconds, the first pass of fluorescein through the retinal and choroidal vasculature is complete followed by recirculation phases. At 10 minutes only a low concentration of fluorescein is present in the circulation. Approximately 80% of the fluorescein is bound to albumin and much of the fluorescence we observe clinically is from free fluorescein.

In the choroid, fluorescein extravasates freely, but in the retinal circulation fluorescein stays intravascular because of the blood retinal barrier (BRB). In a broken BRB, leakage of fluorescein into the retina (and vitreous) occurs. The sclera stains in the late phase of the angiogram. In uveitis, FA can reveal many features of intraocular inflammation and a grading of the uveitis severity has been developed.[18] Besides hyperfluorescence, hypofluoresence can also occur during angiography due to reduced perfusion, ischemia or just blocking of fluorescent light by blood or pigment.
FA technically shows neither the movement of water (the fluorescein molecule is larger than water (18 g/mol, although it will go along with the water flow) nor protein, such as albumin (66500 g/mol), because the fluorescein molecule is too small. Since free fluorescein passes through channels that do not pass protein, 'leakage' on FA does not always indicate protein leakage or edema. Studies on retinal thickness (e.g. on OCT) have shown that fluorescein leakage does not always correlate with retinal thickness. Some areas of fluorescein leakage show little edema, perhaps because the barrier damage is only modest and small molecules are moving quickly through the retina without holding much water. Alternatively, some areas of thickening show little leakage, perhaps because the swelling of cells is more prominent than an accumulation of extracellular fluid. Moreover, angiography with fluorescein or indocyanine green (a fluorescent dye that binds to the large LDL-/HDL-molecules) is worthwhile, because angiography can reveal typical features of choroidal, retinal, RPE- and optic pathology in several ocular diseases.[19] FA reveals physiological information and OCT reveals anatomical information. Discrepancies between OCT and FA have been described in ME of various origins, but results were contradictory. So far, no systematic studies are available comparing specific FA and OCT values for ME in uveitis and analysis of possible discrepancies.

3. Clinical classification of macular edema

Retinal edema is commonly found in the macula and Scholl et al.[20] postulated that the macula is predisposed for the development of an edema due to its unique anatomy which is characterized by:

- maximal retinal densities of cone photoreceptors and their second- and third-order neurons, which cause a high level of metabolic activity and high oxygen and glucose demands. Under normal conditions, the photoreceptor inner segments consume all oxygen supplied by the choroid, and even slightly hypoxic conditions have serious metabolic consequences.
- a relatively long distance for oxygen diffusion from the choroid across the photoreceptor outer segments, which are much longer in the macula than in the peripheral retina.
- a potential reservoir for the accumulation of extravascular fluid due to the thickness and loose binding of inner connecting fibers in the outer plexiform layer;

· a central avascular zone, in which decreased resorption of extracellular fluid occurs.

ME is the accumulation of fluid in the outer plexiform layer/Henle's layer and the inner nuclear layer as well as swelling of Muller cells of the retina. ME can be diffuse or cystoid. Both patterns can be accompanied by a serous retinal detachment (incidence 19.5-29%), but also by an epiretinal membrane.[21] Descriptions of the subtypes are given in Table 1:

Table 1. Anatomical subtypes of ME

subtype	OCT-characteristics
cystoid	hypo-reflective lacunae within the retina. In early CME, the cysts are primarily located in the outer retinal layers. In chronic CME, large confluent cystoid cavities might develop, involving the entire retinal layer.
diffuse	sponge-like thickened retina with reduced intraretinal reflectivity, located particularly in the outer retinal layers
subretinal fluid	shallow dome-shaped elevation of the retina with an optically clear space between the retina and the RPE
vitreoretinal interface abnormalities:	
epiretinal membrane	a highly reflective layer on the inner retinal surface
vitreomacular traction	perifoveal vitreous detachment with focal adhesion to the fovea.

a. Cystoid macular edema

Cystoid ME has a configuration with radially orientated, perifoveal, cyst-like spaces. Larger cysts are frequently surrounded by smaller peripheral cysts. The cysts are actually pseudocysts: areas of the retina in which the cells have been displaced: the fluid-filled compartments are spanned by the trunks of Müller's fibers.[22] In normal condition, it is estimated that 34-68 adjacent bipolar neurons (diameter 0.5 µm) are around the circumference of each Muller cell (diameter 5-10 µm), but in ME the Muller fibers will swell and a loss of Muller fibers and bipolar axons will occur.[23] Figure 2 shows an OCT-image of cystoid ME and its FA-image.

Two angiographic types of cystoid ME can be distinguished. A petaloid appearance in the foveal region on FA is based on cysts in the outer nuclear layer and/or Henle's layer according to the OCT. A honeycomb cystoid appearance at the periphery of the previously mentioned petaloid pattern in FA are cysts in the inner nuclear layer on

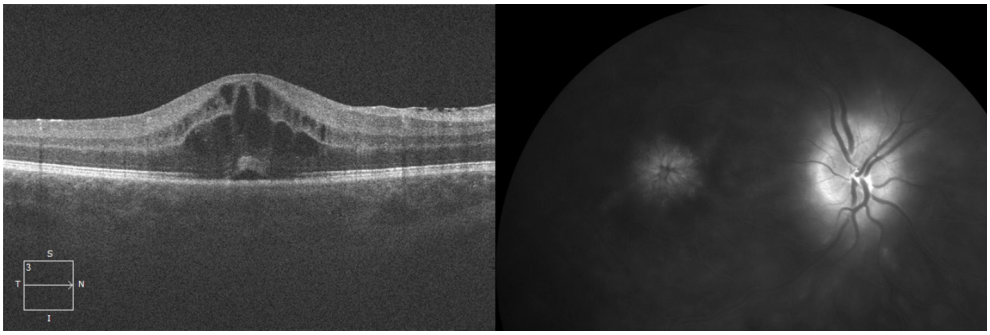

Figure 2. Cystoid macular edema on OCT with corresponding FA-image at 10 minutes after fluorescein injection.

OCT.[24,25] A cystoid (petalloid/honeycomb) pattern of FA leakage is always associated with cysts on OCT, usually in the inner nuclear layer, outer plexiform and outer nuclear layers of the retina.[24,26,27]
The reason of missing microcysts on FA (on a SLO-system) in eyes with diffuse macular leakage, is the higher horizontal resolution of the scanning laser SD-OCT compared to the FA-images.[26]
Multiple authors have reported microcystic changes in the central macula of patients with optic neuropathy of various etiologies, including multiple sclerosis (MS), which predominantly involve the inner nuclear layer. They hypothesized that microcysts developed due to retrograde synaptic degeneration. Recently, it has been shown that the presence of microcysts in the inner nuclear layer is a SD-OCT sign of cystoid ME, that is not specific for optic neuropathies.[28]

b. Diffuse macular edema

Diffuse ME on OCT might be explained by intracellular fluid accumulation and intracytoplasmatic swelling of Muller cells.[29] Diffuse ME is hard to investigate, because the changes are often subtle, as well as the increase of retinal thickness is. Thicknesses >304 µm with the Cirrus OCT (mean plus two standard deviations) is considered pathological and indicative of edema, but the question is whether what is clinically significant. Figure 3 shows an OCT-image of diffuse ME and its FA-image.

Different OCT-devices use different definitions of the outer retinal border,[30] and there is no simple correction available for comparison of retinal thickness measurements.[31] In ME, often only the perifoveal area is thickened, but no large normative database is available on these specific areas. An example of thickening of the perifoveal area is a ring-like pattern of retinal thickening outside the 1 mm foveal center that is frequently observed in active iridocyclitis that usually normalizes after the flare-up.[32-35] Also, retinal

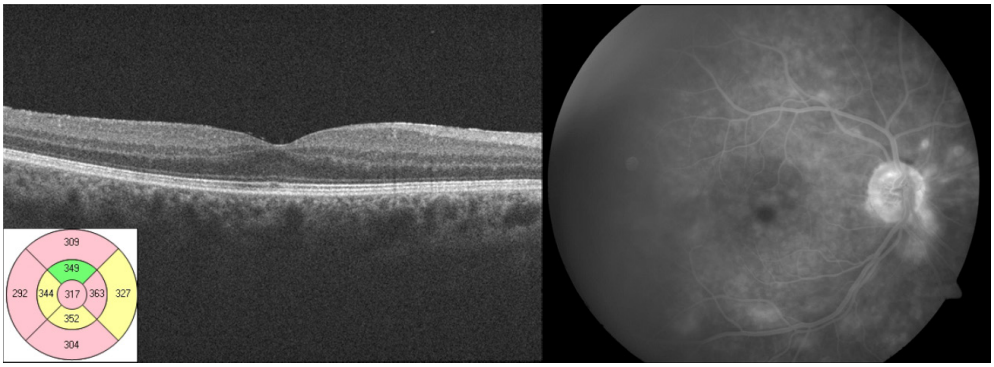

Figure 3. Diffuse macular edema on OCT with corresponding FA-image at 3 minutes after fluorescein injection. Insert on the left: subfield retinal thicknesses (RT) in the central 6 mm of the macula (μm). Pink indicates RT>99th percentile, yellow RT>95th percentile, green RT within normal limits.

thickness depends on race and age of the patients.[36] Individual serial measurements are the gold standard for tracking disease.

c. Subretinal fluid

Both diffuse and cystoid ME can be accompanied by the accumulation of subretinal fluid (SRF) under the fovea. The clinical relevance of SRF in ME is not known. The main question is whether SRF indicates the severity of ME or whether the origin of the subretinal fluid results from a different mechanism. Candidates are (1) dysfunction of outer retinal barrier (2) traction of the Muller cell cone on the external limiting membrane (ELM) and IS/OS junction or (3) dysfunction of the ELM. Clinical studies are needed to gain insight in this phenomenon.

d. Epiretinal membrane

Epiretinal membranes (ERM) often occur in chronic uveitis. In a large study of 598 uveitis patients, 41% were found to have an ERM on SD-OCT imaging, most frequently in intermediate uveitis. In this series, the VA was significantly lower in eyes with an ERM.[37] Secondary membranes in uveitis differ from idiopathic membranes,[38] because they are associated with a thicker retina, lower VA, have more often an associated partial posterior vitreous detachment and more often retinal cysts. In both idiopathic and secondary membranes, diffuse attachment was more common than focal attachment of membranes.[37] ERM in uveitis was found to be associated with the loss of one line in VA, after adjusting for confounding factors as central retinal thickness.[37] In an earlier publication, features associated with poor vision in ERM were an ERM in the foveal center, a focal attachment of ERM to the inner retina with loss of normal anatomic features, a disruption of the IS/OS-junction and a thicker ERM in the fovea. Features

that correlated with CME were focal attachment of the ERM to the inner retina and loss of foveal concavity.[39]

An ERM contributes to the pathogenesis of ME probably by a combination of several mechanisms. Firstly, the intraretinal vessels are distorted due to the traction, resulting in leakage. Secondly, the macular microcirculation is disturbed resulting in a reduced capillary blood flow. Thirdly, a loss of apposition between retina and the RPE-pump occurs.[40] ME secondary to ERM generally is characterized by non-cystic changes on SD-OCT.[26]

Figure 4 shows the development of an ERM in a 62-year-old female patient with ocular sarcoidosis, despite aggressive medical treatment:

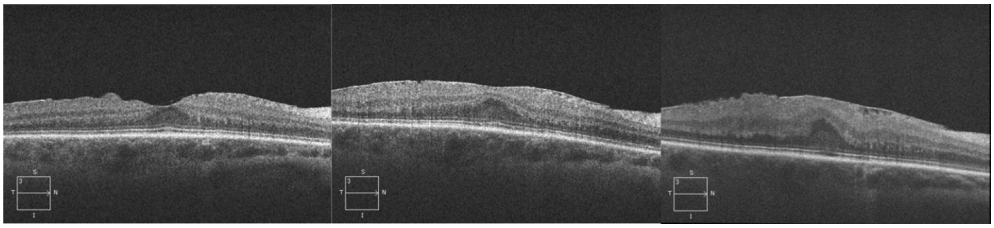

Figure 4. SD-OCT of the macula of a patient with ocular sarcoidosis. Left: visual acuity (VA) is 0.80, middle: 9 months later VA=0.78, right: another 8 months later VA=0.62.

- **Treatment of epiretinal membrane**

The best approach to treatment of ERM associated with uveitis is not yet clear. An ERM often reflects a chronic course of the uveitis. The presence of an ERM was also associated with persistence of ME after 1 year under medical treatment.[41] Recently it was shown that ERMs with surface wrinkling occurring in uveitic ME were associated with poorer VA response to medical therapy and thicker maculae at 6 months.[42] In practice, before considering surgery, medical treatment is usually attempted. Figure 5 is an illustration before and after medical therapy:

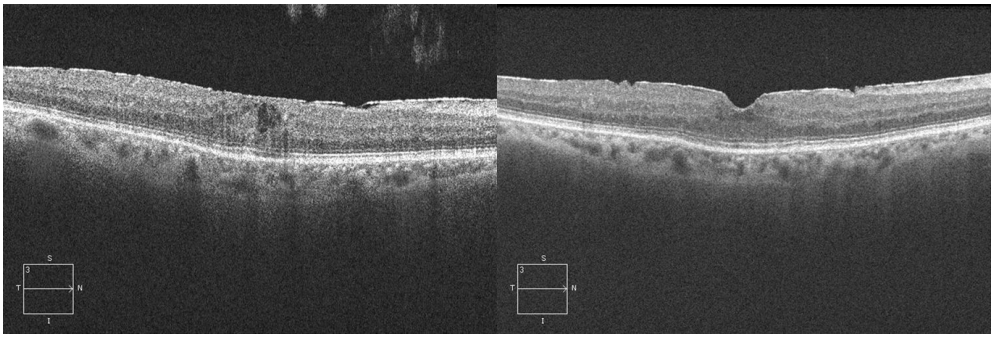

Figure 5. Uveitic macular edema with an epiretinal membrane, left: before medical therapy, VA=0.65, right: 4 years later, after treatment, VA=0.75.

Disturbed binocular vision by metamorphopsia is commonly considered as an indication for surgical removal of the ERM. In case of merely a gradually declining VA, it is more difficult to predict whether surgery would be beneficial for visual functioning. An intact IS/OS-junction line or a smaller thickness of the outer nuclear and outer plexiform layer were found to be a prognosticator for a good visual outcome in removal of idiopathic epiretinal membranes.[43,44] Although the anatomical appearance is often improved after surgery, inevitably, retinal ganglion cells are lost during peeling of the inner limiting membrane.[44] A personalized approach is advised.[45] Ocular surgery in uveitis patients carries the risk of a flare-up of the uveitis and to minimize this risk, surgery should be preferentially performed during inactive periods of uveitis and preventive treatment during surgery with local or systemic steroids is advised.

e. Vitreous traction

Vitreous traction may also play in a role in the development of ME as demonstrated by the findings of Hirokawa and colleagues (1985). They showed that uveitic eyes with complete vitreous detachment tend to have fewer macular changes than the eyes without.[46] The importance of an attached vitreous in ME was demonstrated by the presence of an attached vitreous in 78% of eyes with CME versus in 22% of eyes without CME.[47,48] The indications for pars plana vitrectomy in uveitis remain to be elucidated.

4. General principles of the blood ocular barrier

A dual vascular system supplies oxygen and nutrients to the retina: the retinal and the choroidal capillaries. The retinal capillaries nourish the inner two third of the retina, the choroidal capillaries the outer third of the retina, containing the photoreceptor cells. The retinal capillaries consist of three plexuses in the inner retina: the deep and intermediate plexus in the inner nuclear layer and the superficial plexus within the ganglion cell layer (Figure 6A, left side). At the foveal rim, the three plexuses form an anastomotic ring that is called the central capillary ring, surrounding a central, avascular, foveola.[22]

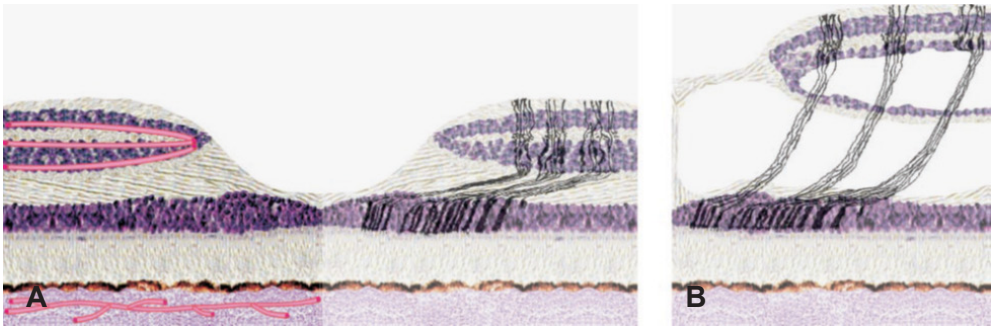

Figure 6. A. Left side: Retinal and choroidal capillaries in the macula. Right side: Z-shaped morphology of the Muller cells in the macula. B. Retinal cysts in the outer plexiform layer and in the inner nuclear layer. Published with permission of dr. A. Bringmann.[22]

In the eye, a blood ocular barrier exists, similar to the blood brain barrier (BBB), composed of the blood aqueous barrier, which is located in the epithelium of ciliary processes, and the blood retina barrier (BRB). The BRB protects the neural retina from potential harmful molecules in the blood circulation. The barrier regulates ion, protein and water flux into and out of the tissue. Various mechanisms make up the blood-tissue barrier:[49]

a. Tight junctions (zonulae occludentes) form the boundary between the apical and basolateral membranes of the endothelial or epithelial cells and actively participate in the intracellular trafficking of membrane proteins. These membrane proteins are distributed asymmetrically among domains of plasma membranes, which is called polarity. Polarity is important for active transport, transcytosis and solute modification (see following items no. 3-5). Besides this fence function, tight junctions also have a gate function: small solutes can diffuse across tight junctions, but the junctions allow some solutes to diffuse more rapidly than others. Tight junctions are complex structures that are dynamically regulated. In fact, we should speak of an apical junctional complex, which is built from tight junctions, adherens junctions[50] and gap junctions (communicating junctions). Tight junctions are composed of proteins that can be grouped into transmembrane (f.e. occludin en claudin), adapter, and effector proteins. Together, they form an interacting network or interactome. Claudins are a family of tight junctional proteins that play an important role in determining ion selectivity and they make junctions leakier or tighter.[49]
b. Facilitated diffusion through channels in the plasma membrane, that only works according the concentration gradient. Channels allow diffusion in either direction, but are specific for certain solutes. It should be noted that lipid-soluble molecules can passively cross a blood-tissue barrier. This transport is proportional to the lipophilicity.[51]
c. Active transport by pump proteins that consume ATP. They accomplish the movement of solutes against a concentration gradient or they establish electrochemical gradients that drive transport through antiporters and cotransporters, which are carriers that couple the transport of one solute with another that diffuses down the electrochemical gradient.
d. Transcytosis: vesicles with contents invaginate and bud from the membrane on one side of the monolayer cell and traverse the cell to the opposite membrane and release the contents there.
e. Solute modification: before a solute has the chance to cross a barrier, it can be degraded or it can be transformed into something else.

5. Blood retinal barrier

The retinal capillaries have a continuous endothelium with a barrier function. The choroidal capillaries have an endothelium that is highly fenestrated and permeable. The BRB can be divided in the inner retinal barrier, located at the retinal endothelium, and the outer retinal barrier, located in the retinal pigment epithelium (RPE). As described above, across this BRB, selectively regulated transport of molecules is possible by two pathways: the paracellular pathway (regulated by dynamic opening and closing of inter-endothelial junctions), and the transcellular pathway (specialized transport vesicles and receptor mediated transport). BRB and BBB capillaries are distinguished from systemic capillaries by the reduced permeability of tight junctions and low rates of transcytosis.
Pericytes, whose number is relatively high in the BRB, contribute to the regulation of the vascular tone. They also secrete extracellular material and they are phagocytic. They induce mRNA and protein expression of occludin and other protein junctions.[52] Pericytes serve for communication with other cell types that are involved in the BRB.
Fluid enters the retina from several sources: (1) intraocular pressure drives fluid from the vitreous humor toward the choroid, (2) the retina has a high metabolic rate, and (3) there are no lymphatic vessels to collect the fluid typically extravasated by capillaries.[19] There is a continuous movement of small molecules (mainly water) from the vitreous cavity into the inner retina and through RPE to the choroid, because a small part of the humor produced by the ciliary body enters the vitreous cavity (the major part flowing to the anterior chamber).The ILM offers only resistance to the diffusion of macromolecules, but water and other small molecules flow through the extracellular tissue spaces.
The movement of fluids across capillary walls can be described by Starlings' rules: net water transport over the endothelium is determined by the sum of hydrostatic pressure and osmotic pressure of the luminal and extraluminal compartments. An increase in tissue osmotic pressure and/or an increase in luminal hydrostatic pressure can lead to edema.
In contrast to smaller solutes, large plasma proteins do not easily diffuse across the vascular wall via the paracellular route. BRB loss for macromolecules is thought to depend mainly on increased transcellular transport by actively enhanced transcytosis.[54] Large plasma proteins play the most important role in formation of tissue edema, creating differences in osmotic pressure between the intra- and extravascular compartment and tissue water homeostasis.
Various cells located in the retina play an additional role in homeostasis: the retinal glial cells, which include Muller cells, astrocytes and microglia.[54] The glial cells that are involved in the BRB, are the Muller cells (in the superficial capillary plexus in the ganglion nerve cell layer) and the astrocytes (in the intermediate and deep capillary plexus in the inner nuclear layer). The Muller cells stretch from the outer to the inner limiting membrane and are in close contact with the neurons and support them (Figure 6B). The cell bodies lie in the inner nuclear layer and irregular processes are projected

towards the inner and the outer limiting membrane. The astrocytes envelop ganglion cell axons and are also associated with the blood vessels in the nerve fiber layer. Both cells have processes that wrap around retinal blood vessels. The main function of these glial cells is the uptake of neurotransmitters from nerve terminals, but they also are involved in the uptake of nutrients and the disposal of waste products and therefore play a major role in the formation and maintenance of the BRB by active communication between neural cells and vascular cells. Glial cells are able to secrete factors which either enhance or decrease the tightness of the barrier provided by the vascular endothelium. The end-feet of Muller cells and astrocytes control the barrier properties of the endothelial cells, for example by enhancing the expression of a tight junction protein.[52]
The outer limiting membrane is constituted by adherens junctions between Muller cells and between photoreceptors and Muller cells. The inner limiting membrane is formed by the conical end-feet of the Muller cells without specialized junctions, covered with a mucopolysaccharide material and thus forming a true basement membrane.[54]

a. Inner retinal barrier

The intercellular spaces between retinal endothelial cells are sealed with many tight junctions. The number of tight junctions is the highest in the retina and brain and they have the highest complexity and smallest intercellular gaps as compared to endothelial cells from other tissues. Endothelial junctions are dynamic junctions with opening and closing to regulate paracellular transport of in particular smaller molecules. The retinal endothelial cells have a relatively low number of vesicles, particularly at the luminal membrane. Moreover, the expression of the main protein in the vesicles named caveolin-1 and of albumin binding-receptors and other molecules is relatively low.[53]
The barrier function of the superficial capillary bed in the ganglion nerve cell layer is also induced by astrocytes, because the continuous endothelial cell layer rests on a basal lamina that is covered by the processes of astrocytes. This function of astrocytes is replaced by Muller cells concerning the intermediate and deep capillary plexus.[49]
The retinal capillaries and astrocytes are surrounded by pericytes and microglia. The astrocytes, Muller cells and pericytes influence the inner BRB by transmitting regulatory signals to the endothelial cells indicating the changes in the microenvironment of the neuronal circuits in the retina.[52]
Under normal conditions, the inner retina up to the outer plexiform layer is continuously dehydrated by glial cells. The subretinal space and the outer retina are dehydrated mainly by the RPE. The water fluxes through glial and RPE cells are facilitated by the expression of waterselective channels, the aquaporins, in the plasma membranes of these cells. In the inner retina, aquaporin-4 water channels are present.[22]

b. Outer retinal barrier

The outer retinal barrier is located in the RPE-monolayer. The tight junctions between apical parts of the pigment epithelium cells maintain the BRB as well as adherens junctions (zonulae adherentes) and desmosomes (maculae adherentes).[20] One of the essential functions of RPE is to regulate the ionic composition of the subretinal space, thereby providing photoreceptors the environment they need to function properly. RPE also provides nutrients, removes waste and water from the subretinal space,[55] thereby preventing ME or serous retinal detachment, and participates in the visual cycle.[49]
On the other hand, the neural retina also regulates the RPE by affecting how proteins are expressed and degraded, how proteins are distributed to the apical and basolateral membranes, and how tight junctions regulate diffusion across the paracellular space.[49]
Solutes are transported from the outer retina into the choroid via the RPE, driven by several active mechanisms, coupled to facilitation of passive movement of solutes. In the apical domain of RPE cells many Na^+/K^+-ATPase and K^+ channels exist while transporters and channels for Cl^- and HCO_3^- are located at the basolateral surface of the RPE. This results in a net transport of ions across the RPE from the outer retina into the choroid leading to a parallel movement of water due to osmotic forces. The water fluxes across the plasma membranes of RPE cells are facilitated by aquaporin-1 (AQP-1) water channels.[22]
RPE secretes vascular endothelial growth factor (VEGF), which induces the formation of fenestrae in the choroidal endothelium on the surface that faces the RPE, which makes them leaky. RPE has mechanisms for maintaining low concentrations of VEGF in the subretinal space. RPE tight junctions are selective for K over Na and Cl. Permeability and selectivity of the junctions are not affected by VEGF, bevacizumab, or ranibizumab.[55]

6. Mechanisms of breakdown of the BRB

In general, hyperglycemia, hypoxia, oxidative stress and inflammation can harm the BRB. In uveitis and Irvine–Gass syndrome, inflammation causes the breakdown of the BRB and the blood aqueous barriers. In experimental models of uveitis it is shown that damage to the BRB occurs as soon as T-cells enter the eye. Hypoxia is the second mechanism in uveitis to cause breakdown of the retinal barrier. In retinal vein occlusion, cytokine release, hypoxia, increased hydrostatic pressure, and vascular stasis are followed by interstitial fluid accumulation according to Starlings law, leading to ME formation. In diabetic retinopathy an increase in hydrostatic pressure occurs due to loss of retinal autoregulatory function and dilation of blood vessels.[53] ME is frequently associated with relative ischemia and a broken foveal capillary ring, which can be shown by FA. The foveal avascular zone may become irregular and enlarged because of non-perfusion of the marginal capillaries.

Nowadays we know that the loss of the BRB is not just an unspecified endothelial cell damage, but that vascular leakage is the result of dynamic adaptations of endothelial cells and other cell types involved in the inner BRB.[53]

1. Increased paracellular permeability
2. Increased transcellular permeability
3. Endothelial cell damage or death
4. Pericyte loss and dysfunction
5. Activating glial cells that overexpress angiogenic cytokines (i.e. VEGF).
6. Loss of the endothelial glycocalyx, the network of membrane bound proteoglycans and glycoproteins at the luminal side of endothelium, which constitutes the first permeability barrier for plasma proteins and adhering leukocytes.

Besides this vascular leakage at the level of the inner BRB, the capacity of the active fluid pump of the RPE may be reduced due to the inflammation.[56] Little is known about the effects of inflammation on the tight junctions between RPE-cells.

7. Histological classification of macular edema

a. Intracellular macular edema

Intracellular edema is a cytotoxic edema which develops as a result of disturbances in the cellular ionic distribution. All cells maintain internal homeostasis by the membrane transport systems that balance ionic movements in and out of the cell. Neuronal cells have a very high rate of ATP-synthesis, resulting in excessive water production. Moreover, the uptake of glucose causes an influx of water into the cells. Water exits the neuronal cells via an uptake by glial cells and is subsequently released into the vitreous or blood by aquaporin-4 water (AQP-4) channels in their end-feet. Potassium fluxes through specialized proteins out of the cell in the end-feet of the Muller cells play a role in the water transport by creating osmotic water fluxes through the AQP-4 channels. Ischemia affects this K^+ release, resulting in accumulation of K^+ in the cells and cell swelling, because a reversed flow of water occurs from blood and vitreous into the Muller cells instead of out of these cells. Retinal glial cells lose K^+ conductivity with increasing age, making the elderly population more vulnerable for ME under hypoxic conditions.[40] Several other mechanisms may contribute to glial cell swelling,[22] such as (1) endocytosis of extravasated serum proteins, leading to intracellular water accumulation and (2) ischemia and reperfusion stimulates neuronal glutamate release causing an elevated glutamate uptake in the glial cells, which induces an influx of Na+ ions and subsequently (driven by the osmotic gradient) intraglial water accumulation. On the other hand, if the normal function of glial cells is disturbed, not only intracellular edema is the result, but also the resolution of extracellular edema is disturbed. It has been suggested that a swelling of glial (Muller) cells significantly contributes to the development of ME, with the cysts being formed by swollen and dying Müller cells.[22] This view would explain the

CME without angiographic signs of vascular leakage. A swelling of Müller cells in the macula is suggested to precede extracellular edema formation. Moreover, in dominantly inherited CME degenerated Müller cells and altered basement membranes were found around intact retinal vascular endothelium.

b. Extracellular macular edema

Extracellular edema is directly related to a breakdown of the BRB[20] and mainly associated with protein leakage. In case of a breakdown of the BRB, proteins such as albumin diffuse into the extracellular space, driven by blood pressure and diffusion gradients. The proteins can leave the retina towards the vitreous cavity at the ILM, which is no barrier. At the ELM level, however, they are blocked and stay within the retinal tissue, because the ELM is composed of zonulae adherentes and partly limit the movement of large molecules. Albumin is able to cross the ELM and the rate of albumin movement across the retina is 4-5% of the concentration difference across the retina per hour.[19] Oncotic pressure develops, accumulating water in the extracellular space and causing extracellular edema. Edema will probably be the greatest near the sites of leakage (retinal capillary layers) and at the sites of protein build-up (ELM).[19] Marmor speculated that the active transport capacity of the RPE is large enough to overcome oncotic effects from protein that had accumulated subretinally, preventing a serous detachment. In practice, a slight serous retinal detachment in uveitic ME often occurs and its exact pathogenesis and prognosis are unknown.
Many of the same pathologic insults (for example, ischemia) that open the BRB also damage membrane ionic channels, which can lead to cellular swelling. Furthermore, an altered extracellular environment may harm the cell membranes, while intracellular decompensation can lead to a release of molecules or free radicals that may in turn affect the BRB.[19]

8. Inflammatory mediators

A variety of inflammatory mediators generated by the underlying uveitic process, including prostaglandins, leukotrienes, protein kinase C, nitric oxide, and various cytokines, such as interleukins, tumor necrosis factor α, and VEGF, may damage the BRB and increase retinal vascular permeability.[57] The three most important mediators are angiotensin II, prostaglandins and VEGF:

a. **Angiotensin II** is an oligopeptide normally present in the blood that causes vasconstriction, increases blood pressure and releases aldosterone from the adrenal cortex. Angiotensin II is also a key mediator of inflammation in the vasculature and is locally produced in the wall of inflamed vessels via the renin-angiotensin

system. Elevated angiotensin II levels lead to a breakdown of the BRB by three effects:

- Recruitment of leucocytes from the circulation to the perivascular space. This is first caused by upregulation of adhesion molecules, followed by a transmigration of leucocytes via, again, an upregulation of several chemokines and cytokines (monocyte chemoattractant protein-1 (MCP-1), interleukins 1, 6, 8 and 12 and tumor necrosis factor-alpha (TNF-α)).
- Increase of vascular permeability induced by increased pressure, release of leukotriens and prostaglandins and an upregulation of VEGF.
- Remodelling of the extracellular matrix: cell proliferation, hypertrophy and fibrosis, mediated by growth factors as VEGF, PDGF etc.

b. Prostaglandins are derived from fatty acids. In inflammation, the enzyme phospholipase releases arachidonic acid from cell walls. Arachidonic acid is then converted into prostaglandins by the enzyme cyclooxygenase 2 and into leukotrienes by the enzyme 5-lipoxygenase. Prostaglandin E_1 causes a breakdown of the BRB by opening the tight junctions.[20]

c. VEGF is produced by endothelial cells, pericytes, monocytes and neural cells.[40] Following binding on VEGF-receptors, the receptors become activated and initiate multiple intracellular signaling pathways. The most important effects are angiogenesis, increase of vascular permeability, neuroprotection, chemotaxis and inflammation. At the outer barrier of the normal healthy retina, VEGF is produced by RPE cells from their choroidal side in order to maintain the fenestrated and highly permeable character of the choroidal vascular endothelium. By contrast, the inner blood-retina barrier is exposed to (significant levels of) VEGF only under hypoxic conditions when Müller cells up-regulate their expression and secretion of VEGF, contributing to a pathological permeability of the barrier.[22,58] Especially the subtype VEGF-A is involved in the development of ME. It causes a breakdown of the BRB by the following mechanisms:

- VEGF binds to leucocytes, and induce their recruitment leading to adhesion and leukostasis, endothelial injury and cell death. Leukostasis is mediated by nitric oxide, adhesion molecules, and other inflammatory mediators. Nitric oxide upregulates intercellular adhesion molecule-1 (ICAM-1) and downregulates the expression of tight junctions proteins.[52]
- Phosphorylation of the tight junction protein occludin causes conformational changes and dissolution of tight junctions of endothelial cells
- Activation of protein kinase C
- Induction of fenestrations and vesiculovacuolar organelles.[20]

Increased concentrations of VEGF in the aqueous humor (and not in the plasma) of patients with uveitic cystoid ME were found when compared with those with uveitis but without cystoid ME,[59] making anti-VEGF therapy rational in the treatment of uveitic ME. The results of this treatment, published in small case series, need to be evaluated.[60] Anti-VEGF drugs also decreased the number of activated retinal and choroidal microglia in experimental ocular inflammation, but the consequences need to be further investigated.[61]

9. Do different manifestations of macular edema reflect severity?

Bringmann and colleagues[20] postulated a theory explaining the variable distribution of cysts in different retinal diseases. The inner and outer plexiform synaptic layers are diffusion barriers for extravasated serum proteins, probably because the extracellular space there is very convoluted and extremely narrow. Also the flow of ionic currents faces a high resistance in these layers, as well as fluid movements. In case of a leaky RPE, serum proteins accumulate in the outer retina leading to cysts in the Henle fiber layer and/or subretinal fluid accumulation. Leaky retinal capillaries in the inner nuclear layer result in cysts in this layer or if the serum leaks from the capillaries in the ganglion cell layer, it may go easily into the vitreous body without formation of cysts.

A different explanation of the distribution of cysts in the different retinal layers is suggested by the response of ME to medical treatment. Cysts located in the inner retinal layers proved to be more resistant to treatment than other types of uveitic edema.[62] Later on, Munk and colleagues[29] found that cysts in the outer nuclear/Henley's layer diminished before those in the inner nuclear layer after intravitreal triamcinolone injection. Dome shaped subretinal fluid disappeared more slowly. From the stepwise resolution of ME in the different layers, the authors tried to explain the development of ME and suggest that different patterns of uveitic ME are in fact different stages: uveitic ME begins with diffuse ME, followed by the appearance of parafoveal cysts in the inner nuclear layer, then cysts in the outer nuclear layer/Henle's layer and subsequently in part of the patients, the development of subretinal fluid.

Whether the differences in fluid accumulation in ME depend on the severity of the breakdown of the BRB and/or the relative contributions of the affected inner and/or outer BRB and/or the diminished RPE-pump function, remains to be elucidated.

10. Retinal atrophy and retinal leakage

Foveal atrophy represents the late consequence of retinal edema, and is correlated with a low VA. In a study of Forooghian and colleagues,[63] foveal atrophy was defined as a center foveal point thickness of <150 µm on the Cirrus HD OCT. In their study 16% of patients with uveitis had a foveal atrophy. In all these eyes, a complete or partial loss of the normal hyporeflective space between the IS/OS junction and the RPE was

observed, suggestive of shortening of photoreceptor outer segments. Some of these eyes had a history of cystoid ME. Other causes of the foveal atrophy in uveitis might include dysfunction/atrophy of the RPE/choroid, a CNV, macular ischemia due to a retinal vasculitis, retinal detachment and retinal autoimmunity.
Birdshot chorioretinopathy is a form of posterior uveitis in which ME and retinal atrophy frequently occurs.[64] The generalized retinal atrophy is probably not caused by longstanding retinal edema, but mainly by immunological mechanisms. In longstanding uveitis already associated with, atrophic, thin retina, a mild thickening is often not recognized especially if no cysts are visible.[65] In Figure 7 the leakage on the fluorescein angiogram in combination with a thin retina on OCT is illustrated in an eye of a patient with birdshot chorioretinopathy. The OCT shows a very thin retina. Because of the focal leakage on the angiogram and the subtle cyst on OCT, oral acetazolamide was prescribed (125 mg 3 times daily). The VA remained unchanged, but the OCT showed a very subtle decrease of the retinal thickness in the parafoveal nasal area. The medication was discontinued, resulting in a more obvious recurrence of focal ME 8 months later.

At this moment, no data is available on the efficacy of treatment of a subtle ME in a thin and possibly vulnerable retina. Already in 1999 Marmor stated: "Anatomic measures of tissue swelling (on OCT) do not necessarily show pathophysiology. Moreover, tissue swelling does not automatically translate into neuronal dysfunction, while the underlying causes of edema (i.e., ischemia) may affect neurons quite independently of the degree of edema or correlate with visual effects".[19] More careful focal evaluation of the retina with techniques such as microperimetry and multifocal ERG are needed to obtain a better understanding of the spatial and temporal relevance of edema to the dysfunction of the retinal neurons and to the development of visual loss.

11. Visual function in macular edema and OCT-features

a. Macular edema and visual acuity

ME has an effect on several aspects of visual functioning. VA ≤0.5 was found in 70% of uveitis eyes with cystoid ME, compared to 13% in uveitis eyes without ME.[66] Visual impairment or blindness was most commonly seen in panuveitis (64%); only 28% patients with intermediate uveitis experienced visual impairment or blindness, but the proportion of CME causing the visual loss was 85%.[8] Significant visual loss caused by CME occurred most often in sarcoidosis and birdshot chorioretinopathy and. In an English study on 315 patients, in 27% cystoid ME was the only cause of visual loss and in 20% in combination with cataract.[67]

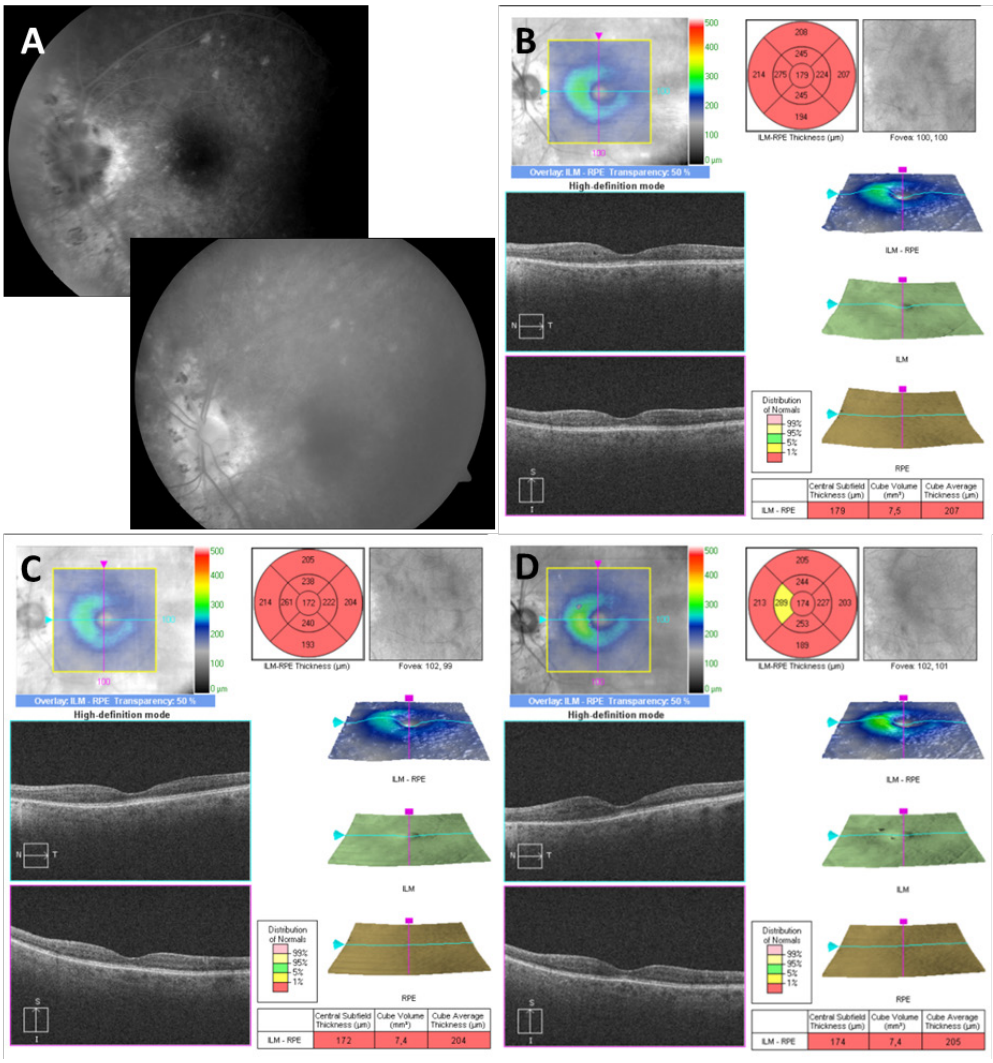

Figure 7. A: Early and late phase angiogram in birdshot uveitis, showing a mild focal macular edema nasally from the fovea. The visual acuity has been stable since several years (0.3). B: OCT at the time of the angiogram in 7A, before the start of acetazolamide. C: OCT while using acetazolamide. D: after cessation of acetazolamide. False color OCT-maps are in 'red', implying that less than 1% of the normal population has these thicknesses.

b. Visual acuity and retinal thickness

Retinal thickness was poorly correlated with VA, because in ME only about 15% of the changes in VA was explained by the retinal thickness.[23,68] The effect of ME on VA was also measured in patients with uveitis, where systemic immunosuppressive therapy was considered necessary to control uveitis.[66] In this study, the presence of cysts was not

significantly associated with lower VA, while retinal thickness ≥240 µm was associated with visual decrease.

c. Visual acuity and retinal layers on OCT

The prognostic significance of the integrity of the inner/outer segment junction (IS/OS-line) for VA has repeatedly been reported.[13,69,70] A second reflection line sometimes can be seen on SD-OCT: cone outer segment tip = COST-line (see Figure 1). This line is also reported to be associated with VA. However, in 4-5% of normal eyes the line is not visible or intact.[71]

A diminished Stiles-Crawford effect (SCE) was measured in uveitic ME (Figure 8).[72] The optical SCE is the phenomenon that light reflected from the fundus is more intense near the center of the pupil than at the pupil edges. A diminished Stiles-Crawford Effect can occur due to a disorientation of the photoreceptor cells and/or change in structure of individual cones and/or loss of photoreceptor cells.[73] In ME, the longitudinal axis of photoreceptors probably does not perfectly point to one spot near the center of the pupil. In central serous chorioretinopathy, it was shown that the SCE recovered slowly after the subretinal fluid had disappeared and the IS/OS- line also reappeared after resolution of the subretinal fluid.[74]

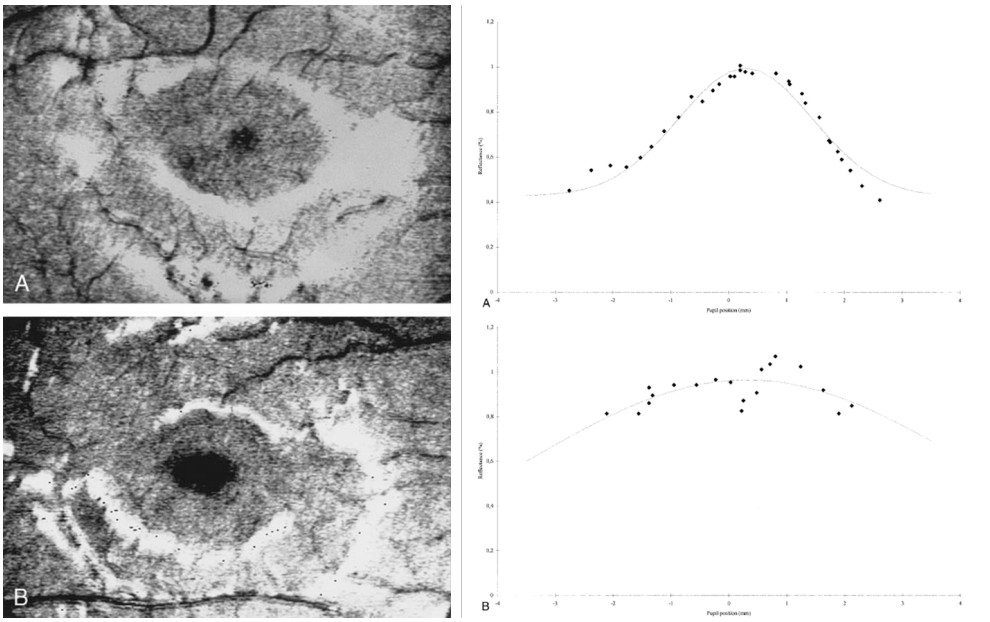

Figure 8. Upper half: normal macula. Lower half: macular edema. Left: the reflection of light in the foveal center is diminished in macular edema (darker fovea). Right: the peakedness of the reflectance curve is diminished in macular edema compared to normal. (from Lardenoye[72], with permission)

Reflections from the COST-line and the reflectivity of the Henle Fiber Layer (the axons of the photoreceptor cells), both measured with a SD-OCT, are also highly directionally dependent.[75,76] In conclusion, in analogy with this SCE, the IS/OS-line on OCT can restore after normalization of the foveal anatomy, e.g. after resolution of central serous chorioretinopathy, macular hole surgery, ERM-removal and also after resolution of cystoid ME (Figure 9). Whether the disturbed IS/OS line in an individual patient will restore (completely or partially (Figure 10) cannot as yet be predicted. An absence of IS/OS line on OCT might be due to a temporary misalignment of the photoreceptors and not necessarily due to a loss of photoreceptor cells. Although a disturbed IS/OS-line is of prognostic significance for VA, it should not be the only reason to refrain from therapy.

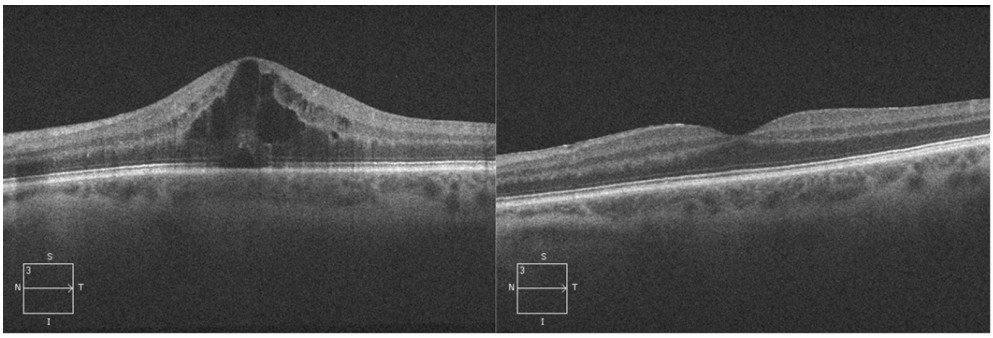

Figure 9. Good recovery of the IS/OS-junction in a patient with an uveoscleritis of unknown cause. Left: prior to treatment. Right: following treatment 3 months later.

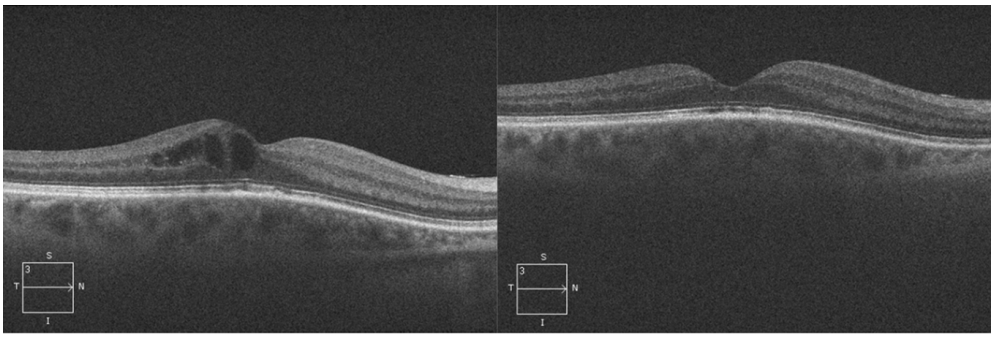

Figure 10. Incomplete recovery of the IS/OS-junction in a patient with a panuveitis of unknown cause. Left: cystoid ME. Right: after resolution of the cysts.

The integrity of other retinal layers is also of importance for visual acuity such as the volume of intact tissue between the two plexiform layers in the central retina on OCT.[23] This seems obvious, but in recent literature, the research has been focused on the IS/OS line, because its integrity is relatively easy to assess. Because of the oblique orientation of the Henle fiber layer (Figure 6), foveal cones may connect to bipolar cells displaced 500 µm radially from the inner and outer segments, because their inner connecting fibers

may be up to 500 µm in length. This explains why a central retinal area of 1000 µm in radius is relevant for the VA: the retinal spared tissue in this area predicts 70% of the variation in logMAR VA in a linear model. Horizontal and amacrine cells will contribute to image processing and VA by integrating signals over a number of photoreceptor cells and ganglion cells, even in case of loss of bipolar cells.[23]

We can conclude that both the integrity of the photoreceptor cells and the ability to transmit the information from photoreceptor cells to the ganglion cells determine the potential VA. ME will harm the transmission of the signals by the stretching of the bipolar axons (and eventually snapping of the axons) and the photoreceptors are influenced by the presence of fluid in the outer retina. Although current therapies cannot replace lost neurons, resolution of cysts will ease the tension on the axons and change the ionic environment around these axons, thereby improving their function.

d. Reading ability and OCT

Reading ability is often more impaired than distance VA in many retinal diseases and also in uveitic ME. Reading words requires a more complex retinal performance than reading single optotypes on a distance and requires a minimal visual span, which might be reduced in CME. The area of the retinal cysts showed a stronger correlation with visual performance than retinal thickness and reading performance was more affected than distance VA.[77] Reading acuity, distance VA and reading speed as well as central retinal thickness and retinal volume on OCT all improved rapidly and simultaneously after an intravitreal triamcinolone injection in a study of 29 eyes with uveitic cystoid ME and an intact ELM and IS/OS line.[78] Half of the patients experienced a gain of at least 40 words per minute 3 months after the triamcinolone injection, compared to baseline.

e. Contrast sensitivity, metamorphopsia, color vision

In daily life, contrast sensitivity is crucial for pattern recognition, for example of a human face. Reduction in contrast sensitivity may be responsible for persistent difficulties experienced by patients despite good Snellen acuity. Little data is available on contrast sensitivity in uveitic ME. In an unpublished study described in the thesis of Lardenoye, the mean contrast sensitivity (measured with the Pelli Robson letter chart) in ME eyes was significantly lower than in the non-CME eyes, in analogy with the VA (0.4 vs. 0.6 respectively).[79]

Metamorphopsia and color vision were not systematically investigated in uveitis. Metamorphopsia in eyes with an ERM correlates with the volume of the inner nuclear layer.[80] Lardenoye showed that 9 out of 80 eyes with CME had an abnormal anomalous quotient with the anomaloscope.[79]

f. Microperimetry, multifocal ERG

In addition to VA, monitoring the (relative) scotoma in the central visual field seems useful for assessment of the functional damage due to ME. Since a few years, microperimetry has become more routinely used in patients with ME. As expected, retinal sensitivity in microperimetry is negatively correlated with logMAR VA, but fixation stability did not correlate with logMAR VA, retinal sensitivity or the presence/absence of retinal cysts.[68] The multifocal ERG (mfERG) might be used to monitor the functional consequences of ME.[81] LogMAR VA and mfERG measurements improved often in a study of 33 eyes that were treated for uveitic ME, but no correlation between the final logMAR VA and pre-treatment OCT and mfERG measurements was detected.[82]

12. Therapy

Preventing a disease is usually better than treating it. Thus, the ideal approach for ME would be not to let it occur. In uveitis this implies the treatment of the inflammation that causes the BRB to open or the prevention of a recurrence of the inflammation. Early treatment has been repeatedly recommended, also for patients with early subclinical CME forms, without significant and/or any decrease in VA. However, the therapy of ME might have serious side-effects, so a stepwise approach is advised (in detail described in Chapter 5). In unilateral cases of non-infectious uveitis, local steroids can be chosen (topical, periocular). In bilateral cases systemic treatment is often advised, oral steroids being the first choice, but steroid-sparing immunosuppressive medications can be chosen in the long term to avoid the serious side effects. When inflammation is being treated or under control and ME persists, oral acetazolamide or intramuscular somatostatin analogues can be prescribed to enhance the pump function of the RPE. Until now, the efficacy of various symptomatic treatment regimens has not been systematically investigated. It is known that ME in active uveitis responds better to therapy. ME in eyes with ongoing inflammation despite treatment, ME in eyes with an inactive uveitis and ME in eyes with severe inflammation at the time of presentation (hypotony or posterior synechiae), have less chance to improve.[83]

Why some patients continue to have CME despite adequate control of their inflammation is a controversial issue and may be explained by chronic damage to the blood-retinal barrier, the RPE-pump and/or the persistent low-grade presence of intraocular inflammatory cytokines.

13. Macular edema in sarcoidosis-associated uveitis

The prevalence of macular edema (ME) differs among the anatomical types of uveitis and its specific entities. The prevalence of ME was found to be 33% for the total uveitis population, reaching the highest prevalence in intermediate uveitis (63%) and lowest in anterior uveitis (11%).[8] The specific entities associated with a high prevalence of ME are

sarcoidosis, birdshot chorioretinopathy and acute retinal necrosis. Other uveitis entities frequently complicated by ME are juvenile rheumatoid arthritis, Behcet's disease and immune recovery uveitis.

Sarcoidosis-associated uveitis is a common entity among uveitis in diverse populations and its prevalence in large surveys is observed in 7-10% in developed countries.[6,84,85] The development of ME in sarcoidosis-associated uveitis was found in approximately 57%,[8,86] especially in patients with chronic uveitis. While the acute type of anterior uveitis typically occurs at younger age, chronic sarcoidosis-associated uveitis develops predominantly in elderly patients, who have a higher chance to develop severe ME. Sarcoidosis-associated uveitis is frequently associated with epiretinal membranes (30%).[86,87]

a. Systemic sarcoidosis

Sarcoidosis is a systemic disorder of unknown cause characterized by a granulomatous inflammation in affected organs. The prevalence of sarcoidosis varies around the world between 4.7-64 per 100 000.[88] The highest rates are among Scandinavians and African-American individuals, particularly in women. Sarcoidosis is one of the most important systemic associations of uveitis in Japan and Europe. The disease occurs at all ages, but 70% before the age of 50 years, with a peak incidence at 20-39 years, and a lower second peak between 50-69 years in women.[88,89,90] Late-onset sarcoidosis (≥ 65 years) is characterized by preponderance of females (70-83%), uveitis, asthenia, specific skin lesions and less chest radiograph abnormalities and erythema nodosum.[91] The incidence of late onset sarcoidosis is 10 per 100 000 per year.[90] The course of the disease is variable, because sarcoidosis has acute (<2 years) and chronic phenotypes (≥3-5 years) and it can manifest itself in different organs. The disease severity is not different between older and younger patients, but the 5- and 10-year survival after diagnosis is worse in the older group, most likely as a result of aging.[90]

Granulomas are compact collections of macrophages and epithelioid cells, encircled by lymphocytes (primarily CD4+ T cells).[89] A persistence of non-degradable antigens from e.g. proprionibacteria or mycobacteria, forming a nidus for granuloma formation has been described.[88] Upregulation of T-lymphocytes and mononuclear cells occur, which secrete pro-inflammatory molecules.

The granulomatous reaction might be an exaggerated response on unidentified antigens (infectious or non-infectious exposures) in a person that is genetically susceptible. Monozygotic twins have an 80-times increase in risk and it is thought that genetic factors might account for two-third of disease susceptibility.[88] The genetic risk profile is made up of many variant genes. Specifically, human leucocyte antigens (HLA) class II alleles are associated with sarcoidosis susceptibility, phenotype and prognosis. For example, HLA-DRB1*03 predisposes for acute disease and HLA-DRB1*14 and *15 for a chronic course.[88] Also some HLA class I alleles have influence on disease

susceptibility, i.e. HLA-B7 and B8 increase the risk of sarcoidosis.[92] HLA-DRB1*04 was found to be protective against systemic sarcoidosis, but was a significant risk factor for ocular sarcoidosis and the other features associated with Heerfordt´s syndrome, consisting of cranial nerve palsy (most often the facial nerve), parotid and/or salivary gland enlargement and fever.[92] In Caucasian patients, specific single nucleotide polymorphisms (SNPs) in the genes coding for heat shock proteins were associated with sarcoidosis associated uveitis compared to non-uveitis sarcoidosis patients.[93] Heat shock proteins have a function in protein folding. Differences in genetic backgrounds, immunological responses and causative agents lead to different subsyndromes, probably needing different therapeutic approaches.
Sarcoidosis can affect different organs. Lungs and lymph nodes are the primary organs involved and the higher mortality among sarcoidosis patients is mainly due to pulmonary fibrosis. Cardiac sarcoidosis is potentially life-threatening and can manifest itself as atrioventricular block, ventricular arrhythmias, congestive heart failure, sudden death, and consequences of impairment in sympathetic nerve activity. Neurosarcoidosis can involve all parts of the nervous system. The skin is involved in about 30% of the patients. In 10% of the patients, serum aminotransferase and alkaline phosphatase levels are elevated. In 70% of the patients, fatigue is present. Neurologic symptoms occur in 10% of the patients and cognitive failure is a common problem.
Prednisone is the first choice of treatment at disease onset. To avoid the adverse effects of prolonged steroid use (obesity, diabetes, osteoporosis), steroid sparing drugs are used, with methotrexate being the first choice. Azathioprine is a possible second choice. Relapses mostly occur 2–6 months after corticosteroid withdrawal, and are rare after 3 years without symptoms. TNF alpha antagonists are increasingly being used in corticosteroid-refractory sarcoidosis.

b. Ocular sarcoidosis

Eyes and adnexa are involved in 10-50% of the American and European sarcoidosis patients and in 60-90% of the Japanese sarcoidosis patients.[89,94,95] The most common ocular manifestations are uveitis (30-70%) and conjunctival nodules (40%).[96] Anterior uveitis is the most common manifestation: 41-75% of the cases. Panuveitis accounts for 9-30% of the cases. The incidence of ocular sarcoidosis has two peaks: at ages 20-30 and at ages 50-60 with a female preponderance. In 10-20% of sarcoidosis patients, ocular manifestation was the presenting symptom.[94] A granulomatous anterior segment inflammation was more common in African American patients in a series of 63 American patients and Caucasian patients were more likely to present when they were older than 50 years.[98] African-American patients are younger at presentation of the uveitis.[95] Uveitis in the elderly is more often caused by sarcoidosis than at younger ages.[99]

Ocular sarcoidosis can present itself with different features and is generally bilateral (80-90%). It may be a silent uveitis, not giving many complaints, until the permanent ocular damage has occurred.
All anatomical locations of uveitis have been reported in sarcoidosis. An anterior uveitis can present itself with an acute or a chronic course. A patient can also have an intermediate uveitis with vitritis and snow ball infiltrates in combination with a peripheral vasculitis. Snow balls infiltrates however, are not specific for sarcoidosis. A posterior uveitis often includes a subtle or extensive periphlebitis with or without retinal ischemia, choroidal lesions, optic disc inflammation, and ME. Sometimes macro-aneurysms can be seen. The differential diagnosis for ocular sarcoidosis is broad, and especially tuberculosis is important to exclude.[100] Many symptoms which can be found in ocular sarcoidosis can also occur in other disorders. Mutton fat keratic precipitates are common in other (granulomatous) diseases, such as Vogt-Koyanagi-Harada disease, toxoplasmosis, herpes virus infections, multiple sclerosis and other disorders. A retinal phlebitis can be seen in many uveitis entities other than sarcoidosis, such as in birdshot chorioretinopathy or Behcet disease. The combination of features suggests ocular sarcoidosis.
A separate clinical entity within the spectrum of ocular sarcoidosis is peripheral multifocal chorioretinitis (PMC), either a posterior or panuveitis characterized with vitritis and peripheral retinal punched out lesions located in the peripheral retina. PMC has been previously reported as a distinct clinical entity, which has a strong association with sarcoidosis. The prognosis and the best treatment of this clinical entity preferentially occurring in elderly patients, is currently unknown.

c. Diagnostic criteria for (ocular) sarcoidosis

Sarcoidosis is often asymptomatic and approximately 50% of cases come to light incidentally by chest radiograph.[101] The diagnosis of sarcoidosis is based on histological findings from a biopsy sample that typically shows non-caseating epithelioid granuloma. At chest radiograph, bilateral hilar lymphadenopathy or diffuse micronodular pulmonary infiltration associated with a typical lymphatic distribution or a galaxy sign on CT are typical. Some authors argue that biopsy sampling is not always necessary.[88,101] Endobronchial ultrasound-guided endo- and transbronchial needle aspiration is a highly effective proof in mediastinal and hilar lymphadenopathy. 18F-FDG PET accurately assesses inflammatory activity. Bronchoalveolar lavage shows a moderate lymphocytosis in 80% of cases with sarcoidosis and a T-lymphocyte CD4:CD8-ratio >3.5 in lavage is found in half of cases.
The diagnostic criteria for ocular sarcoidosis are described in Table 2, the laboratory investigations in Table 3 and the ocular clinical signs suggestive for sarcoidosis in Table 4.[102]

Table 2. Diagnostic criteria for ocular sarcoidosis*

All other possible causes of uveitis, in particular tuberculous uveitis, have to be ruled out.		
1.	Definite ocular* sarcoidosis	Biopsy supported diagnosis with a compatible uveitis
2.	Presumed ocular* sarcoidosis	Biopsy not done; presence of bilateral hilar lymphadenopathy (BHL) with a compatible uveitis
3.	Probable ocular* sarcoidosis	Biopsy not done and BHL negative; presence of three of the suggestive intraocular signs and two positive investigational tests
4.	Possible ocular* sarcoidosis	Biopsy negative, four of the suggestive intraocular signs and two of the investigations are positive

* Used in the sense of intraocular inflammatory lesions both in patients with systemic disease and in patients with disease seemingly limited to the eye without any clinically detectable involvement of another organ.

Table 3. Laboratory investigations in suspected ocular sarcoidosis

1.	Negative tuberculin test in a BCG-vaccinated patient or having had a positive PPD (or Mantoux) skin test previously
2.	Elevated serum angiotensin converting enzyme (ACE) and/or elevated serum lysozyme*
3.	Chest x-ray; look for bilateral hilar lymphadenopathy (BHL)
4.	Abnormal liver enzyme tests (any two of alkaline phosphatase, ASAT, ALAT, LDH or γ-GT)
5.	Chest CT scan in patients with negative chest x-ray

*Test required in patients treated with ACE inhibitors.

Table 4. Clinical signs suggestive of ocular sarcoidosis

1.	Mutton-fat KPs (large and small) and/or iris nodules at pupillary margin (Koeppe) or in stroma (Bussacca)
2.	Trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS)
3.	Snowballs/string of pearls vitreous opacities
4.	Multiple chorioretinal peripheral lesions (active and atrophic)
5.	Nodular and/or segmental peri-phlebitis (± candlewax drippings) and/or macroaneurism in an inflamed eye
6.	Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule
7.	Bilaterality (assessed by clinical examination or investigational tests showing subclinical inflammation)

In lung sarcoidosis, serum angiotensin-converting enzyme (ACE) and soluble interleukin 2 receptor (sIL-2R) are markers for disease activity: decreases in both markers correlated with an increase in lung function.[103] ACE is physiologically present

in many tissues, such as in plasma and in vascular endothelium. It converts Angiotensin I to Angiotensin II, causing vasoconstriction and sodium retention and inactivates the vasodilator bradykinin.[104] ACE concentration in serum is dependent on a insertion or deletion polymorphism in the ACE-gene and causing a high level of interindividual variability.[105,106] In sarcoidosis, ACE is produced by the granulomas, while sIL-2R is secreted by activated T-helper type 1 cells and thus stimulating T-cell proliferation.

d. Laboratory findings in ocular fluids in ocular sarcoidosis

In patients suspected from ocular sarcoidosis, often no evidence can be found for the diagnosis of systemic sarcoidosis. In a group of experts, only 21% was convinced that sarcoidosis is a systemic disorder and that no limited ocular form exists. Others were convinced that a limited form of sarcoidosis occurs that only manifests in the eye.[107] In addition, it is known that ocular sarcoidosis can be the first site of manifestation of systemic sarcoidosis: in a large group of 1800 sarcoidosis patients ocular involvement was the first sign of systemic disease in 21% of the cases.[108] In 76% was the first presentation an anterior uveitis and in 17% an intermediate uveitis.

The sensitivity of ACE and sIL-2R levels in serum for the diagnosis of ocular sarcoidosis is low: a combination of ACE and sIL-2R gives a sensitivity of 0.55 and a specificity of 0.96.[109] Efforts have been made to diagnose ocular sarcoidosis in ocular fluids. Aqueous humor cytokine studies of patients with sarcoidosis are scarce.[110,111] More information is available from vitreous analysis. In a study of 8 vitreous specimens, non-caseating granulomas were found in all.[112] The CD4/CD8-ratio of vitreous lymphocytes was also higher. The sensitivity and specificity of the vitreous CD4/CD8 ratio>3.5 were 100% and 96.3%, respectively, for the diagnosis of intraocular sarcoidosis, suggesting a diagnostic value comparable to that of the CD4/CD8 ratio in BAL lymphocytosis for pulmonary sarcoidosis.[113] However, the specificity and sensitivity of vitreous analyses for the diagnosis of sarcoidosis was not systematically examined. It would be useful to determine the potential role of aqueous analysis in the diagnosis of ocular sarcoidosis. In chapter 8 of this thesis, a study on intraocular ACE and sIL-2R is described.

Aims of the thesis

In general, this thesis aims to enhance our knowledge of macular edema and vitreoretinal interface abnormalities in uveitis, with emphasis on sarcoidosis related uveitis. Current knowledge was summarized in Chapter 1. New and improved retinal imaging techniques have been introduced in the last ten years. Do these new techniques enhance our insight in macular edema associated with uveitis and how can we implement imaging in the management of our patients? Many issues were unresolved, which lead to the following specific questions and aims, to be explored in the chapters between parentheses.

1. What imaging techniques are currently available for macular edema and what can we learn from the new information the techniques have brought us? (Chapter 2).
2. What is the clinical impact of a serous retinal detachment associated with uveitic macular edema? (Chapter 3).
3. Are optical coherence tomography (OCT)-findings and fluorescein angiography (FA)-findings in uveitic macular edema consistent with each other? (Chapter 4).
4. Are discrepancies between OCT-findings and dye leakage associated with certain clinical characteristics? (Chapter 4).
5. What are the current treatment options for uveitic macular edema and how to use them? (Chapter 5).
6. What is the current knowledge on complications and visual outcome of peripheral multifocal chorioretinitis (PMC)? (Chapter 6).
7. What is the prevalence of macular edema and the visual prognosis of PMC in a long term follow-up? (Chapter 7).
8. Can we improve the diagnosis of ocular sarcoidosis using intraocular fluid instead of serum analysis for specific biomarkers? (Chapter 8).

Chapter 9 provides the summary and conclusions of this thesis.

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CHAPTER 2

Imaging methods for inflammatory macular edema

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Introduction

Macular edema (ME) is the major cause of visual impairment in uveitis.[1] ME develops because of a breakdown of the inner and/or outer blood retinal barrier caused by inflammation, followed by an influx of proteins and fluid from plasma. ME may persist even after the inflammation has subsided due to a permanently compromised blood retinal barrier. Uveitis entities frequently associated with ME are sarcoidosis-associated uveitis and birdshot chorioretinopathy.[1] Macular thickening on optical coherence tomography (OCT) was found in 42% of 43 unilateral acute anterior uveitis compared to the normal fellow eye.[2] The presence of ME is linked to the visual outcome of uveitis, and all cases irrespective of their concurrent visual acuity should be treated before the definitive structural changes have set in.[3] Herein we summarize recent developments regarding the use of imaging techniques for inflammatory ME.

Ophthalmoscopy

Slit lamp biomicroscopy of the fundus may reveal gross retinal thickening, an abnormal foveal reflex, and/or intraretinal cysts located around the fovea. Stereoscopic fundus photography can help document the extent and source of retinal thickening.

Fluorescein angiography (FA)

FA represents a functional imaging of the retina and to a far lesser extent the choroid, and depicts the leakage through inflamed vessels and retinal pigment epithelium. In the early phase, dilated perifoveal capillaries and/or an enlargement of the avascular zone may be observed. Associated window defects indicate structural changes in the retinal pigment epithelium and are probably because of a long-standing ME. In the late phases, FA identifies the cysts and leakage in the macular area, and documents the overall activity of the uveitis and leakage of the retinal vessels and the optic nerve. The drawbacks of FA are mainly its invasiveness (with a low prevalence of severe allergic side effects) and its qualitative and therefore subjective evaluation, the limited axial resolution as well as a loss of detail on late frames in cases with extensive leakage. To date, quantification of fluorescein leakage has not been possible.

Classification of ME on FA

FA allows distinction of diverse types of ME including cystoid and diffuse ME. Two distinct patterns were recognized within the cystoid ME, specifically the petalloid and the honeycomb pattern. In clinical practice however, all cases of inflammatory ME are termed cystoid ME, even in the absence of the cysts which complicates the comparison of diverse reports. Repeated efforts were made to grade the severity of ME on FA, but so far, there is no widely accepted FA classification.[4-6] The Angiography Scoring for Uveitis

Working Group proposed a grading system of ME based on FA images at 10 minutes which aimed to grade the leakage in the macular area (Table 1).[7] This grading is part of a FA scoring system for uveitis activity, is simple and useful, however makes no distinction between extrafoveal and foveal ME.

Table 1. Grading of ME on FA according to ASUWOG[7]

Macular area at 10 minutes FA images	Grade
Faint hyperfluorescence	1
Incomplete ring of leakage	2
Complete ring of leakage	3
Pooling of dye in cystic spaces	4

ASUWOG indicates Angiography Scoring for Uveitis Working Group; FA, fluorescein angiography; ME, macular edema.

Correlation of visual acuity (VA) and FA images

The prognostic significance of specific FA features on the visual outcome in uveitic ME has not been recently systematically assessed. Poor association of VA with macular leakage on FA has been noted previously.[8,9] In ME of other origins, the enlarged foveal avascular zone was associated with poor VA and centrally located cysts on the OCT images.[10]

Preferable indications

FA is especially valuable in ME cases that require a follow-up of the overall activity of uveitis. Anti-inflammatory treatment is required in patients with active inflammation, whereas in ME cases without FA signs of an active inflammation but with persistent ME, other therapeutic options are recommended. Specific complications of uveitis as a subretinal neovascularization are most easily detected with FA and/or infracyanine green angiography (ICG), and might give the only impression of intraretinal edema on OCT.

OCT

The introduction of the time-domain OCT provided a noninvasive imaging method with a detailed morphologic view of ME and quantitative data. The spectral domain OCT (SD-OCT) was another breakthrough, mainly due to its higher resolution and shorter acquisition time, allowing to axially resolving cellular layers in the living retina. In a few SD-OCT devices, averaging of multiple B-scans for enhanced imaging of the retina has become possible.[11] Gray-scale images show better tissue details than false-color images, because the false-color presentation reduces the information of all gray levels.

The border between the inner and outer segments (IS/OS) of the photoreceptor layer is represented by a highly reflective line and its abnormalities can be documented (Fig. 1). In addition, the vitreoretinal interface can be evaluated and reveals abnormalities more frequently than previously thought. The presence of vitreomacular adhesion, traction, or the formation of epiretinal membranes can be visualized (Fig. 2). It became apparent that in many posterior or panuveitis patients, a certain degree of formation of epiretinal membranes occurs.[12] These epiretinal membranes induce ME mechanically, do not react sufficiently to medical treatment, but ME may resolve after their surgical removal. An important problem arose from the introduction of 9 different machines of the SD-OCT each with different features.[13] Specifically, the definition of the outer retinal border varies. Depending on which machine is used, the value for the retinal thickness differs: the central retinal thickness (CRT) is largest in the Zeiss Cirrus and the Heidelberg Spectralis OCT.[14] Unfortunately, no correction algorithm is available and the images obtained on 1 machine cannot easily be compared with an OCT scan from a different device. Therefore, in research settings and specifically in multicenter studies, the same device should be used, although Heussen et al[15] showed that a uniform accurate manual correction of the outer retinal boundary is possible for the Spectralis OCT, Cirrus, and the Topcon 3-dimensional (3D) OCT-2000.

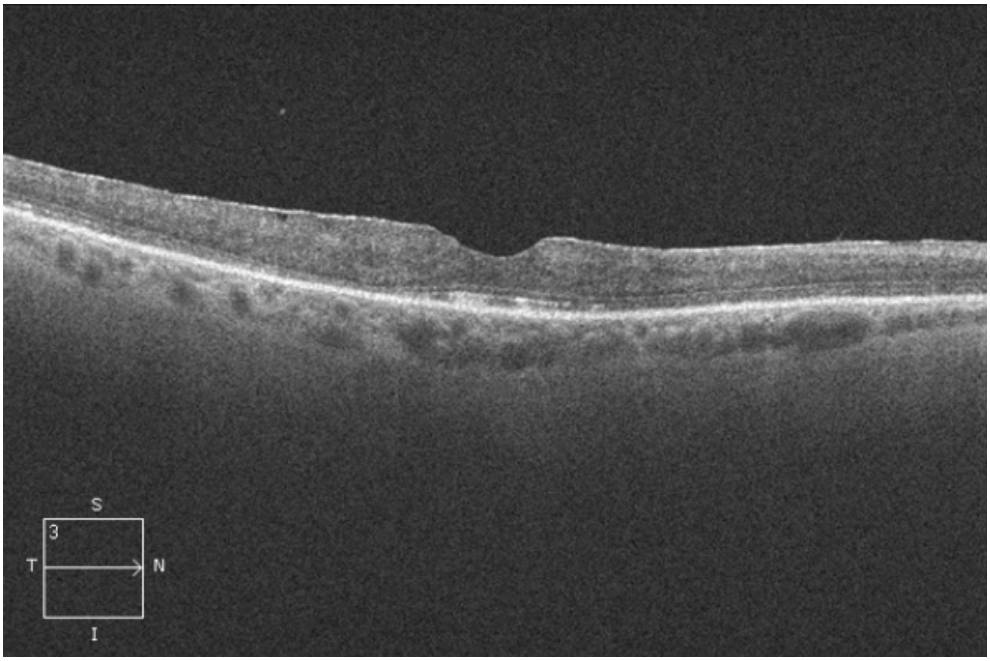

Figure 1. Loss of the reflective line, representing the junction between inner en outer segments of the photoreceptors, temporal of the foveal center, due to long-standing uveitic macular edema in a patient with birdshot chorioretinopathy.

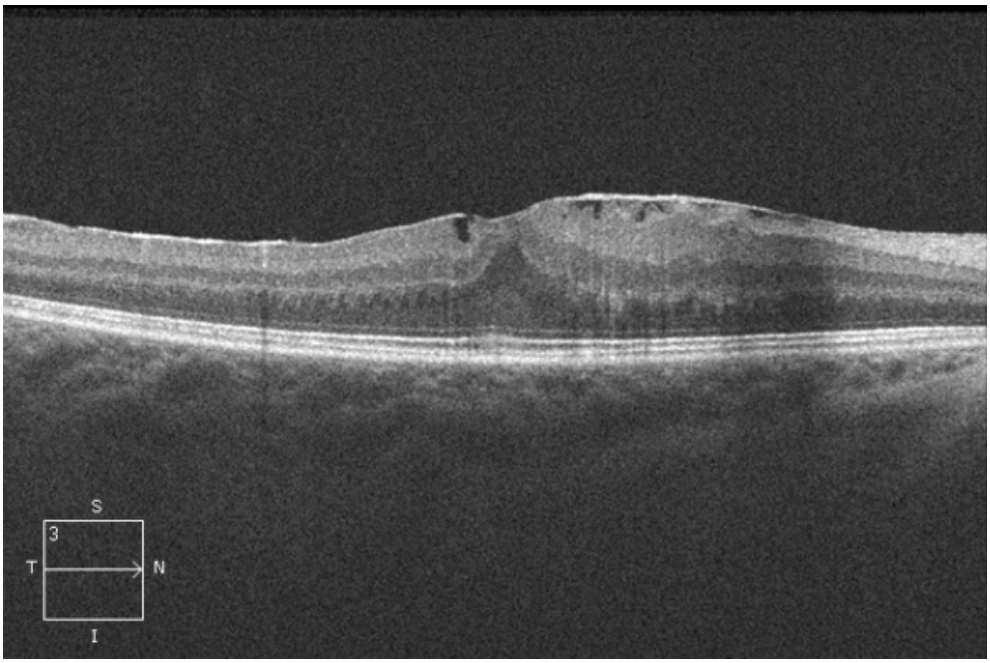

Figure 2. An epiretinal membrane in a patient with an idiopathic chronic panuveitis and macular edema.

Classification of ME on OCT

Rough normative data on the CRT become available for the individual OCT devices. However, retinal thickness depends on many variables such as race and age and the systematic information on CRT in large populations is not yet available. Recently, the first normative data of the parafoveal region in 3 SD-OCT devices were provided.[16] The Diabetic Retinopathy Clinical Research Network defines ME as the CRT >250 µm on Zeiss Stratus or above 310 µm on a SD-OCT (http://publicfiles.jaeb.org/drcrnet/Misc/OCT_Certification_Manual_4_12_11_FINAL.pdf). However, the presence of cysts within the retina also indicates ME. ME on OCT is divided in four groups: (1) diffuse ME; (2) cystoid ME; (3) subretinal fluid (Fig. 3) and (4) alterations in the vitreoretinal interface (Table 2).

Correlation of VA and morphologic features on OCT

VA correlates better with the retinal thickening than with the amount of leakage on FA.[9,17] In the Multicenter Uveitis Steroid Treatment trial, for each 100-µm lower retinal thickness, the VA was 5.3 letters higher after 6 months of follow-up.[18] Ouyang et al[19] showed that 3D-OCT was more sensitive and reproducible than FA for the detection of ME by trained expert graders. The Spectralis OCT was noted to have the best intersession repeatability.[14] Payne et al[20] found out that a logarithmic transformation

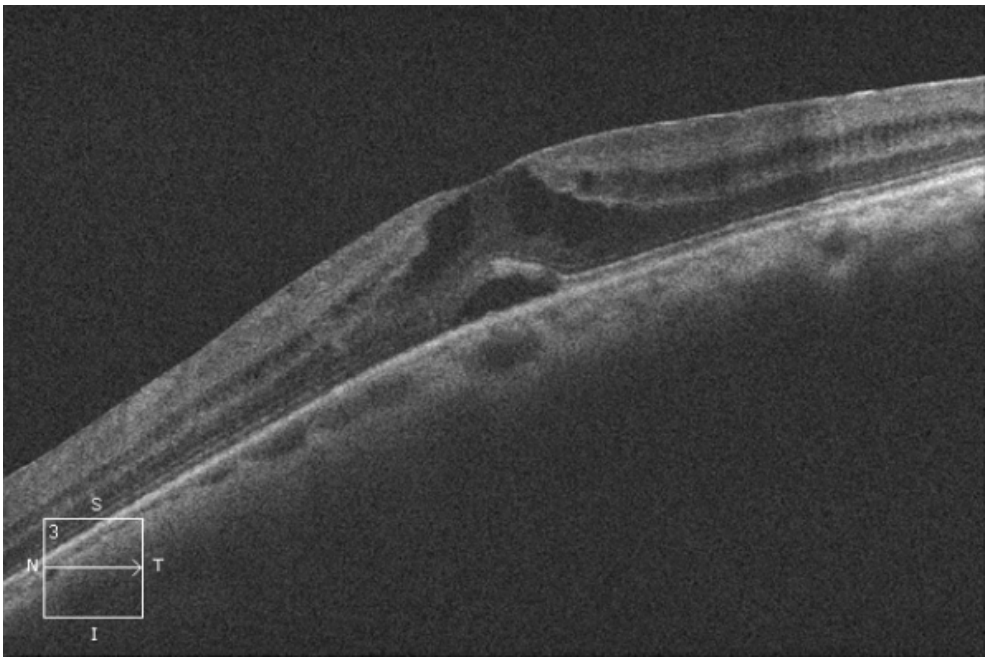

Figure 3. A subfoveal serous retinal detachment accompanying cystoid macular edema in ocular sarcoidosis.

Table 2. Classification of ME on OCT

Type of ME	Description
Diffuse	Sponge-like thickened retina with reduced intraretinal reflectivity, located particularly in the outer retinal layers
Cystoid	Hyporeflective lacunae within the retina. In early CME, the cysts are primarily located in the outer retinal layers. In chronic CME, large confluent cystoid cavities might develop, involving the entire retinal layer
Subretinal Fluid	A shallow dome-shaped elevation of the retina with an optically clear space between the retina and the RPE
Vitreoretinal interface abnormalities	Epiretinal membrane: a highly reflective layer on the inner retinal surface Vitreomacular traction: perifoveal vitreous detachment with focal adhesion to the fovea

CME indicates cystoid macular edema; ME, macular edema; RPE, retinal pigment epithelium; OCT, optical coherence tomography.

of SD-OCT data in uveitis-associated ME provided a more normal distribution and positively correlated with logMAR VA. A strong correlation was shown between the VA in patients with cystoid ME and the volume of tissue between the 2 plexiform layers in the central retina as determined by OCT.[21]

It became clear that the visual prognosis depends on the integrity of the reflection line of the external limiting membrane (ELM) and the IS/OS-line. Recently, Wanek et al[22] succeeded in extracting the photoreceptor integrity from the OCT images and provided a 3D map. However, it was documented that a fragmentation of the foveal cone outer segments tips lines and a fragmentation or disruption of the IS/OS junctions and ELM lines could be an artifact caused by a hyperreflectivity at the foveal pit surface casting acoustic shadows.[23] An absent cone outer segments tip line at the fovea was found in 4% to 5% of normal eyes.

The predictive value of the CRT showed inconsistent results and was a better prognosticator in cystoid than in diffuse ME. Multivariate analysis showed that cystoid ME of all retinal layers and cysts in the inner retinal layers were the variables negatively associated with final VA.[24] A subfoveal serous retinal detachment (SRD) in inflammatory edema was associated with good visual recovery, whereas it forms a poor prognostic sign in diabetic ME. In uveitis patients, a subfoveal SRD was associated with a lower VA and developed typically in the early stages of uveitis and ME, but responded well to conventional treatment.[24,25] The presence of an epiretinal membrane was an important factor associated with medical treatment failure.

Preferable indications for OCT

The OCT is the preferred method of monitoring ME and evaluating the treatment results, because of its quantitative data, the delineation of the vitreoretinal interface and non-invasiveness. OCT can detect early stages of ME, but does not evaluate the activity of the uveitis. Therefore, the monitoring of uveitis patients with OCT solely might be incomplete and lead to inappropriate therapeutic decisions. In contrast, OCT allows a better delineation of vitreoretinal interface valuable for evaluation of mechanical forces and forms an indication for vitreoretinal surgery.

Discrepancies between FA and OCT

The discrepancies between OCT and FA imaging in inflammatory ME were reported with variable prevalences. [9,26-28] Consistent results were found in severe ME, in mild cases discrepancies were frequently found.[29] FA leakage might point out mild cases of (diffuse) ME, sometimes associated with a CRT within the normal limits. This phenomenon can also be present in long-standing uveitis with retinal atrophy with decreased CRT despite the presence of ME (Fig. 4). Retinal thickening on OCT without fluorescein

leakage occurred more often in inactive uveitis, suggesting that the accumulated fluid may persist in the retina without the ongoing inflammation.
The presence of a subfoveal SRD in ME is a feature newly recognized on OCT and invisible on FA.

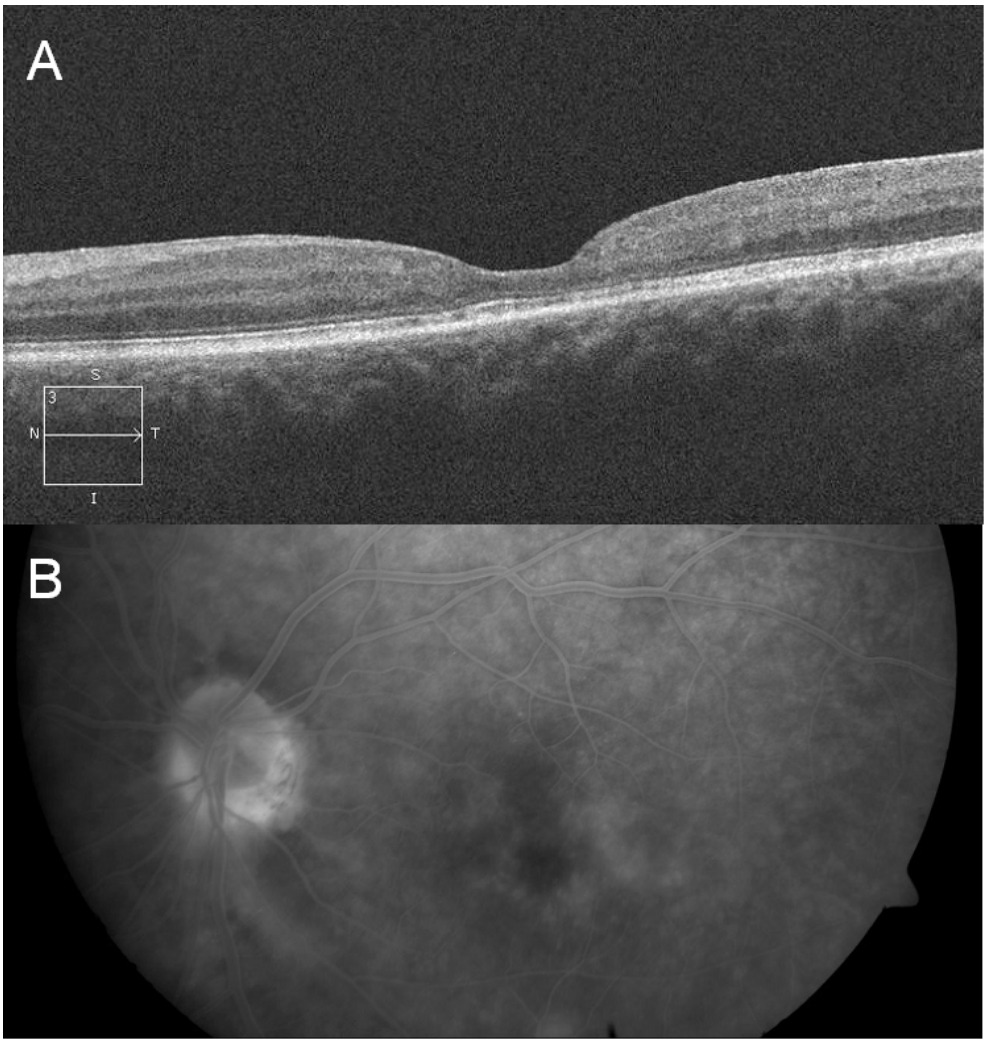

Figure 4. Discrepancy between optical coherence tomography (OCT) and fluorescein angiography (FA) in a patient with a chronic ocular sarcoidosis. The OCT was made 1 week after the FA without intervening therapy. A, OCT image suggesting a central foveal atrophy without macular edema. B, FA reveals macular edema. Because of the thinning of the central retina and the absence of intraretinal cysts, the macular edema was missed on OCT.

Use of FA and OCT for diagnosis and follow-up in inflammatory ME

FA provides physiological and the OCT morphological information and the use of these two methods are complementary. In situations where the presence of ME would affect the treatment policy and with 1 test (FA or OCT) negative for ME, is the other test –in our view- indicated. FA is additionally valuable in making the diagnosis of the underlying uveitic disorder and the quantification of ME makes the OCT superior to FA in evaluating the changes overtime.

Ultrahigh-resolution OCT (UHR-OCT)

Unlike the axial resolution, the lateral resolution of SD-OCT is limited by the quality of the eye's optics (monochromatic and chromatic aberrations) and the beam diameter at the eye's pupil (diffraction), increasing the spot size at the retina, and limiting the ability of SD-OCT to image the 3D retina at the cellular level. A strategy that has been successfully employed to correct monochromatic aberrations across a large pupil (>6mm) in SD-OCT is adaptive optics (AO). In the recent years, first the fundus camera, second the scanning laser ophthalmoscope, and then the OCT, have been combined successfully with AO for cellular resolution imaging.[30] Cone row-to-row spacing and outer segments lengths were measured.[31] In addition, recent improvements in acquisition speed and sensitivity of research-grade OCT instruments now permits clear and reliable imaging of the cone mosaic in young healthy volunteers without AO at eccentricities of >4 degrees. However, AO with wave front correction is required to allow cellular resolution imaging near the fovea. The UHR-AO-OCT system in combination with an achromatizing lens is capable of achieving a volume resolution of 3x3x3 μm^3.

The in vivo cellular resolution refers so far only to the cone photoreceptor mosaic. The exact mechanism that determines the distribution of excess fluid in retinal layers, formation of cysts, and intracellular edema has not yet been identified. Until now, these UHR techniques have only been described in healthy eyes and might not be feasible in patients with media opacities.

ICG

The role of indocyanine or infracyanine green angiography (ICG) in ME imaging is limited, because ME is predominantly a retinal phenomenon and hardly visible on ICG-angiograms. However, the source of the intraretinal edema might be sometimes discovered with ICG, as choroidal infiltrates with or without a subretinal neovascularization in the macular area with overlying ME in multifocal choroiditis (Fig. 5).

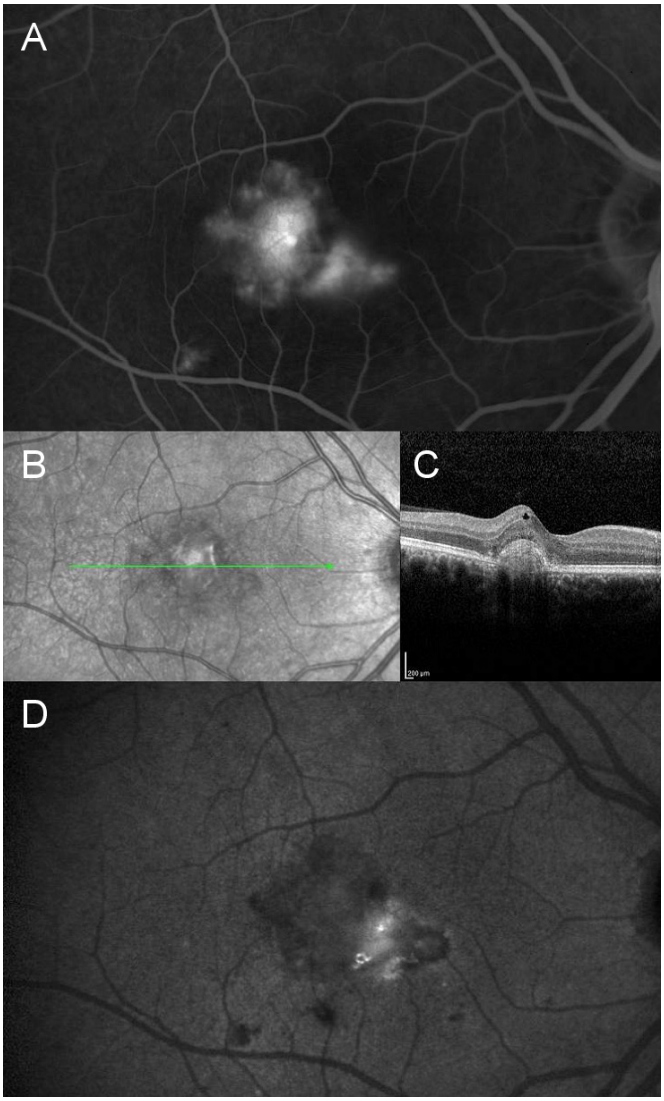

Figure 5. Underestimation of the severity of the pathology with the optical coherence tomography in a patient with an active subretinal neovascularization and an active choroiditis. A, Fluorescein angiogram at 10 minutes, showing extensive leakage from the choroiditis and the subretinal neovascularization. B, Infrared image with the scanning line of the OCT. C, OCT, showing the subretinal scar and only minimal intraretinal and subretinal fluid. D, Averaged infracyanine green angiogram at 30 minutes. The choroidal activity is visible as hypofluorescent spots, the central hyperfluorescence is due to the leakage from the neovascularization.

Autofluorescence

Autofluorescence is another non-invasive way to visualize ME. The foveal autofluorescence (FAF) was increased in 24/53 eyes with inflammatory ME and related to worse VA.[32]

The sensitivity of FAF for angiographically proven ME was limited. The increase of FAF might be explained by a displacement of macular pigment by cystoid spaces in the retina or an accumulation of lipofuscin.

Fundus Reflectometry

Fundus reflectometry provided evidence for the disturbance of the directional properties in inflammatory ME.[33] A diminished or absent Stiles-Crawford reflex was also present in subclinical ME cases.

Infrared Imaging

Infrared imaging often reveals macular pathology more clearly than color fundus photography. OCT reveals macular cysts in cross-sectional images. However, Yahamoto et al[34] showed that infrared en-face images from a scanning laser ophthalmoscope in the retro-mode visualizes cystoid ME even more clearly than FA.

Ultrasound

The role of ultrasound in ME imaging is very limited and gives only a rough indication of ME in occasional cases with severe media opacities. It has, however, an important role in detection of the cause of ME in patients with posterior scleritis by demonstration of a thickened chorioretinoscleral complex in combination with a T-sign.

Microperimetry

Imaging of the retina can be correlated with functional testing with devices performing microperimetry. Often the VA is not a reliable tool to monitor the damage due to ME and microperimetry offers the possibility to measure a loss of retinal sensitivity in areas with ME.

Summary

OCT has become the most common way to image ME. It represents morphologic characteristics of ME in detail, allows the quantitative measurements of ME, and depicts the integrity of the photoreceptor layer important for the visual prognosis and further evaluates the otherwise invisible changes of the vitreoretinal interface. Normative data for the different devices are scarce and data from different devices cannot be compared. FA retains its crucial role in determining the activity of the uveitis and also forms an important diagnostic tool. OCT and FA imaging in inflammatory ME are complementary methods, each with its specific indications and outcomes. Ultrahigh-resolution OCT's will bring a further understanding of the pathogenesis of inflammatory ME.

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CHAPTER 3

Subfoveal serous retinal detachment in patients with uveitic macular edema

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Abstract

Objective: To assess the clinical characteristics and effect on visual acuity (VA) of a subfoveal serous retinal detachment (SRD) associated with macular edema (ME) in patients with uveitis.

Methods: Clinical and optical coherence tomograph characteristics were retrospectively assessed in 37 patients with uveitic ME with a subfoveal SRD (case individuals) and 61 patients with uveitic ME without a subfoveal SRD (control individuals), matched for uveitis location, sex, and age. Scans of the case and control individuals took place between September 19, 2003, and July 21, 2008.

Results: Patients with a subfoveal SRD had a shorter history of uveitis (P = .03) and ME (P = .03) and a lower VA (P = .003). Mean total retinal thickness (TRT) in cases exceeded that of controls (449 vs 326 µm; P < .001). The median subfoveal SRD duration was 2 months, and 29 of 36 SRDs (81%) had disappeared at the 3-month follow- up examination. The improvement in VA and the decrease in TRT after 3 months were better in the subfoveal SRD group than in the control group (P = .001 for VA and P = .001 for TRT), resulting in similar VA and TRT after 3 months.

Conclusions: A subfoveal SRD was associated with lower VA and developed typically in the early stages of uveitis and ME. The subfoveal SRD and VA reacted favorably to treatment with periocular and systemic steroids and/or oral acetazolamide.

Introduction

Macular edema (ME) is a major cause of poor visual acuity (VA) in patients with uveitis.[1-3] Frequently, ME also complicates the course of various other ocular disorders such as diabetic retinopathy and retinal vein occlusions, and might develop after intraocular surgery.

After the introduction of optical coherence tomography (OCT) in 1995, it was observed that some patients with ME of diverse origins also have an associated subfoveal serous retinal detachment (SRD). The clinical effect of a subfoveal SRD in ME has not yet been extensively studied, and its consequences in uveitis have not yet been identified, to our knowledge. In patients with diabetic retinopathy, however, a subfoveal SRD was associated with poor visual outcome after grid laser photocoagulation and vitrectomy.[4,5] Similarly, in branch retinal vein occlusions, the presence of a subfoveal SRD seemed to delay the absorption of ME and the recovery of VA after grid laser photocoagulation.[6] The clinical relevance of a subfoveal SRD in uveitis patients remains unclear. In this study, we evaluate the visual impact of a subfoveal SRD in inflammatory ME.

Methods

Ours was a retrospective case-control study at the Department of Ophthalmology of the University Medical Center Utrecht, Utrecht, the Netherlands. Approval was obtained from the institutional review board of the hospital. For the evaluation of the clinical effect of a subfoveal SRD, we randomly selected 37 affected eyes of 37 uveitis patients with ME with a subfoveal SRD (case individuals) from our OCT database (numeric code). As control individuals we selected 61 eyes of 61 patients with ME without a subfoveal SRD from our OCT database, matched for anatomical location of uveitis, sex, and age. The OCT scans of the cases and controls took place between September 19, 2003, and July 21, 2008. There was no statistical difference in the time span of uveitis in which no OCTs were available (before September 19, 2003) between cases and controls (median of 4.3 years in the 21 cases vs 7.2 years in the 45 controls; Mann-Whitney $P = .55$). The time the first OCT with a subfoveal SRD present was diagnosed was considered to be the time of onset of the subfoveal SRD. For the cases, the start of analysis (t=0) was the time of the diagnosis of the subfoveal SRD. After the matching for age, location of uveitis, and sex, we used the first OCT in that particular year in the controls. The date of this OCT was considered to be t=0.

We reviewed the medical records of the cases and the controls and registered sex, age at onset of uveitis, age at onset of ME, age at diagnosis of subfoveal SRD, type of uveitis according to anatomical location and/or specific diagnoses, duration of uveitis and ME at t=0, associated general and ocular diseases, total retinal thickness (TRT), the presence or absence of vitreomacular traction or an epiretinal membrane, and VA at t=0, 3, and 6 months. In addition, we registered treatment regimens used before

t=0 and thereafter. Treatment regimens were registered as topical, periocular, and systemic, which was divided into a group of immunosuppressive agents (prednisone, azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and infliximab) and a group composed of acetazolamide and octreotide acetate. Before t=0, no differences in treatments with immunosuppressive agents or acetazolamide were identified (P = .33 and P = .78, respectively). No differences in the use of systemic or periocular steroids were observed between the subfoveal SRD cases and the controls (P = .70 and P = .12, respectively). All patients were classified using uveitis nomenclature according to the recommendations of the Standardization of Uveitis Nomenclature working group.[7]

The OCT was performed with a STRATUS OCT (model 3000; Carl Zeiss Meditec, Jena, Germany), and analysis was based on 6-mm 6 radial scan lines of each eye, centered on the patient's fixation point. The OCTs of the cases and controls were reviewed and coded in a masked fashion for the various types and features of ME.[8] Patients were included if their TRT was greater than 210 µm in the 1-mm region and/or greater than 300 µm in the 3-mm region. Diffuse ME was characterized by increased retinal thickness, disturbance of the layered retinal structure, or spongelike low reflective areas. Cystoid ME was characterized by the formation of clearly defined intraretinal cystoid spaces.[8] A subfoveal SRD was defined as fluid separating the neurosensory retina from the RPE, which was visible on OCT as an optically clear space between the retina and RPE. The subfoveal SRD height was measured at the fixation point manually at its thickest point using calipers and was defined as the average distance between the RPE and the outer neurosensory retinal surface on vertical and horizontal scans (Figure). The neuroretinal thickness (NRT) was defined as the distance between the inner and outer neuroretinal layers at the fixation point (Figure). The TRT was measured automatically with OCT retinal mapping software in the central 1-mm region and was defined as the sum of the NRT and the subfoveal SRD. Good reproducibility of these measurements using OCT mapping software has been demonstrated.[9] For simplicity, in the "Results" section of the text, the TRT in controls is called the NRT when compared with the NRT of the cases.

Fluorescein angiograms were available for 32 patients within 3 months of the date of the OCT and available in 13 patients on the same day. The angiograms were examined for signs of central serous chorioretinopathy.

For statistical analyses the t, Pearson χ^2, and Fisher exact tests were used whenever appropriate (SPSS statistical software version 15.0 for Windows; SPSS Inc, Chicago, Illinois). The χ^2 or Fisher exact test was used to compare categorical data. To compare means of nonnormally distributed variables, we used the Mann-Whitney or Kruskal-Wallis test, and $P < .05$ was considered statistically significant. We transformed Snellen VA to the logarithm of the minimal angle of resolution (logMAR) to perform statistical analysis and afterward converted the results back to Snellen equivalents. Values in the text and Table are converted from logMAR to Snellen VA. Results are represented

according to the distribution of the calculated variables, which means the mean is given if the variables have a normal distribution (Kolmogorov-Smirnov $P > .05$) and the median if the distribution is nonnormal. Using univariate linear regression analysis, the correlation of the variables duration of uveitis, duration of ME, type of ME, height of the subfoveal SRD, TRT, NRT, and presence or absence of cataract with logMAR VA (all at t=0) were analyzed. These variables were also included in a multivariate regression analysis.

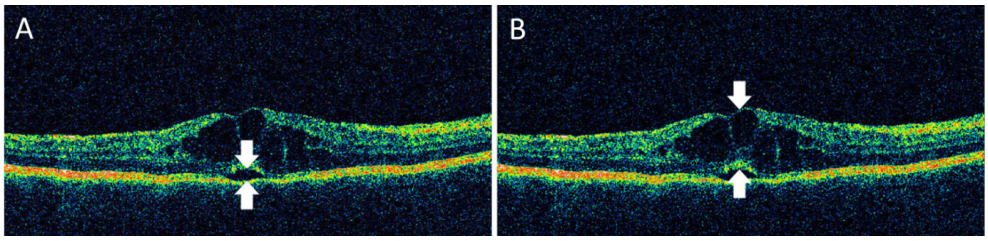

Figure. Horizontal optical coherence tomograph (OCT) showing inflammatory cystoid macular edema with a subfoveal serous retinal detachment (SRD). The subfoveal SRD is visible as an optically clear space between the neurosensory retina and the retinal pigment epithelium filled with serous fluid in the central foveal area. A, Arrows point to measurements of the subfoveal SRD height. B, Arrows point to measurements of the neuroretinal thickness. Both measurements were performed using calipers in the OCT analysis program.

Results

General characteristics and demographic data of the cases and the controls are summarized in the Table. Because of the matching, no significant differences in sex, age, and anatomical location of the uveitis were found. Furthermore, no differences in uveitis origin were observed between the cases and the controls. Diabetes mellitus was not present in any of the cases but was present in 8 controls, all of whom were without diabetic retinopathy ($P = .02$); systemic hypertension was present in 7 cases and 9 controls. The uveitis was bilateral in 28 of the 37 cases (76%) and in 49 of the 61 controls (80%; $P = .60$). Macular edema was present in 19 of the 35 fellow eyes (54%) of the subfoveal SRD cases (OCTs were not available for 2 fellow eyes). In 8 of these 19 eyes, a subfoveal SRD was also noted (in 5 simultaneously).

At t=0, subfoveal SRD-positive cases exhibited a shorter median duration of uveitis (33 months for cases vs 62 months; $P = .03$) and a shorter median duration of ME (2 months for cases and 17 months for controls; $P = .03$). In contrast, median VA at t=0 was worse in the subfoveal SRD group: 0.30 in cases and 0.50 in controls ($P = .003$).

The median TRT (including the subfoveal SRD) was higher in the cases than in the controls (449 vs 326 µm; $P < .001$; Table). The median NRT was 359 µm in cases, which was not different from the NRT in the controls (326 µm; $P = .92$). In 8 of the 35

cases (23%; thickness data not completely available in 2 patients), no thickening of the neuroretina was found (NRT <210 µm) at the time of a subfoveal SRD.

When the patients were subdivided according to type of ME, the prevalence of the cystoid type was higher in the cases (28 of 37 (76%)) compared with the controls (36 of 61 (59%)), but this difference was not significant (P = .09). The median TRT in diffuse ME was lower than in cystoid ME (289 µm (range 125-626 µm) vs 443 µm (range 169-777 µm), P < .001).

Evaluation of the angiograms revealed that the subfoveal SRDs were not visible on fluorescein angiography (possibly also because of associated cystoid ME). None of the available angiograms showed the typical signs of central serous chorioretinopathy: no pigment epithelial detachments, retinal pigment epithelial alterations, or other foci of subretinal leakage were present. The subfoveal SRDs were much smaller than the subretinal fluid collections in central serous chorioretinopathy.

Median VA at the 3-month follow-up examination improved in both groups (P < .001 for cases and P = .03 for controls), but this finding was much more prominent in the subfoveal SRD group (P = .001, Table). An improvement in VA of at least 2 Snellen lines after 3 months was identified in 18 of the 36 cases (data for 1 case missing at 3-month follow-up) and 12 of the 53 controls (data for 8 controls missing at 3-month follow-up) (P = .007).

At the 3-month follow-up, the median TRT decreased from 449 to 275 µm (P < .001) in the subfoveal SRD group and from 326 to 289 µm (P < .001) in the control group. The decrease in the TRT after 3 months was more prominent in the subfoveal SRD group than in the controls (P = .001). The median NRT after 3 months was 261 µm in the subfoveal SRD group and 289 µm in the controls (P = .18). After 3 months the NRT had decreased significantly in both groups: 87 µm in the cases (range, –239 to 426 µm, P = .002) and 44 µm in the controls (range, –22 to 357 µm, P <. 001); however, there was no significant difference between both groups (P = .28).

The median subfoveal SRD duration was 2 months, and 29 of the 36 subfoveal SRDs (81%; data for 1 subfoveal SRD missing) had disappeared at the 3-month follow-up OCT examination. The OCT examination results were not available in 7 patients with a subfoveal SRD at 3-month follow-up, but in 5 of them, OCTs within the first 3 months had already shown that the subfoveal SRD had disappeared. The range of the subfoveal SRD duration was 6 days (resolution after periocular betamethasone injection) to longer than 19 months (in the individual in question, the subfoveal SRD was still present on the last OCT).

Using univariate linear regression analysis, only the TRT was significantly associated with logMAR VA (R = 0.25, P = .02). In the subfoveal SRD group, the height of the subfoveal SRD did not correlate with the NRT (R = –0.13; P = .50). Using the NRT and the height of the subfoveal SRD (which was 0 in the controls) as the variables in a linear regression analysis, only the height of the subfoveal SRD was significantly

Table. General and ocular characteristics of patients with inflammatory ME and a subfoveal SRD

Variables	ME with subfoveal SRD (n=37)	ME without subfoveal SRD (n=61)	*P* value
Age, mean (range), y	50 (10-79)	52 (13-85)	.33
Male to female ratio	15:22	21:40	.54
Origin, No. (%) of patients			.21
- Associated systemic diseases	15 (41)	23 (38)	
-sarcoidosis	4 (11)	13 (38)	
-HLA-B27	4 (11)	3 (2)	
-multiple sclerosis	1 (1)	3 (5)	
-other	6 (16)	4 (7)	
- Intraocular infections	5 (14)	5 (8)	
- Established clinical entities	1 (3)	2 (3)	
- Undetermined	16 (43)	31 (51)	
Duration of uveitis until t=0, median (range), mo	33 (0-309)	62 (0-459)	.03
Duration of ME until t=0, median (range), mo	2 (0-112)	17 (0-288)	.03
Total retinal thickness at t=0, median (range), µm	449 (225-777)	326 (125-579)	<.001
Neuroretinal thickness at t=0, median (range), µm	359 (60-645)	326 (125-579)	.92
Subfoveal SRD height, median (range), µm	116 (24-257)	NA	
Duration of subfoveal SRD, median (range), mo	2 (0.2->19)	NA	
Treatment before t=0, No. (%) of patients			
- Periocular injections	7 (19)	5 (8)	.12
- Systemic steroids	5 (14)	10 (16)	.70
Type of ME, No. (%) of patients			
- Diffuse	9 (24)	25 (41)	.09
- Cystoid	28 (76)	36 (59)	.09
Vitreoretinal traction, No. (%) of patients	5 (14)	5 (8)	.50
Epiretinal membrane, No. (%) of patients	8 (14)	24 (39)	.07
Snellen visual acuity, median (range)			
- Visual acuity at t=0	0.30 (0.1-0.6)	0.50 (0.02-1.0)	.003
- Visual acuity at t=3 mo	0.60 (0.05-1.0)	0.65 (0.01-1.2)	.48
- Visual acuity at t=6 mo	0.60 (0.1-1.0)	0.60 (0.00-1.2)	.53
Start treatment with acetazolamide after t=0, No. (%) of patients	14 (38)	17 (28)	.30
Total retinal thickness after 3 mo, median (range), µm	275 (191-580)	289 (171-546)	.50
Neuroretinal thickness after 3 mo, median (range), µm	261 (50-580)	289 (171-546)	.18
Immunosuppressive treatment during follow-up, No. (%) of patients	19 (51)	28 (46)	.60

Abbreviations: ME, macular edema, NA, not applicable; SRD, serous retinal detachment.

associated with logMAR VA (β = .23, *P* = .03). In a stepwise linear regression analysis using the variables duration of uveitis, duration of ME, NRT, height of the subfoveal SRD, type of ME, and presence or absence of cataract, again, only the height of the subfoveal SRD was significantly associated with logMAR VA (β = .22, *P* = .04).

Treatment of the cases and controls during follow-up did not differ. No differences in the start of acetazolamide (or octreotide) therapy, periocular injections, systemic steroid therapy, or all immunosuppressive therapy were found (*P* = .37, *P* = .79, *P* = .37, and *P* = .15, respectively) after OCT at t=0.

Comment

We documented that a subfoveal SRD developed typically in the early stages of uveitis and ME and reacted well to the recommended treatment given for inflammatory ME (periocular or systemic steroids and/or acetazolamide). Despite the presence of a subfoveal SRD and lower VA at onset, VA at 6-month follow-up was similar for patients with and without a subfoveal SRD. Our findings on subfoveal SRD-positive ME in uveitis are distinct from some of the studies on ME of other origins. Diabetic subfoveal SRD-positive ME was associated with a poor visual outcome 6 months after a grid photocoagulation was performed[4] and with a poor visual outcome after vitrectomy.[5] Recovery of VA after grid laser photocoagulation in branch retinal vein occlusion was also slower if a subfoveal SRD was present.[6] Our findings are, however, consistent with those of Gaucher et al,[10] who reported that a subfoveal SRD was associated with early-stage ME. Previously, Markomichelakis et al[8] found a subfoveal SRD to be associated with decreased VA in patients with uveitis. In contrast, Catier et al,[11] and more recently Tran et al,[12] could not identify a significant association between a subfoveal SRD and VA in uveitic patients. Our results indicate that VA of subfoveal SRD-positive eyes is worse during the presence of a subfoveal SRD; however, follow-up VA (at 3 and 6 months) was similar for both groups.

We hypothesize that in the early stage, VA is negatively influenced by the presence of a subfoveal SRD and its disappearance during follow-up might explain the larger visual gain but similar follow-up VA as the controls. One might argue that the controls had a longer duration of uveitis and ME and their improvement would be therefore limited. However, the decrease of the NRT in the cases was not significantly different from that in the controls (*P* = .28).

Our series included 8 patients with diabetes mellitus, all in the control group. Although none of the diabetic patients had documented retinopathy, we cannot entirely exclude the possibility that changes in retinal vascular permeability might negatively influence the visual gain in the controls.

We also demonstrated a positive correlation between the TRT and logMAR VA (*P* = .02) in uveitis patients, independent of the presence of a subfoveal SRD. This association was also reported by Tran et al.[12] The Diabetic Retinopathy Clinical Research Network

found a modest correlation between TRT and VA in diabetic ME.[13] In addition, an increased TRT in patients with a subfoveal SRD was strongly correlated with lower VA compared with their nonsubfoveal SRD counterparts (Table).

The prevalence of subfoveal SRD-positive ME was reported in approximately 20% of uveitic eyes with OCT-proven ME.[8,14] The exact occurrence of a subfoveal SRD in uveitic ME is difficult to examine because it is temporary. Ideally, the incidence and prevalence of a subfoveal SRD should be determined in a long-term follow-up study of all patients with newly developed inflammatory ME by frequent OCT examinations.

A possible hypothesis explaining the pathogenesis of subfoveal SRD could be the high resistance of the retinal tissue layers to the influx of fluid in the early phase of fluid accumulation (and inflammation). Therefore, the excess of fluid may first accumulate under the retina, resulting in a subfoveal SRD. Later, when more inflammatory damage develops and/or fluid volume increases, the retinal resistance may become insufficient, and as a consequence the fluid may enter the neuroretinal tissue and form cysts. After this extracellular cyst formation, the fluid finally would enter the intracellular environment. The transient aspect of a subfoveal SRD in uveitis and favorable response to treatment also support this hypothesis and the observation by Tran et al[12] and Gaucher et al[10] that a subfoveal SRD might also be documented in patients with normal NRT and without edema. In our study, 8 of the 35 cases (23%; data missing for 2 cases) had an NRT of less than 212 µm. In addition, Gaucher et al[10] reported that 20% of the patients with subfoveal SRD-positive ME and diabetes had a normal NRT. Of interest, they observed that the subfoveal SRD could resolve itself despite worsening of the diabetic ME.

Also, using multivariate linear regression analysis, the height of the subfoveal SRD was associated with VA. The NRT in patients with a subfoveal SRD was not different from that in controls. This observation suggests that the presence of a subfoveal SRD itself has a negative influence on VA in patients with inflammatory ME. Possible explanations might include the impaired renewing of the photoreceptor cells or their inadequate nutrition in the presence of a subfoveal SRD. Another possible explanation for decreased VA in subfoveal SRD might include the diminished directional sensitivity (ie, optical Stiles-Crawford effect) and disorientation of the foveal cone photoreceptors.[15,16]

Macular edema develops in disorders accompanied by a compromised inner and/or outer blood retinal barrier (BRB). To our knowledge, the exact mechanism that determines the distribution of excess fluid in retinal layers, formation of cysts, and intracellular edema has not yet been identified.[17] Intraretinal fluid distribution is restricted by 2 diffusion barriers, the inner and outer plexiform layers.[18] In cases with a compromised outer BRB, the accumulation of fluid in the subretinal space, especially in the early stages, may be expected. In contrast, the accumulation of fluid in cases with a compromised inner BRB is not easily explained. Subfoveal SRD also develops in patients with (branch) retinal vein occlusions, in whom the primary lesion lies in the inner BRB. Kang et al[19] postulated that in broken inner BRB, fluid and albumin might reach the subretinal

space through the permeable external limiting membrane. However, the pathogenesis of subfoveal SRD in patients with a broken inner BRB deserves further investigation.

Obviously, our study has several shortcomings related to the character of the case-control study. We have chosen to match for age, sex, and anatomical location of uveitis. The matching for various additional factors involved in uveitis (eg, etiologic diagnosis, onset of uveitis, and onset of ME) was not feasible.

Our study was not designed to evaluate various treatment strategies for ME and subfoveal SRD. Overall, the systemic treatment modalities in the cases and controls did not differ. An important issue is the occurrence of an SRD after the use of steroids in various administrations.[20] However, it is unlikely that a subfoveal SRD in our patients developed owing to steroid medication. First, the number of patients taking systemic or periocular steroids did not differ between the cases and controls. Second, a subfoveal SRD in ME reacted favorably to steroids. Finally, the small subfoveal SRDs in inflammatory ME have clinical characteristics distinct from those of central serous chorioretinopathy.

In conclusion, a subfoveal SRD developed typically in the early stages of uveitis and ME and was at the time of diagnosis associated with lower VA compared with the nonsubfoveal SRD group. The subfoveal SRD and VA of affected patients with uveitis reacted favorably to treatment with periocular and systemic steroids or acetazolamide.

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CHAPTER 4

Discrepancies between fluorescein angiography and optical coherence tomography in macular edema in uveitis

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Abstract

Purpose: To assess the frequency and characteristics of discrepant findings between fluorescein angiography (FA) and optical coherence tomography (OCT) in uveitic macular edema (ME).

Design: Retrospective cross-sectional study on 112 eyes of 78 patients with uveitic ME on FA, OCT, or both.

Methods: ME was graded on OCT and FA of uveitis patients attending the University Medical Center Utrecht. The frequency and severity of discrepant findings were analyzed, and the clinical findings at the time of imaging were assessed. The imaging studies were compared with the clinical characteristics.

Results: Positive results of both imaging methods (FA+/OCT+) were observed in 61 (54%) of 112 eyes, whereas discrepant results occurred in 51 (46%) of 112 eyes. The FA+/OCT- discrepancy occurred in 34 (30%) of 112 eyes and FA-/OCT+ discrepancy in 17 (15%) of 112 eyes. No correlations between the discrepant imaging results and age, gender, duration of uveitis or ME, visual acuity or cause of uveitis were identified. FA+/OCT- and FA-/OCT+ discrepancies comprised typically mild degrees of ME. The FA+/OCT- discrepancy occurred in 50% of eyes with birdshot chorioretinopathy (7/14) and the FA-/OCT+ discrepancy occurred more often in intermediate uveitis than in other anatomic locations. While the FA+/OCT+ consistency was noted frequently in active uveitis, the FA-/OCT+ discrepancy was common in eyes with inactive uveitis (8/18, 44% of inactive eyes).

Conclusions: Our results emphasize that FA and OCT are complementary investigations, each revealing different aspects of the pathophysiology of uveitic ME.

Introduction

Macular edema (ME) is a condition characterized by intraretinal accumulation of fluid in the macula, which is a major cause of decreased visual acuity in multiple ocular disorders, including uveitis.[1-3] Clinical signs may manifest first when severe macular involvement has already developed. In contrast, therapeutic interventions are effective mostly in the early stages of ME. Until the introduction of the optical coherence tomography (OCT), fluorescein angiography (FA) was the most widely used method to evaluate the retinal vascular perfusion and the integrity of the inner blood-retinal barrier. OCT has become increasingly important in the assessment of ME by revealing quantitative data about retinal thickness and information on anatomic abnormalities of the retinal layers.
Although both FA and OCT are able to verify the presence of ME, discrepancies occasionally have been reported.[4–11] Contradictory results from these examinations complicate clinical decision making. In this study, we investigated the incidence and nature of discrepancies between FA an OCT in a large group of patients with uveitis and attempted to clarify the factors causing these discrepancies.

Methods

In this study we retrospectively included all 78 patients (112 eyes) with uveitis and ME who underwent both FA and OCT within an interval of 2 weeks at the University Medical Center Utrecht during a 21-month period from January 2007 through September 2008 and who did not undergo any therapeutic interventions between the FA and the OCT. Excluded from study were 4 patients in whom poor quality or misaligned OCT scans were obtained. Criterion was whether the software program could make a good fit on the inner and outer border of the retina. Medical charts of patients were reviewed for sex, age, duration of uveitis and of ME at the time of the imaging studies, anatomic classification, cause of uveitis, and best-corrected visual acuity. Our uveitis population included 22 patients with associated systemic diseases and 40 patients with an unknown cause of uveitis (Table 1). Fluorescein angiograms and OCT scans were assessed in a masked fashion for characteristics of ME by 2 observers (J.O.-v.N., L.P.C.). All FA photographs were recorded using a Zeiss digital fundus camera (Zeiss FF 450 plus fundus camera; Carl Zeiss AG, Oberkochen, Germany). Fluorescein angiograms were graded according to a modified grading system (Table 2), that is, a combination of the criteria reported by Yannuzzi and the proposed grading system of the Angiography Scoring for Uveitis Working Group.[12,13] In addition, we registered the number of affected clock hours separately. ME was assessed on images obtained at least 5 minutes after intravenous injection of 5 mL 20% sodium fluorescein. In this study, only the cases in which there was obvious leakage in the center (grades 2 through 4) were classified and analyzed as ME.

OCT was performed with the Stratus OCT (Stratus OCT 3000, software version 4.0.1; Carl Zeiss Meditec, Inc, Dublin, California, USA). Mean central retinal thickness (CRT; inner 1000 µm) was recorded, and 6 radial line images were reviewed on screen for the presence of ME, intraretinal cysts, associated central serous retinal detachment (CSRD), epiretinal membranes, vitreoretinal attachment with or without traction (vitreoretinal traction vs -adhesion), or a combination thereof. Poor quality or misaligned OCT scans were excluded from the analysis (n=12). The following characteristics of ME were registered: diffuse macular edema, cystoid macular edema, and CSRD. Diffuse ME presented as diffuse thickening of the retina, disturbance of the orderly layered retinal structure, spongelike low reflective areas, or a combination thereof. Cystoid macular edema was characterized by clearly defined intraretinal cystoid spaces. In a CSRD, a separation between neurosensory retina and retinal pigment epithelium was present in addition to ME.[14] Based on a meta-analysis of 3 large studies investigating retinal thickness in northern and northwestern Europeans using the Stratus OCT,[15–17] we chose an upper limit value of 249 µm for CRT, which is 2 standard deviations above the mean central retinal thickness (pooled mean of 205.5 ± pooled standard deviation of 21.7 µm). ME on OCT was considered in cases with CRT higher than 249 µm or when evident cystoid spaces could be observed on radial lines (n= 5).

The activity of the uveitis was classified as active or inactive, based on the presence or absence of aqueous or vitreous cells, or both, signs of activity on fluorescein angiography[13] (such as vasculitis, optic disc leakage, and capillary leakage outside the perifoveal area), or a combination thereof.

An analysis of variance was used to test for differences in mean age, duration of uveitis, duration of ME, visual acuity and CRT between eyes with ME on both examinations, ME solely on FA and ME solely on OCT. The Dunnett post hoc test was applied to determine any differences between separate groups. A chi-square equation was used to calculate differences between groups for frequencies of cause, location of uveitis, FA-grade, presence of CSRD, presence of epiretinal membranes and presence of vitreoretinal traction. All statistical analyses were performed using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, Illinois, USA). We included all eyes with ME in our analyses because, in bilateral cases, no correlation was found in the occurrence of discrepancies and CRT measurements between the left and the right eyes (P = .78).

Table 1. Discrepancies according to the cause of uveitis and the baseline characteristics of the patients

	FA+/OCT+ (n=43)	FA+/OCT- (n=26)	FA-/OCT+ (n=9)	Total (n=78)
Cause				
Associated systemic diseases	14	7	1	22
- Sarcoidosis	12	4	1	17
- HLA-B27	0	1	0	1
- Multiple sclerosis	0	0	0	0
- Other	2	2	0	4
Intraocular infections	1	1	1	3
Established clinical entities[a]	6	14	3	13
Undetermined[b]	22	14	4	40
Mean age[c] (range), y	55 (13-83)	52 (18-77)	49 (26-73)	53 (13-83)
Median duration uveitis[c] (range), y	2.8 (0-24.9)	2.0 (0.03-31.9)	1.6 (0.01-6.2)	2.8 (0-31.9)
Median duration ME[c] (range), y	1.0 (0-16.1)	0.5 (0-9.9)	0.6 (0-6.0)	0.7 (0-16.1)
Median Snellen VA[c] (range)	0.5[d] (0.01-1.2)	0.65 (0.1-1.2)	0.6 (0.01-1.2)	0.6 (0.01-1.2)

FA = fluorescein angiography; ME = macular edema; OCT= optical coherence tomography; VA = visual acuity.

[a] Includes birdshot chorioretinopathy, peripheral multifocal chorioretinitis, M. Eales.

[b] This group also includes all patients with pars planitis.

[c] Only the left eye is included, unless the uveitis is unilateral in the right eye.

[d] Not significant (Kruskal-Wallis test).

Table 2. Modified fluorescein angiographic grading system for macular edema

Grade	Characteristics
0	No perifoveal hyperfluorescence.
1	'Faint' perifoveal hyperfluorescence: specific localisation of hyperfluorescence too difficult because of very minimal leakage.
2	Evident perifoveal hyperfluorescence in an area centred on the fovea less than one optic disc diameter.
3	Evident perifoveal hyperfluorescence in an area centred on the fovea between one and one-and-a-half optic disc diameter.
4	Evident perifoveal hyperfluorescence in an area centred on the fovea more than one-and-a-half optic disc diameter.

Results

One-hundred twelve eyes of 78 patients (mean age, 53 years; range, 13-83 years) fulfilled the diagnostic criteria of ME either on FA or on OCT. Our study cohort comprised 21 eyes (19%) with severe ME that was FA leakage group 3 and 4 and 16 eyes (14%) with a CRT of more than 400 µm.

ME present in both imaging examinations (FA+/OCT+ group) was present in 61 (54%) of 112 patients, and discrepancies were documented in 51 (46%) of 112 eyes (Table 3). ME visible solely on FA (FA+/OCT- discrepancy) was noted in 34 (30%) of 112 eyes (34/51, 67% of those with discrepancies) and ME was identified solely on OCT (FA-/OCT+ discrepancy) in 17 (15%) of 112 eyes (19/51; 37% of those with discrepancies). In Figures 1 and 2, 1 illustration is given of each type of discrepancy. The CRT of the FA+ group (FA+/OCT+ and FA+/OCT-) did not differ from the FA- group (269 vs. 274 µm, P = .98). A CSRD was present in 15% of the eyes with ME and was not correlated with 1 of the 3 groups.

Clinical characteristics:

The FA+/OCT+ group and both groups with discrepancies (FA+/OCT- and FA-/OCT+) did not differ in gender, age, duration of uveitis, duration of ME and visual acuity (Table 1). Specifically, a longstanding uveitis (duration >5 years) was not associated with a specific type of discrepancy. The CRT did not differ between the patients with duration of uveitis longer and shorter than 5 years (P = .2). There was a high correlation between a cystoid appearance of the ME on FA and the appearance of cysts on OCT (R = 0.66, P = .000). Cystoid ME on OCT was found more often in the FA+/OCT+ group compared to the FA-/OCT+ group (34/61 eyes vs. 4/17 eyes, P = .03). The FA+/OCT+ group was characterized by the most severe ME with the highest CRT (median, 318 µm;

Table 3. Distribution of eyes with discrepancies to the location of the uveitis, the severity of the macular edema on optical coherence tomography and fluorescein angiography, and the presence or absence of an epiretinal membrane

	FA+/OCT+ (n=61)	FA+/OCT- (n=34)	FA-/OCT+ (n=17)	Total (n=112)
Location				
Anterior	1 (50%)	1 (50%)	0	2 (100%)
Intermediate	6 (37.5%)	4 (25%)	6 (37.5%)[a]	16 (100%)
Posterior	22 (61%)	9 (25%)	5 (14%)	36 (100%)
Pan	32 (55%)	20 (34%)	6 (10%)	58 (100%)
OCT				
Median CRT	318	215[b]	274[c]	270
(range), µm	(188-615)	(187-248)	(160-464)	(160-615)
FA-grade				
0 or 1[d]			17	17
2	43[e]	31		74
3	9	2		11
4	9	1		10
FA				
Median clock hours, n	12[f]	10	0	10
(range)	(1-12)	(1-12)	(0-7)	(0-12)
OCT				
Epiretinal membrane	31[g]	8	5	44
Uveitis				
Active	56[h]	29	9	94
Inactive	5	5	8	18

CRT= central retinal thickness; FA= fluorescein angiogram; OCT, optical coherence tomography.
The grade of leakage, the number of clock hours involved, and the presence of an epiretinal membrane did correlate between the 2 eyes (r = 0.39, *P* = .02, r = 0.31, *P* = .07 and r = 0.55, *P* = .001, respectively). The analyses after including 1 eye per patient resulted in the same conclusions as described above, except tor the milder (grade 2) leakage, which was also significantly more prevalent in the FA+/OCT- group than in the FA+/OCT+ group (25/26 eyes versus 30/43 eyes, *P* = .03).

[a] Relatively more eyes with intermediate uveitis eyes in the FA-/OCT+ group (macular edema solely on OCT) compared to the other uveitis locations (*P* = .016).

[b] Biased by selection criterion of CRT < 249 µm for FA+/OCT- group.

[c] The CRT is significantly lower for FA-/OCT+ group (macular edema solely on OCT) compared with the (nondiscrepant) FA+/OCT+ group (*P* = .007, Mann-Whitney test).

[d] Grade 1 of macular edema was not included in this study (see Methods).

[e] FA+/OCT+ vs FA+/OCT- (*P* = .076).

[f] FA+/OCT+ vs FA+/OCT- (*P* = .01).

[g] Comparing all 3 groups: *P* = .02.

[h] Comparing all 3 groups: *P* = .002.

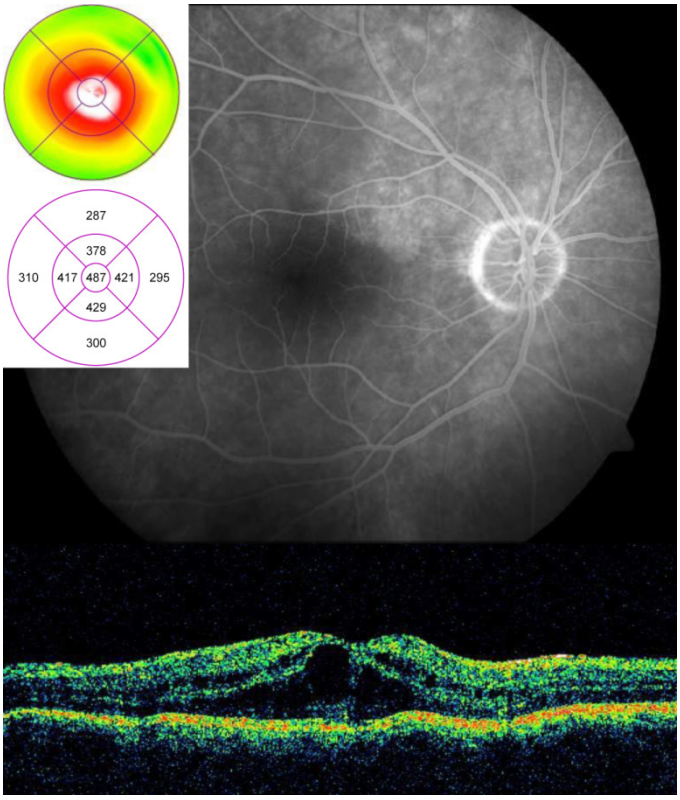

Figure 1. Images from a 13-year-old boy with an intermediate uveitis and a discrepancy between fluorescein angiography and optical coherence tomography. (Top) No fluorescein leakage is visible in the macular area, although on optical coherence tomography the fovea is thickened (Top left, central retinal thickness 487 μm) with (Bottom) large intraretinal cysts. His left eye showed a similar discrepancy.

range 188-615 μm) compared to the FA-/OCT+ group (median, 274 μm; range 160-464 μm), *P* = .007, Table 3) and a higher number of affected clock hours compared to the FA+/OCT- group (median 12 vs. 10, *P* = .01). Moreover, the grades of FA-leakage were higher in the FA+/OCT+ group: 9 (15%) of 61 eyes in the FA+/OCT+ group had grade 4 leakage compared to 1 (3%) of 34 eyes in the FA+/OCT- group (Table 3), however this was not significant (*P* = .09).

The 112 eyes were subdivided according to the activity of the uveitis. The FA+/OCT+ consistency was more frequently observed in active than in inactive uveitis (56/94 versus 5/18, *P* = .019). Moreover, the FA-/OCT+ discrepancy was the largest group in the inactive eyes (8/18 eyes, Table 3) and nearly half the eyes in the FA-/OCT+ group had an inactive uveitis (8/17 eyes).

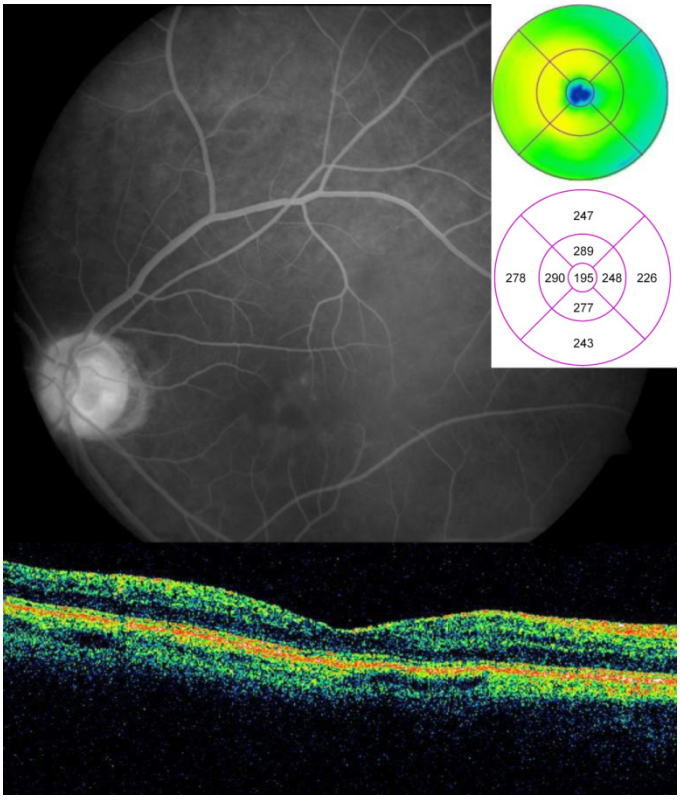

Figure 2. Images from a 49-year-old woman with idiopathic panuveitis and a discrepancy between fluorescein angiography and optical coherence tomography results. (Top) A grade 2 macular leakage is visible on fluorescein angiography, but (Bottom) optical coherence tomography shows a retina of average thickness (Top right, central retinal thickness 195 μm). (Bottom) All 6 radial lines showed the same appearance of the retina without obvious retinal cysts (bottom panel). The leakage is a mild form of grade 2, but is still evident. The optic disc is hyperfluorescent. Her right eye showed a more active uveitis, with obvious cystoid macular edema on fluorescein angiography and optical coherence tomography.

Anatomic classification:

FA+/OCT+ consistency was the most frequent finding for all anatomical entities of uveitis, with the exception of intermediate uveitis. Intermediate uveitis exhibited a FA-/OCT+ discrepancy in 6 (38%) of 16 eyes, in contrast to other anatomical types of uveitis (P = .016; Table 3). The mean age was lower in the group of intermediate uveitis compared with the other groups: 37 vs. 56 years (P = .000).

Cause:

No associations were observed between the specific etiologies of uveitis and FA/OCT discrepancies (Table 1). The FA+/OCT- discrepancy was observed in 7 (50%) of 14 eyes

in patients with birdshot chorioretinopathy (BSCR) compared to 5 (19%) of 27 eyes with sarcoidosis and 22 (30%) of 74 eyes with other diagnoses. Compared with the entire group of eyes with diagnoses other than BSCR, this difference was not statistically significant (P = .09). In addition, the CRT was lower in BSCR patients, compared with the other uveitis groups, but did not reach the level of significance (14 eyes, median, 240 µm; range 187 to 396 µm vs. median, 274 µm; range, 160-615 µm, P = .07).

Additional features on optical coherence tomography:

The presence of an epiretinal membrane on OCT in the 3 groups is shown in Table 3. The ME eyes with associated epiretinal membranes on OCT (n=44) exhibited a higher CRT than the ME eyes without epiretinal membranes (median, 342 vs. 273 µm, P = .000). Surprisingly, the eyes with ME and associated epiretinal membranes had a smaller incidence of the FA/OCT discrepancies than the eyes with ME but without epiretinal membranes (13/44 (30%) vs. 38/68 (56%), P = .007). The frequency of severe (=grade 4) FA leakage was higher in the group with an epiretinal membrane (7/44 vs. 3/65, P = .047). Vitreomacular traction was seen on the OCT in 3.5% (4/112) of all ME eyes, and vitreomacular adhesion was visible in an additional 2.7% (3/112).

Discussion

Discrepant results of FA and OCT in eyes with inflammatory ME were identified in 46% of eyes (51/112) and were present predominantly in mild degrees of ME. The FA+/OCT- discrepancy was the most frequent type of discrepancy and occurred in 50% of patients with BSCR. The FA+/OCT- discrepancy occurred more often in young patients with intermediate uveitis.

The results suggest that the FA+/OCT- group may concern atrophic retinas, in which macular edema remains unnoted if there are no cysts. Because the increased CRT was a selection criterion, we could not test our hypothesis of atrophic retinas with ME and negative OCT results in the present study. The occurrence of retinal cysts on OCT scans in retinas with normal thickness (< 252 µm) recently was reported in eyes with various causes of ME.[18]

The frequency of discrepant results in our study is higher than previously reported. Earlier studies on uveitic macular edema reported an incidence of discrepant results in 11% to 13%[9–11]; however, these studies used other inclusion criteria, different methods for the assessment of ME on FA and OCT (eg, not recording the CRT), their design was not aimed at detecting all FA/OCT discrepancies, or a combination thereof. Moreover, in the study of Antcliff and associates, FA photographs were graded as early as 3 minutes after fluorescein injection and an OCT device with poorer axial resolution (OCT 2000 scanner; Humphrey Instruments, San Leandro, California, USA) was used.[11] In a recent study of Brar and associates, eyes with ME on FA (with various causes) were analyzed

for their findings on spectral-domain (SD) OCT.[4] Four (3.7%) of 107 eyes did not show OCT abnormalities, but in 17 eyes (15.9%), microcysts on SD OCT were found, which likely would have been missed with the Stratus OCT. Their lower percentage of FA+/OCT-discrepancies also may be the result of the bias that the examiners did know that the FA showed ME, and therefore were more prone to detect subtle changes in the OCT scan, which would have been unnoted otherwise. Recently, more studies on the correlation between FA and SD OCT in ME were published, however, with no or a very limited number of uveitis patients[5-8] or only consideration of cystoid changes on OCT and FA.[6]

The occurrence of discrepancies between FA and OCT could be explained by the following hypotheses. First, insufficient resolution of the time-domain OCT apparatus, compared with the SD OCT, may explain the missing of microcysts. The lower prevalences of FA+/OCT- in the studies using the SD OCT confirm this hypothesis. However, in this study, the criterion of an increased retinal thickness is not influenced negatively by using a time-domain OCT instead of an SD OCT. Second, the media opacities frequently present in uveitic patients negatively influence the signal-to-noise ratio and might result in false-negative results.[20] Third, some of the discrepancies may be explained by the arbitrary ceiling value of CRT, which may not represent the clinical significance and could lead to overestimation or underestimation of ME on OCT.

Several hypotheses explaining the occurrence of the true discrepancies were put forward. Patients with retinal atrophy may exhibit FA leakage, whereas the atrophic retina may not exceed the boundary of 249 µm, which could explain FA+/OCT- discrepancy. Our study included many patients with a long duration of uveitis and ME, and it is possible that in these patients, thinning of the retina associated with lower CRT values developed gradually. In these patients, the longstanding vascular leakage still may be present and may clarify the FA+/OCT- discrepancy. This phenomenon is supported by the finding of frequent FA+/OCT- discrepancies in patients with BSCR who also exhibited lower CRT values compared with the other uveitis entities (median, 240 µm; range, 187 to 396 µm vs median, 274 µm; range, 160 to 615 µm; P = .07). The averaging of the central retinal thickness on OCT may be a second cause of a lesser sensitivity for ME in some cases, especially in patients with a slight focal leakage in only a few clock hours.

The FA-/OCT+ discrepancy may be explained by the initial accumulation of fluid in the intracellular spaces or in the subretinal space, leading to retinal thickening but (as yet) no evident leakage.[20–22] In patients with previous uveitis, the leakage across the vascular wall may be absent, whereas (the remainder of) accumulated fluid still may be present. Our results support this hypothesis, because nearly half of the eyes with an inactive uveitis exhibited this discrepancy, in contrast to the active eyes (P = .002). In addition, it was suggested that tractional membranes may lead to ME with minimal or absent fluorescein leakage, however this phenomenon was not observed by us, probably due to the low prevalence in our study.[23]

Inevitably, there are some shortcomings in our study. First, the definition of ME on FA and OCT differ. The diameter of the optic disc for defining grade 2 ME on FA is larger than the area of the central 1 mm of the OCT-scan. Second, the grading of macular leakage on FA is imprecise, but this is the case for all studies. It is not possible to grade the severity of the ME on FA by registration of the pixels gray value, because this value is dependent on several confounding factors (media opacities, pigmentation level of the macula etc.) and moreover, not linearly related to the concentration of fluorescein, due to quenching. Instead, we chose to use the diameter of the ME-area (as other investigators) and the number of clock hours as 2 ways to grade the severity of the ME. In addition, our study includes uveitic ME in different stages of disease activity. Future studies of FA and OCT in patients with sufficient numbers of patients in diverse stadia or types of ME might reveal the additional characteristics of FA/OCT discrepancies and help to clarify the pathogenesis of ME in uveitis.

In conclusion, we report on discrepant FA and OCT findings in 46% of uveitic eyes, predominantly occurring in eyes with mild ME. While the FA+/OCT- discrepancy was predominantly present in eyes with BSCR, the FA-/OCT+ discrepancy was associated with an intermediate location of uveitis. While the FA+/OCT+ consistency was frequently noted in an active uveitis, the FA-/OCT+ discrepancy was common in eyes with an inactive uveitis. Our results show that FA and OCT are complementary investigations, each revealing different aspects of the pathophysiology of uveitic ME and this might influence the therapeutic decisions.

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Reply to: Discrepancies between fluorescein angiography and optical coherence tomography in macular edema in uveitis

Jeannette Ossewaarde-van Norel
Aniki Rothova

American Journal of Ophthalmology 2013;155(3):609-10.

CORRESPONDENCE

Evaluation of Discrepancies Between Fluorescein Angiography and Optical Coherence Tomography in Macular Edema in Uveitis

EDITOR:

THIS LETTER REFERS TO THE ARTICLE "DISCREPANCIES between Fluorescein Angiography and Optical Coherence Tomography in Macular Edema in Uveitis," by Ossewaarde-van Norel and associates.[1] The authors analyzed the time-domain optical coherence tomography (TD OCT) and fluorescein angiography (FA) scans of 112 eyes with active or inactive uveitis for the presence of macular edema and observed discrepancies between the findings of the 2 investigational tools in nearly 46% of eyes. We congratulate the authors for the concept of the study, but have a few comments to make.

First, the authors did not mention the TD OCT scanning protocol that was used for image capturing and analysis. Using TD OCT, 6 radial line scan images can be acquired using 2 protocols: the fast macular thickness protocol in which 128 A-scans for 1 line scan are obtained and the macular thickness protocol in which 512 A-scans for 1 line scan are acquired. The fast macular thickness protocol decreases the chances of motion blur, but compromises on image resolution. If the fast macular thickness protocol was the sole protocol used for image acquisition and analysis, it may have led to an increase in false-negative results (higher chances of cysts being missed) and would be a serious limitation of the study.

Second, we also believe that a high proportion of FA-positive and TD OCT-negative reporting could be the result of missing cysts in the perifoveal area. The 6 radial line scan protocol has a propensity of missing perifoveal pathologic features, which are present in the intervening area between the 2 line scans.

Third, the authors' statement regarding their inability to test their hypothesis of atrophic retinas with macular edema and negative TD OCT results because of increased central retinal thickness being a selection criterion may not be entirely true, because it was not the only selection criterion and in all the patient subgroups (FA positive/TDOCTpositive, FA positive/TDOCT negative, FA negative/TD OCT positive), the lower range of thickness was less than 249 μm (the defining thickness for macular edema in this study).

Fourth, the clinical application of the study would be more relevant if the pattern of discrepancies in eyes with an initial episode of intraocular inflammation, a recurrent episode of uveitis, and inactive uveitis were described separately.

In a study at our center, we compared the FA and spectral-domain (SD) OCT image findings in patients with active intermediate uveitis with macular edema (unpublished). We observed discrepancies in 4 (7%) of 56 cases. In 1 eye (1.7%), there was presence of fluoroscein leakage without cystoid macular edema on SD OCT, and in 3 eyes (5.1%), the SD OCT showed cysts without fluoroscein leakage. A low proportion of discrepancy in our series can be attributed to the study population, comprising mainly patients with a primary attack of intermediate uveitis and early presentation. The other reason is the use of SD OCT, which detects intraretinal cysts better and is able to acquire better images in hazy media compared with TD OCT.[2,3] The absence of leakage with presence of cysts in our patients can be ascribed to treatment response with corticosteroids with a residual anatomic defect.

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ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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Reply

WE THANK KHANDUJA AND ASSOCIATES FOR THEIR interest in our work and their thoughtful comments.[1] Our time-domain optical coherence tomography (TD OCT) study was performed using the radial lines protocol, in which 512 pixels per line were obtained. In addition to these 6 radial lines, a fast macular thickness protocol was performed, resulting in a map with the values of the retinal thickness in the central 1-, 3-,

and 6-mm area. Because of the nature of the irradiating 6 radial lines, the further from the foveal center, the higher the chance of missing small retinal cysts. In spectral-domain OCT machines, scanning protocols of vertical and horizontal lines can be chosen, but in clinical practice, there is always a compromise in choosing the scan width and a chance of missing abnormalities. It is possible theoretically that some of our discrepancies were caused by missing small isolated retinal cysts in between the scanning lines in a retina of normal thickness. However, it is more probable that the FA-positive/OCT-negative discrepancies were caused by true differences in combination with the limited resolution of the TD OCT scan, although the highest resolution (512 pixels/line) was used.

In their comment, Khanduja and associates suggest that atrophic retinas with macular edema (ME) could be discovered on OCT by the presence of cysts. However, diffuse macular edema manifests without cysts.[2,3] Purely relying on the presence of retinal cysts can be misleading. Retinal thickening in an already atrophic retina resulting from long-standing edema or inflammation then may remain unnoticed. Longitudinal measurements of the changes in the retinal thickness are needed to note an excess of fluid present in an atrophic retina and to make the diagnosis of ME.

The suggestion to compare the patients with a first attack, a recurrent attack, and inactive uveitis is valuable. Our study was based mainly on patients with chronic macular edema and including the patients with macular edema in its very early phase may reveal different percentages of discrepancies compared with our results. However, we assessed our population for the duration of the uveitis and ME, and we did make the difference between active versus inactive uveitis and found that the duration of the ME and the activity of uveitis did not differ between the FA-positive/OCT-negative group and the FA-positive/OCT-positive group.

We agree that, in addition to the higher-resolution OCT, the differences in the composition of the study group of Khanduja and associates and our study groups might have contributed to the differences in the prevalence of the discrepancies between FA and OCT imaging.

In conclusion, we point out that discrepancies between the FA and OCT findings occur because these 2 investigations reveal different ME characteristics, specifically morphologic and functional features. The ophthalmologists caring for the patients with ME should be aware of possible pitfalls using only 1 of these imaging methods.

CONFLICT OF INTEREST DISCLOSURES: SEE THE ORIGINAL article[1] for any disclosures of the authors.

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CHAPTER 5

Clinical review: Update on treatment of inflammatory macular edema

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Ocular Immunology and Inflammation 2011;19(1):75-83

Abstract

The aim of this review is to summarize the recent developments in the treatment of inflammatory macular edema (ME). Inflammatory ME represents a major cause of visual loss in uveitis and its adequate management is crucial for the maintenance of useful vision in patients with uveitis. Recent studies favor early treatment of inflammatory ME, even in patients with full visual acuity. After recapitulating the standard treatment modalities for inflammatory ME the authors address the novel corticosteroid implants. They review the literature on the efficacy of anti-VEGF agents for inflammatory ME and point out their beneficial, but transient effects. Further, they present recent data on the value of systemic biologics in uveitic ME and evaluate the effectiveness of vitrectomy. Finally, they propose an algorithm for the treatment of inflammatory ME and point out that the individual risk-benefit ratio, especially with systemic immunosuppressive therapy, should always be considered.

Introduction

Inflammatory macular edema (ME) is the accumulation of fluid within the central area of the retina as a consequence of the breakdown of the inner and/ or outer blood-retina barrier due to severe or prolonged intraocular inflammation. The pathogenesis of inflammatory ME is not yet entirely clear. The predominant theory is that the inflammation incites a release and/or diffusion of inflammatory mediators which damage the function of retinal cells, vessels and retinal pigment epithelium (RPE), resulting in leakage of fluid into the retina and its accumulation in the macular area with a characteristic distribution of fluid usually located in the outer plexiform layer. Additional factors that may be important in the pathogenesis include mechanical forces, age, duration of inflammation and smoking.[1-3] The principal manifestations of inflammatory ME include distortion of vision and visual loss. The extent of visual loss is influenced primarily by the location, severity and duration of ME. Cysts and macular (pseudo)hole may result from the distortion of anatomical relations within the retinal tissue. The early stages of ME might be treated more easily than the chronic forms, which may have caused permanent structural anomalies and retinal atrophy. Even if treatment reduces ME without obtaining a visual improvement, the treatment is worthwhile, because a nonedematous macula has a better prognosis for maintaining the visual acuity.[4]

Previous studies documented various prognosticators of poor visual outcome in uveitic ME including a prolonged duration of the uveitis and of CME itself, a large foveal avascular zone, the presence of an incomplete vitreous detachment, and an increased macular thickness on optical coherence tomography (OCT).[4-6] The advanced age of patients was reported to form an independent factor for the early development and poor outcome of CME in uveitis.[1,4]

So far, there are no consistent guidelines for the treatment of inflammatory ME; especially there is no agreement on treatment of subclinical ME forms without a decrease in visual acuity (VA). It was recommended to treat any form of ME until its disappearance.[6] Treatment of inflammatory ME should principally include the treatment of the underlying disease, symptomatic medical management and sometimes surgical interventions as well as lifestyle alterations (e.g., smoking cessation for patients with uveitis).[6,7] The appropriate choice of treatment is usually based on clinical and imaging assessment, including the evaluation of OCT images for the presence of epiretinal membranes. The medical treatment possibilities include the administration of various anti-inflammatory drugs and carbonic anhydrase inhibitors. Recently, the usage of anti-vascular endothelial growth factor (VEGF) drugs and somatostatin analogues has been suggested. The surgical options are aimed at the release of traction and removal of possible toxic mediators present in the vitreous. The definite choice for local and/ or systemic treatment modalities is influenced by the severity of inflammation and ME as well as uni- or bilaterality of the underlying disease and ME. Anti-inflammatory

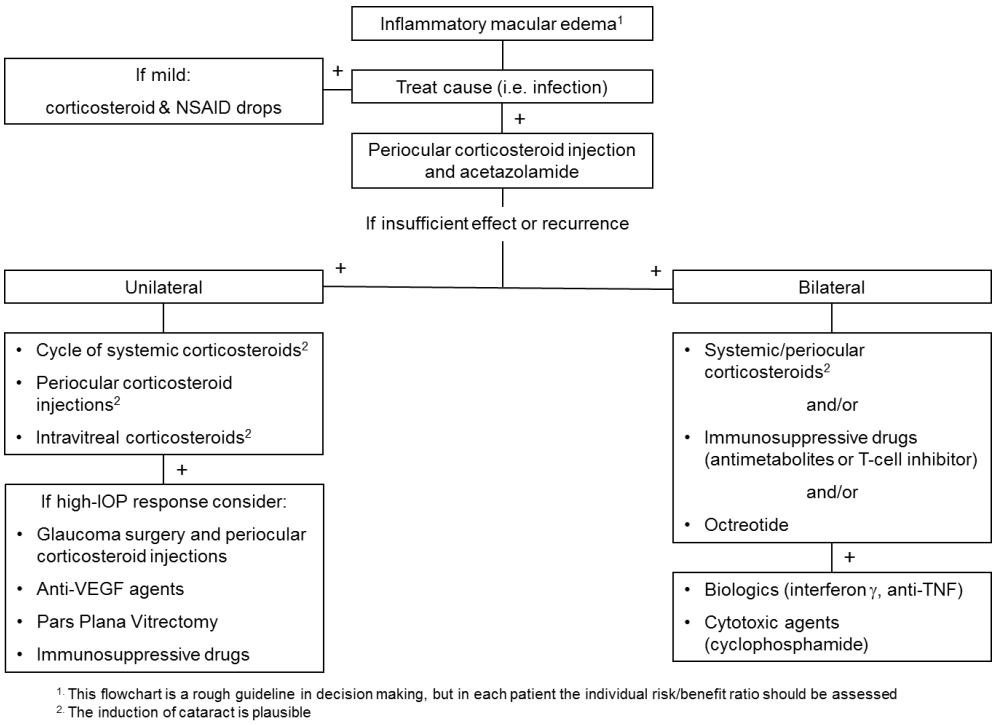
treatment is imperative in patients with ME who still have active inflammation. With ongoing inflammation, the effect of symptomatic treatment on ME is temporary and recurrence of ME might be expected. In this review we further address the current knowledge on treatment of macular edema in patients with uveitis and do not include other ME etiologies.

Evaluation of treatment outcomes for inflammatory ME

In patients with ME, the efficacy of treatment has most often been measured by assessment of visual acuity (VA), OCT and/ or fluorescein angiography (FA) imaging. Several factors complicate the evaluation of the effect of ME treatment of patients with uveitis in trials: the presence of active inflammation, which might widely vary among the included patients, and the optimal visual acuity that can be achieved (included are usually chronic or resistant cases with limited visual gain). In addition, ME is a time-dependent phenomenon and its overall prognosis is linked to the exact cause of inflammation. For example, ME in uveitis of limited duration (e.g. toxoplasma, acute anterior uveitis) will disappear in most cases when the disease activity subsides. In contrast, ME in chronic uveitis entities (birdshot chorioretinopathy) might become chronic and persist even in cases with low-grade inflammatory activity. The severity of ME on fluorescein angiography has been classified by several staging systems.[8-11] However, the practical use of a classification scheme is limited, as there is no correlation between the stage of ME and the visual prognosis with treatment. So far, there is no widely used classification for ME on OCT. Usually, measurement of central retinal thickness is used together with the indication of the characteristic pattern of ME seen on OCT (diffuse ME, cystoid ME, subfoveal retinal detachment, epiretinal membrane, vitreomacular traction). In diabetic ME, it has been shown that distorted vision was associated with the thickening of the inner nuclear layer.[12]

Medical treatment

Most anti-inflammatory drugs have a beneficial effect on ME by reducing inflammation, which is the primary cause of the ME. In recent years, new immunosuppressive drugs have become available and novel drug delivery systems have been developed, but so far, significant progress in the treatment of inflammatory CME has not been made.[13] Local treatment modalities are preferred as the initial strategy- possibly, in combination with low-dose acetazolamide administration. In unilateral ME, the possibility of a surgical approach should be considered before long-term treatment with immunosuppressive drugs is chosen. The adverse effects of long-term treatment with systemic immunosuppressive drugs might be substantial and therefore not preferred by patients with a unilateral disease. Based on the available data, we propose an algorithm for the treatment regimens of inflammatory ME (Figure).



[1] This flowchart is a rough guideline in decision making, but in each patient the individual risk/benefit ratio should be assessed
[2] The induction of cataract is plausible

Figure. An algorithm for the treatment regiments of inflammatory ME.

Nonsteroidal anti-inflammatory drugs

Although NSAIDs are regularly prescribed for inflammatory ME, their effect is often disappointing.[14] Recently, intravitreal diclofenac (500 µg/0.1 mL) has been administered in 10 patients with ME of various etiologies, including 1 patient with uveitis. While VA showed some improvement, unfortunately no effect was seen on the central macular thickness measured by OCT. Electroretinogram abnormalities or other toxic effects of intravitreal diclofenac were not observed.[15]

Corticosteroids

Corticosteroids are widely used immunosuppressive drugs that inhibit the expression of proinflammatory proteins and restore the function of the blood/retina barrier. Unfortunately, multiple systemic and ocular side effects limit their long-term administration. Therefore, corticosteroids are recommended for their quick effect in the initial phase of treatment and should be subsequently replaced by steroid-sparing agents. Long-term administration of corticosteroids was associated with more frequent and more numerous side effects.[16,17] Types of local steroid administration include drops, periocular and intraocular injections, and intraocular long-term working devices. The

administration of drops has probably mild effect (if any) on ME and is predominantly used in active anterior uveitis.

Periocular corticosteroid injections

Posterior subtenon injections were reported to have a beneficial, though temporary effect on ME. Different methods of periocular administration of corticosteroids (subtenon injection, subtenon cannula and orbital floor injections) were compared in a small study of 30 patients and their effect on ME did not differ.[18] Single subtenon injections had limited influence on IOP increase and cataract development, but with repeated applications these side effects increased.[19]

Intravitreal triamcinolone application (IVTA)

In the last decade, IVTA in variable dosages (usually ranging from 2 to 20 mg) has been widely used for various types of ME. Many publications on IVTA efficacy and its adverse effects have emerged.[20] Intraocular application of triamcinolone showed better response than the periocular triamcinolone injections on inflammatory ME but had also more side effects.[20] It became clear that IVTA has an excellent effect in the majority of ME cases, however this effect is transient and the injections are associated with frequent and potentially severe adverse effects. The rate of posterior subcapsular cataract formation is high, especially in the elderly population and in those requiring repeated injections. The rise in intraocular pressure (IOP) occurred in 20-60% of injected eyes and was more common in young patients with uveitis than in elderly patients with noninflammatory ME and increased with multiple injections.[21-24] A study comparing the effects of subtenon TA to IVTA in ME of various causes showed that there was a significant difference in the frequency of high IOP response (>30 mmHg) and in the need of antiglaucoma medications. Risk factors for IOP elevation included higher baseline IOP, young age, and presence of uveitis.[25] It was recommended to perform a provocation test with topical dexamethasone to assess the risk of IOP rise after IVTA.[26] Noteworthy is also the immediate IOP peak following the injection. Although elevation of IOP may last only for a few minutes, it still may cause damage to fragile retinal structures. Routine paracentesis before intraocular injections has, however, not been recommended.[27] Risk of endophthalmitis is usually indicated between 0.05% and 0.1%, and might be higher in the uveitis population.[28-30] The significant risk profile of IVTA has motivated the application of lesser dosages and it seems that as little as 1 mg IVTA might be effective and has fewer adverse effects.[31] However, the duration of clinical effects of IVTA is dose dependent.[32]

Corticosteroid implants

Sustained corticosteroid-release implants have been developed as new treatment potentials for noninfectious uveitis and associated ME. Essentially, two types of implants

are being explored: nonbiodegradable implants (e.g. fluocinolone acetonide intravitreal implant), which have to be replaced when their efficacy is expired, and biodegradable formulations (e.g. dexamethasone intravitreal implant). An intraocular sustained-release implant containing fluocinolone acetonide has been approved for use in noninfectious uveitis affecting the posterior segment and is currently being evaluated in clinical trials. A large multicenter trial consisting of 255 patients compared fluocinolone acetonide implants to systemic therapy for noninfectious uveitis.[34] So far, this study demonstrated that fluocinolone implants significantly reduced uveitis recurrences and improved or stabilized VA.[34-36] However, most treated eyes required cataract extraction and 40% required intraocular pressure-lowering therapy followed by glaucoma surgery associated with a high rate of hypotony.[36,37] The fluocinolone implant was able to control ocular inflammation for an average of three years after initial insertion. Placement of a new implant maintained the affected eyes in a quiet state.[38] Adverse events during insertion of a new implant were exceptional, but 3 patients with implant exchange suffered a dissociation of the medication reservoir from its attachment.[39]

The dexamethasone drug delivery system (DDS) is composed of a biodegradable copolymer of lactic acid and glycolic acid. As dexamethasone is released, the polymer slowly degrades into carbon dioxide and water.[40] Since the implant dissolves completely, sequential implants can be placed into the eye over time without a need for surgical removal. Animal studies showed that the implants were well tolerated, the release of dexamethasone was gradual, and biodegradation slow.[40] In 306 patients with persistent ME of diverse origins, a 3-month follow-up study showed a good response in VA and in fluorescein leakage.[41] The visual results were better in 700-µg than in 350-µg dexamethasone implants. Adverse effects were uncommon during the 3 months of follow-up. However, 11% of treated eyes exhibited an IOP increase of more than 10 mm Hg. Also, in a subgroup of 41 patients with persistent ME secondary to uveitis or Irvine-Gass syndrome, 350- and 700-µg dexamethasone DDS implants produced improvement in VA and fluorescein leakage, but IOP elevation occurred in 5/13 patients with 700-µg and 1/12 patients with 350-µg dexamethasone DDS implants.[42] The development of biodegradable implants with ME-modifying drugs might become a preferred treatment for uveitic ME in the future.[43,44] The realization of high intraocular levels of anti-inflammatory drugs and avoidance of systemic adverse effects are the major attractive characteristics of intraocular implants. However, atrophy of ocular structures after (repeated) steroid administration as well as diverse intraocular infections might be a hazard of this treatment approach.[45]

Systemic corticosteroids

Systemic corticosteroids are typically used for the treatment of bilateral inflammatory ME and for ME resistant to topical treatment. It is recommended to commence the treatment with high doses to achieve an anatomical recovery of the macula and prolong

their use until the optimal visual acuity is achieved. Steroid-sparing medications are started and the corticosteroids are tapered off slowly. An OCT study documented a more rapid decrease of ME with oral administration than with periocular steroid injections, so an initial treatment with oral steroids might be preferred or added to other treatment modalities if rapid recovery is essential.[5] Long term use of systemic steroids has been abandoned because of their side effects.[16,17,46]

Acetazolamide and somatostatin analogues

The classical study from 1988 has pointed out a beneficial effect of acetazolamide on inflammatory ME in about one-third of patients with uveitis.[47] The potential role of topical forms of carbonic anhydrase inhibitors on CME in retinitis pigmentosa has been claimed, but has not yet been investigated in uveitis.[48] Somatostatin has a positive effect on the apical-basal direction-oriented fluid transport in the retinal pigment epithelium. Octreotide is a somatostatin analogue and has been reported to be effective in chronic ME in uveitis 70% of 20 eyes.[49]

Anti-vascular endothelial growth factor (anti-VEGF) treatment

Because VEGF increases vascular permeability, intravitreal application of anti-VEGF drugs has been suggested as a powerful option for treatment of ME of different origins. Moreover, VEGF has multiple proinflammatory effects, including a positive effect on chemotaxis and migration of monocytes and the induction of B- and T-lymphocytes.[50-52] VEGF antagonists therefore also possess an anti-inflammatory potential. In experimental autoimmune uveitis (EAU), the expression of VEGF in the retina was markedly increased.[53] However, the involvement of VEGF in the pathogenesis of inflammatory ME is not yet clear and data on intraocular VEGF levels in inflammatory ME are contradictory.[54-56]

The effect of anti-VEGF treatment of inflammatory ME has not yet been systematically investigated. Supporting data on its efficacy in inflammatory ME are derived from clinical experience based on a small number of patients. In most cases, bevacizumab was injected into the eyes with persistent ME and inactive uveitis. Three reports, together comprising 51 eyes, showed a significant reduction of the central retinal thickness, which was transient in most of the patients.[54,57,58] The percentage of eyes that had an increase in visual acuity of at least two lines 4-12 weeks after one injection was reported as 38%-64%.[54,58,59] Due to a temporary effect, repeated injections were regularly required. One-year follow-up of 29 eyes with ME has shown that the visual acuity improved significantly and the mean retinal thickness decreased.[57] Weiss et al. reported that patients with inflammatory ME responded well to bevacizumab treatment, unless an extensive leakage from the choroid or a leakage of the optic disk was detectable on FA. In these patients, only intravitreally administered triamcinolone led to a reduction of ME.[54] One additional

study included 11 eyes with active uveitis treated with bevacuzimab. In these patients, neither central retinal thickness nor visual acuity changed significantly over the course of the follow-up (median 13 months, range 1-20).[60] However, the authors concluded that bevacizumab played a role in the stabilization of the visual acuity. In a study of Behçet patients treated with bevacizumab, the visual acuity significantly improved in 7/12 eyes and remained unchanged in 5/12 eyes, but no significant improvements were noted on OCT and FA.[61] Ranibizumab was used in 6 patients with inflammatory ME and a beneficial effect on retinal thickness and visual acuity after 6 months was documented.[62] Due to the transient effect of anti-VEGF intraocular injections, this treatment modality is not suitable for ME in active chronic uveitis, but might be valuable in patients with a uveitis in remission and persistent ME.

Neither ranibizumab nor bevacizumab has been evaluated for safety in the setting of uveitis, although both of these agents seem to be well tolerated in various ocular diseases.[63] Recently, a debate restarted on an increased risk of cerebrovascular events after intraocular anti-VEGF injections in AMD patients.[64,65] In addition to the risk of endophthalmitis, local risks include development of uveitis after ranibizumab of bevacizumab injections. Ranibizumab is associated with subsequent development of uveitis in 0.7 to 1.79%[66,67,69] of the injections and bevacizumab in 0.14 to 1.96%.[68,69] Although the bevacizumab molecule (being a full-length antibody) is theoretically more immunogenic than the ranibizumab molecule (being only an antibody fragment), no difference was found in the risk of uveitis after bevacizumab injections vs. ranibizumab injections.[71] The pathogenesis of this type of uveitis is not understood, but possible explanations include contamination of the medications with bacterial endotoxin, formation of antibodies against the immunogenic anti-VEGF molecules, and leaching of contaminants of disposable syringes into its contents. None of the studies on the use of anti-VEGF injections in uveitic patients reported a recurrence or an exacerbation of inflammation. However, Okada reported on a uveitic patient who refused systemic immunosuppressive therapy and experienced an anterior uveitis twice after bevacizumab injections.[70] Whether patients with uveitis have an increased risk on developing uveitis after anti-VEGF injections remains to be investigated.

Immunomodulatory drugs, including interferons and anti-tumor necrosis factor-α

In the long term treatment of macular edema, corticosteroid-sparing agents are preferred to avoid the side effects of corticosteroids. The antimetabolites methotrexate, azathioprine, mycophenolate mofetil and T-cell inhibitors like cyclosporine act primarily as an anti-inflammatory and are therefore beneficial for ME. In general, studies report on the efficacy of medications to achieve a remission of the uveitis. One study focussed on ME in 19 uveitic patients who were unresponsive to traditional immunosuppressants and who were treated with mycophenolate mofetil.[71] Mycophenolate mofetil proved

to be safe and very effective in controlling ME and in reducing the uveitis relapse rate. Intravitreal methotrexate was given in 15 eyes to treat ME with a promising effect.[72]
When the uveitis and/or the macular edema is unresponsive to these drugs, biologics can be used. Interferons (IFN) influence both innate and adaptive immune responses[73] and play a role in the defense against viral infections and tumor growth. In autoimmune diseases, IFNs appear as double agents, involved in both supportive and suppressive action. IFNs have been successful in the treatment of multiple sclerosis and Behçet disease. Mackensen reported on a beneficial effect of IFN-β1a in 7/13 eyes in patients with multiple sclerosis-associated intermediate uveitis complicated by ME.[73] Interferon-α has also been shown to be effective in treating inflammatory ME resistant to standard treatment.[74-76] In a recent study, IFN-α-2a was effective in 15 out of 24 patients and partially effective in 6/24 patients with chronic inflammatory ME.[77] The response to therapy was very quick; in the majority of patients an almost complete ME resolution occurred within 2 weeks. The initial dose of 3 or 6 million IU per day subcutaneously was tapered to the lowest possible dose to maintain the absence of ME. Side effects occurred frequently, including flu-like symptoms, fatigue, and increased liver enzymes and were dose-dependent. Another serious side effect of IFN-treatment is depression and this occurred in one patient. The authors suggested that the mode of action of IFNs might be enhancement of the barrier function of the vascular endothelium.
Tumor necrosis factor (TNF)-α is a key proinflammatory cytokine and high intraocular levels were found in experimental autoimmune and human uveitis.[78-80] Biological agents including anti-TNF-α are attractive treatment options because they offer a more targeted suppression of immune effector responses.[81] In contrast to other medical disciplines such as reumatology, uveitis literature consists mainly of uncontrolled trials or case series. Three anti-TNF-α agents are currently available: etanercept, infliximab and adalimumab. Etanercept is not being recommended for the use in patients with uveitis, and the development of uveitis was even considered to be one of its side effects. The use of biologicals for the treatment of ME included a small series of 10 patients treated with infliximab.[82] A complete regression of ME (assessed by OCT) was observed in 8/14 eyes of 10 patients within 2 months. Diaz-Llopis et al. reported on the use of adalimumab in uveitis and noticed a complete resolution of ME in 18/33 eyes with an active uveitis and ME.[83] The safety of biologicals, especially in long-term use, is an important issue. Various infections, development of auto-immune and demyelinating diseases, occurrence of malignancies and congestive heart failure were all reported. Due to its mouse protein content, an acute allergic reaction may occur (approximately 5% of the intravenous infusions with infliximab), but most patients can be treated adequately. Adalimumab is a fully humanized antibody that is administrated subcutaneously and the risk of allergic reaction is much lower.

Surgery

The possible efficacy of pars plana vitrectomy (PPV) in inflammatory ME has been studied for many years,[84] but randomized trials are lacking, except for one: a beneficial effect on visual function and angiographic findings is reported in a randomised controlled pilot study compared to a slighter effect of systemic treatment with steroids and immunosuppressants.[85] Theoretically, the value of PPV for inflammatory ME might be even better than in ME of other origins since many inflammatory mediators accumulate in the vitreous and a removal of these mediators may have a good effect on ME; in addition, an enhanced fibrosis of the vitreoretinal interface occurs often and may result in the formation of epiretinal membranes and subsequent macular edema. The presence of an epiretinal membrane has been proven to be a significant factor associated with medical treatment failure[86] and a removal of this membrane can help to reduce ME. Gutfleisch et al. performed a PPV with ILM peeling and injection of 4 mg triamcinolone in 19 patients with refractory ME and found in 44% of the eyes a decrease of ME on FA, but in 22% of all eyes a worsening of the visual acuity.[87] Schaal et al. reported a positive effect of a surgical posterior vitreous detachment on retinal thickness and visual acuity.[88] The authors indicated that even the presence of a Weiss ring does not insure the absence of adherent vitreous to the macula. Also, in pediatric uveitis, PPV might improve ME and lead to decrease of systemic immunosuppressive therapies.[89]

Conclusions

Despite expanding knowledge on the pathophysiology of inflammatory ME and the ability to accurately diagnose and monitor ME, its treatment remains challenging. Recent studies favor an early and aggressive approach to uveitic ME, even in patients with full visual acuity. First priority in treatment of inflammatory ME is to diminish the inflammatory activity. Since the permanent structural changes and subsequent macular atrophy regularly develop in patients with long-standing ME, it is essential to evaluate and treat ME until its disappearance. The therapeutical approach to inflammatory ME differs according to its locality: in unilateral ME, local treatment modalities are preferred, while the use of systemic immunomodulatory drugs might be necessary to achieve remission of inflammation in bilateral cases. Therapeutical trial with acetazolamide or octreotide might bring improvement in patients with show insufficient response to anti-inflammatory treatments. Anti-VEGF therapy seems to give favorable, but transient results. Because of its relative safety, it deserves a role in the treatment of inflammatory ME; however its exact place in the treatment strategy for inflammatory ME is not yet well defined. PPV shows a promising potential for those with a pathologic vitreoretinal interface and needs to be further investigated in clinical trials. In addition, in unilateral ME, the possibility of PPV should be considered before long-term treatment with

immunosuppressive drugs is initiated. Growing experience with interferons shows promising beneficial effects, but adverse effects regularly occur. Although elimination of ME is crucial for maintenance of visual acuity in patients with uveitis, the individual risk-benefit ratio, especially with systemic forms of immunosuppressive therapy, should always be considered. The development of new systemic biologicals and the development of intraocular biodegradable implants will expand our treatment repertoire for ME in the future.

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CHAPTER 6

Peripheral multifocal chorioretinitis: complications, prognosis and relation with sarcoidosis

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Abstract

Purpose: To investigate the prognosis and complications in patients with peripheral multifocal chorioretinitis (PMC). PMC is a posterior or panuveitis characterized by chronic bilateral vitritis and punched-out lesions in the peripheral retina which occurs commonly in elderly white women and is associated with sarcoidosis. Prognosis and complications are largely unknown.

Methods: A structured literature search in PubMed, Embase and Cochrane was performed to identify relevant articles. Articles were screened, and the remaining articles were critically appraised based on relevance and validity.

Results: The search yielded 267 articles. Eight relevant articles were retrieved.

All studies reported on moderate visual impairment. Macular oedema occurred in 60% of the patients with PMC (range, 0–71%), glaucoma in 27% (range, 25–43%) and an epiretinal membrane in 21% (range, 0–28%). In total, 47% had proven or presumed sarcoidosis. Treatment usually comprised topical corticosteroids, periocular steroid injections and systemic corticosteroids regularly in combination with methotrexate.

Conclusion: The prognosis of patients with PMC is characterized by a rather poor visual outcome and the relatively high prevalence of complications. PMC is strongly associated with sarcoidosis. Solid proof for the treatment efficacy of PMC is lacking.

Introduction

Peripheral multifocal chorioretinitis (PMC) is a clinical entity of chronic posterior or panuveitis characterized by multiple, small, round, punched-out lesions in the peripheral retina diagnosed predominantly in elderly women. PMC manifests commonly as a bilateral disorder and is regularly associated with sarcoidosis.

The entity of multifocal choroiditis was originally reported by Nozik and Dorsch in 1973 (Nozik & Dorsch 1973). Later, the clinical entity *multifocal choroiditis and panuveitis* (MCP) was introduced. In addition to this type, two distinct entities were distinguished (Dreyer & Gass 1984). The first group consisted of young myopic women with multiple round retinal lesions at the posterior pole and macular choroidal neovascularisation (Watzke & Claussen 1981; Dreyer & Gass 1984; Cantrill & Folk 1986; Spaide et al. 1990, 1991a,b, 2002; Parodi et al. 2006). These patients present commonly with sudden unilateral visual loss owing to subretinal neovascularisation in the macular area. The second entity comprises usually older women with a chronic, bilateral form of multifocal choroiditis characterized by an intraocular inflammation in combination with multiple punched-out lesions localized in the peripheral retina. In contrast to the first entity, the central retinal lesions are absent and there is no association with myopia. The gradual visual loss is often attributed to cystoid macular edema (CME) and not to a macular subretinal neovascularisation. This report will focus on the latter group with peripheral multiple chorioretinal lesions (PMC).

PMC is commonly treated with various administrations of corticosteroids, which is not attractive within the older group of patients. To make evidencebased considerations on treatment regimens in this uveitis entity, we performed a literature review of PMC focussing on the visual prognosis, treatment regimens and their complications.

Material

Search strategy and selection

A literature search performed on 6 July 2011 applied a search filter with synonyms for *peripheral multifocal chorioretinitis* and *visual prognosis* (Table 1). Title and abstract were screened for the inclusion criteria (Fig. 1). For this review, the criteria according to Lardenoye et al. were used (Table 2) (Lardenoye et al. 1997). Briefly, patients with PMC had to fulfil all of the following three criteria: (1) the presence of multiple (>10), small, round, punched-out lesions in the peripheral retina, (2) the absence of central chorioretinal lesions and (3) the presence of intraocular inflammatory reaction.

In total, 267 articles were retrieved (Fig. 1), of which eight studies were considered useful after full text screening. The search yielded several articles about ocular sarcoidosis containing a subanalysis of patients with both PMC and sarcoidosis.

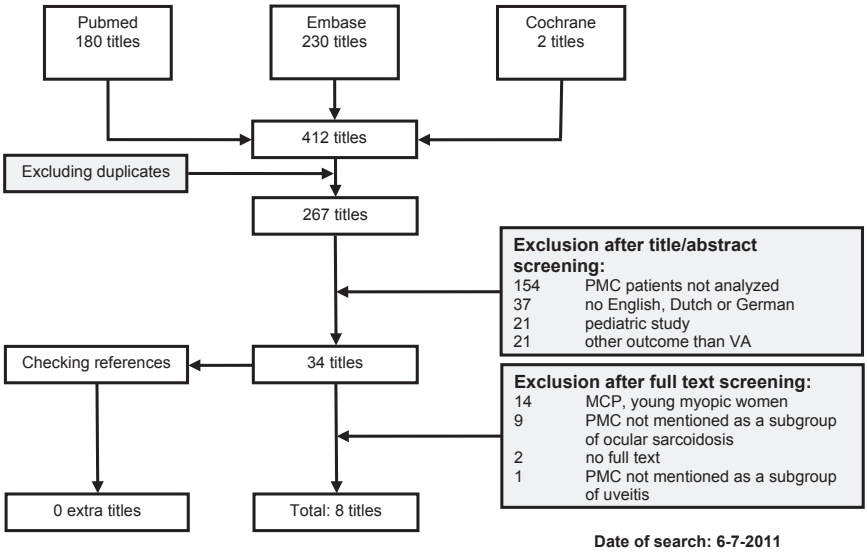

Fig. 1. Flow chart of the literature search strategy.

Critical appraisal

The selected articles were appraised by two authors. Validity was scored on design, missing data, standardized outcome, masking for clinical characteristics and number of patients included in a study. We extracted data on demographic characteristics of patients, visual acuity (VA), ocular manifestations and complications. For all calculations with VA data, we converted Snellen VA to the logarithm of the minimum angle of resolution (log-MAR), but for easier understanding, the logMAR results were converted back to Snellen VA. The total mean VA for the worse and the better eye and the total mean of separate complications were weighted for the size of the study population. Definitive diagnosis of sarcoidosis was biopsyproven disease; however, the employed tests and criteria for presumed sarcoidosis differed in various included studies. All results were summarized per study in Table 2.

Results

All eight included studies were retrospectively designed (Nölle & Eckardt 1993; Lardenoye et al. 1997; Nölle et al. 1998; Thorne & Brucker 2000; Lobo et al. 2003; Abad et al. 2004; Khalatbari et al. 2004; Lee et al. 2009). The PMC criteria applied fully for three included studies (Table 2) (Lardenoye et al. 1997; Thorne & Brucker 2000; Abad et al. 2004). Additionally, five studies were also incorporated although the absence of central chorioretinal lesions was not clearly described (Nölle & Eckardt 1993; Nölle et al. 1998; Lobo et al. 2003; Khalatbari et al. 2004; Lee et al. 2009).

Table 1. The syntax used for the literature search.

Database	Syntax
PubMed	Peripheral multifocal chorioretinitis OR multifocal chorioretinitis OR multifocal choroiditis OR PMC OR [(sarcoidosis OR Besnier Boeck) AND (uveitis OR ocular OR ophthalmic OR opthalmic)] AND Visual prognosis OR visual acuity OR cystoid macular edema OR cystoid macular oedema OR CME OR glaucoma
Embase	Syntax used in PubMed with Embase characteristics
Cochrane	Syntax used in PubMed with Cochrane characteristics

Table 2. Critical appraisal; the eight selected articles were scored for the items mentioned under relevance and validity.

	Abad et al. 2004	Khalatbari et al. 2004	Lardenoye et al. 1997	Lee et al. 2009	Lobo et al. 2003	Nolle et al. 1998	Nolle & Eckardt 1993	Thorne & Brucker 2000
Relevance*								
Criteria by Lardenoye	+	–	+	+/–	+/–	+/–	+/–	+
Age	+	–	+	+†	–	+	+	+
Gender	+	–	+	+†	–	+	–	+
Outcome	+	+	+	+	+	+	+	+
Validity‡								
Design	–	–	–	–	–	–	+	–
Missing data	–	–	+	–	–	–	+	–
Standardized outcome	+	+	+	+	+	+/?	?	+
Blinded diagnosis	+	?	?	–	–	–	?	+
Number of patients	37	18†	53	3§	7§	20	9	7

*Criteria by Lardenoye: presence of multiple (>10), small, round, punched-out lesions in the peripheral retina, absence of central chorioretinal lesions and an associated intraocular inflammatory disease +, same criteria as above, but patients with central chorioretinitis are not excluded +/–, inclusion criteria solely based on the presence of punched-out lesions-. Age: mean age: >55 years +, <55 years –. Gender: ≥80% female +, other –. Outcome: visual acuity and complications (such as CME, glaucoma, or sarcoidosis) +, only visual acuity –.

†Subgroup of white female patients (83% with punched-out lesions).

‡Design: prospective +, retrospective –. Missing data: ≥80% had all ophthalmologic, laboratory and radiological tests +, other –. Standardized outcome: standardized testing of visual acuity +, other –. Blinding: diagnosed by a person who is blinded for clinical data +, no blinding –. Number of patients included.

§Subgroup of patients with PMC-associated ocular sarcoidosis.

Patient demographics

Lardenoye et al. reported that 53 (6.4%) of 828 patients with uveitis in their cross-sectional series in a uveitis referral centre had PMC (Lardenoye et al. 1997). All studies noted the predominance of female gender and elderly age (Table 2) (Nölle & Eckardt 1993; Hershey et al. 1994; Lardenoye et al. 1997; Nölle et al. 1998; Thorne & Brucker 2000; Abad et al. 2004; Lee et al. 2009). The percentage of white women in PMC series varied between 76% and 96%. Khalatbari et al. showed that white patients with posterior segment involvement in ocular sarcoidosis had significantly higher rates of choroidal 'punched-out' lesions than black patients (p = 0.002) (Khalatbari et al. 2004).

Association with sarcoidosis

All studies showed a clear relation between PMC and sarcoidosis. When considered together, biopsy-proven sarcoidosis was diagnosed in 16/85 (19%: range, 14–20%) and presumed sarcoidosis in 24/85 (28%: range, 5–57%) of the patients with PMC (Table 3) (Lardenoye et al. 1997; Thorne & Brucker 2000; Abad et al. 2004). Lardenoye et al. concluded that the clinical presentation and course of uveitis did not differ between patients with and without sarcoidosis (Lardenoye et al. 1997). On the contrary, Abad et al. found that PMC patients with proven or presumed sarcoidosis had a significant worse VA in the worse eye than nonsarcoidosis PMC patients (VA = 0.25, 0.21 and 0.53, respectively; p = 0.03). Moreover, CME was more frequent in PMC patients with proven or presumed sarcoidosis (57% and 61%, respectively) versus remaining patients with PMC (17%; p = 0.08) (Abad et al. 2004).

White women with PMC were older, and CME was more frequent than in other demographic groups (Khalatbari et al. 2004). Remarkably, Thorne et al. report on a mean delay in diagnosis of systemic sarcoidosis in patients with PMC of 6 years. The same report also concluded that fine white choroidal lesions might represent an early marker for sarcoidosis (Thorne & Brucker 2000).

Visual acuity

Visual acuity over time was studied in 147 patients and resulted in a weighted mean of VA for the better eye of 0.46 (range, 0.31–1.00) and for the worse eye of 0.29 (range, 0.18 – 0.43; Table 3). In the study by Lobo et al. (2003), mean visual acuities were not calculated, but poor visual outcome (defined as final acuity of £0.5) was presented in five of seven eyes (71.4%).

Clinical manifestations

Patients showed predominantly bilateral involvement (78–91%), usually asymmetrical, especially at the onset of PMC. Anterior uveitis was reported in 11/37 (30%) patients

Table 3. Overview of the main outcomes of each individual article divided in visual prognosis and sarcoidosis-related outcome.

	Visual prognosis					Sarcoidosis-related outcome
	VA in Snellen (logMAR)					
	Worse eye	Better eye	CME (%)	Glaucoma (%)	ERM (%)	Visual acuity is displayed in Snellen decimals
Abad et al. (2004) (n = 37) logMAR	0.29 (0.54 ± 0.43)	0.5 (0.31 ± 0.29)	46	–	–	19% (7/37) proven, 49% (18/37) presumed, 32% (12/37) indeterminate sarcoidosis Significant worse VA in proven/presumed sarcoidosis (0.25 and 0.21, respectively) than in indeterminate sarcoidosis patients (0.53; p = 0.03) CME was more frequent in PMC patients with proven or presumed sarcoidosis than in indeterminate sarcoidosis patients (57% and 61%, respectively, versus 17%; p = 0.08)
Khalatbari et al. (2004) (n = 18)* Snellen	0.33 (0.48)	1.00 (0.00)	61	–	28	White women are a different subgroup in ocular sarcoidosis White women had the highest mean age and CME was diagnosed significantly more frequent
Lardenoye et al. (1997) (n = 53) logMAR	0.31† (0.51)	0.31† (0.51)	72	25	–	25% (10/41) of the PMC patients had sarcoidosis (eight proven, two presumed)
Lee et al. (2009) (n = 3)	0.43 ± 0.06 (0.37 ± 0.06)	0.67 ± 0.29 (0.20 ± 0.17)	0	33	33	Poor visual outcome was more frequent in patients with PMC than in patients with anterior or intermediate uveitis (p < 0.05)
Lobo et al. (2003) (n = 7)	71% ≤ 0.5†	71% ≤ 0.5†	29	43	0	PMC appears to be associated with a worse visual prognosis despite immunosuppressive agents (71.4% (5/7) of the eyes)

Nolle et al. (1998) (n = 20)	0.20 ± 0.21 (1.22 ± 1.18)	0.31 ± 0.22 (0.65 ± 0.51)	70	–	–	–
Nolle & Eckardt (1993) (n = 9)	0.18 ± 0.17 (1.20 ± 1.13)	0.38 ± 0.34 (0.79 ± 0.92)	56	–	–	–
Thorne & Brucker (2000) (n = 7)	0.29 ± 0.28 (0.82 ± 0.58)	0.49 ± 0.27 (0.44 ± 0.33)	55	–	–	71% (5/7) PMC patients had sarcoidosis (one proven, four presumed) The delay in diagnosis was 6 years
Weighted mean	0.29‡ Range: 0.18–0.43	0.46‡ Range: 0.31–1.00	60 Range: 0–72	27 Range: 25–43	21 Range: 0–33	19% (16/85) of the PMC patients had proven sarcoidosis§ 28% (24/85) of the PMC patients had presumed sarcoidosis§

VA, visual acuity; logMAR, the logarithm of the minimum angle of resolution; CME, cystoid macular edema; ERM, epiretinal retinal membrane; PMC, peripheral multifocal chorioretinitis.

*Outcomes for white women, 83% had punched-out lesions.

†Mean logMAR is calculated without differentiating between a worse or better eye.

‡Visual acuity of Lobo et al. is left out.

§These values resulted from three studies which examined the prevalence of sarcoidosis in a homogenous population of definite PMC patients according to the Lardenoye criteria: Abad (n = 37), Lardenoye (n = 41) and Thorne (n = 7).

with PMC (Abad et al. 2004), while cells in the anterior chamber were noted in the majority of the patients from other series (Nölle & Eckardt 1993; Nölle et al. 1998; Thorne & Brucker 2000). Lardenoye et al. reported iritis in 31/53 (58%) patients and iris granuloma in 3/53 (6%) patients. Vitritis was a common feature of PMC, reported in 73–100% (Nölle & Eckardt 1993; Lardenoye et al. 1997; Nölle et al. 1998; Thorne & Brucker 2000; Abad et al. 2004; Khalatbari et al. 2004). The punched-out lesions (Fig. 2), constituted a selection criterion and seemed to worsen overtime (Thorne & Brucker 2000; Abad et al. 2004).

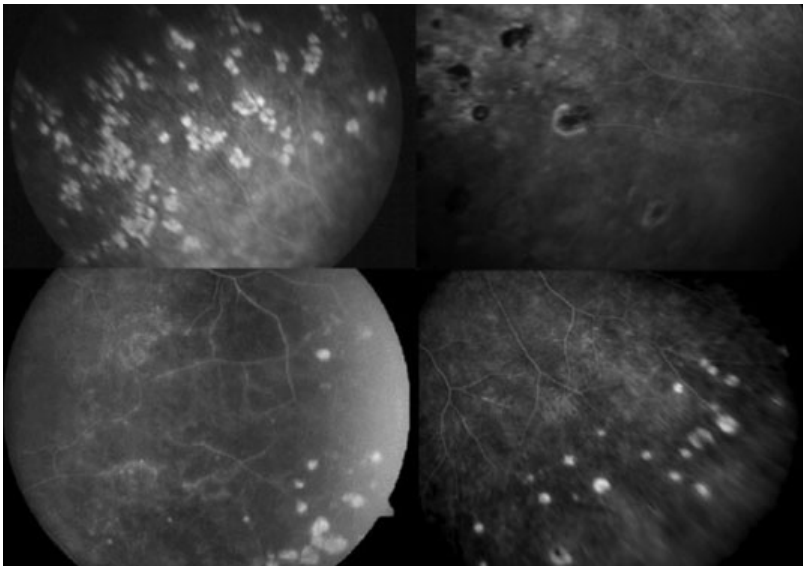

Fig. 2. Four patients with peripheral multifocal choroiditis and multiple punched-out lesions located in the periphery of the retina.

Imaging in PMC

The presence of CME and/or papillitis in the included articles was predominantly clinically assessed. Only one study included fluorescein angiography (FA) and/or optical coherence tomography (OCT) to confirm the diagnosis of CME or papillitis. Obviously, with the advanced imaging modalities, more accurate diagnosis and follow-up of ME and of epiretinal membranes can be performed; however, no systematic studies on PMC were so far available.

Sporadic angiographic studies in MCP are available (Altan-Yaycioglu et al. 2006). On FA, active chorioretinal lesions were hypofluorescent in the early phase and become hyperfluorescent on the later frames. On indocyanine green angiography (ICGA), both active and inactive lesions remained hypofluorescent during the entire angiogram. On ICGA, multifocal choroiditis lesions appeared more numerous and involved a much wider area than was appreciated on FA (Slakter et al. 1997). Dilatation and leakage

of choroidal vessels was noted in the intermediate and late frames (adjacent to the hypofluorescent dots) and suggests the presence of choroidal vasculitis. OCT scans of punched-out lesions in MCP revealed a disruption of the photoreceptor layer and thinning of the retina. Also, a thinning of the choroid and occlusion of choroidal vessels has been reported (Yasuno et al. 2009). Vance et al. (2011) reported the presence of sub-RPE material below these lesions, which appeared to improve over time. One study on autofluorescence revealed tiny hypoautofluorescent spots in the posterior pole. New clinically evident chorioretinal scars could be predicted in earlier autofluorescence photographs (Haen & Spaide 2008).

Arterial ectasias and macroaneurysms were repeatedly reported in 17% of the patients with PMC and on angiography. The authors proposed that arterial hypertension might increase the pressure on the arterial wall that is already weakened by inflammation (Rothova & Lardenoye 1998; Verougstraete et al. 2001). However, the association with arterial hypertension has not yet been proven, but the macroaneurysms were associated with the presence of cardiovascular disease.

Complications

When taking all studies together, the mean prevalence of CME was 93/158 of affected eyes (weighted mean of 60%; range, 0–72%; Table 3). In the demographic study of Khalatbari et al. (2004), it was stated that CME was significantly more frequent in white women than in other demographic groups ($p = 0.002$). Lardenoye et al. reported a worse VA in patients with CME (Snellen VA, 0.24) than in patients without CME (Snellen VA, 0.4) (Lardenoye et al. 1997). Lobo et al. (2003) also noted that poor visual outcome was associated with the high prevalence of CME and glaucoma.

Solely three studies mentioned an incidence of glaucoma (Lardenoye et al. 1997; Lobo et al. 2003; Lee et al. 2009), which was observed in 17/63 (27%; range, 25–43%). Lardenoye reported that 9/81 of the affected eyes (11%) showed corticosteroid-induced high intraocular pressure (Lardenoye et al. 1997). The mean incidence of ERM was approximately 6/28 (21%; range, 0–33%) (Lobo et al. 2003; Khalatbari et al. 2004; Lee et al. 2009).

Treatment

The first step in the treatment of PMC was corticosteroids. Periocular steroid injections were applied in different frequencies ranging from 27% to 85% (Lardenoye et al. 1997; Thorne & Brucker 2000; Abad et al. 2004). Systemic corticosteroids alone were prescribed in 27–43% (Lardenoye et al. 1997; Thorne & Brucker 2000; Abad et al. 2004). Immunosuppressive medications such as MTX or cyclosporine were used in <20% of patients (Lardenoye et al. 1997; Abad et al. 2004).

The proportion of patients with CME relapses after a mean treatment period of more than 6 months tended to be lower among patients receiving MTX than among those receiving only systemic corticosteroids (20% versus 75%; $p = 0.1$) (Abad et al. 2004). Systematic data on efficacy of immunosuppressive medication in PMC is otherwise lacking. Thorne et al. points out that although each patient showed some short-term effect of steroid treatment on inflammatory activity, all patients had a recurrence of their uveitis (Thorne & Brucker 2000).

Discussion

PMC represents a chronic form of uveitis which affects predominantly elderly white women. It exhibits a high association with sarcoidosis, and its major complication, CME, regularly causes permanent retinal damage and in consequence deterioration of the visual acuity. Data on treatment efficacy in PMC are lacking. Systematic studies on visual prognosis were not performed; however, our analysis shows that the visual outcomes were limited as the mean weighted visual acuity for the better eye was 0.47 and for the worse eye 0.29.

All studies showed a clear relation between PMC and sarcoidosis, indicating that approximately half of the patients with PMC have proven or presumed sarcoidosis. The majority of patients were discovered to have sarcoidosis during the evaluation of PMC or developed sarcoidosis later in the course of the disease. The tests used for the determination of sarcoidosis were variable, and lung biopsy was rarely attempted in patients with mild uveitis and typical hilar adenopathy on imaging examinations. It is therefore feasible that the prevalence of sarcoidosis in patients with PMC might substantially increase if all patients underwent a standardized diagnostic protocol. Controversy remains how extensive the examinations should be to determine the presence of associated (mild) systemic sarcoidosis in patients with PMC. The exact diagnosis is important in cases with severe ocular disease or when indications for prolonged systemic treatment exist as well as in cases with a suspicion of malignant disorder.

Tissue biopsy showing noncaseating granulomas is valuable proof for the diagnosis of sarcoidosis. Lung biopsy is not an attractive procedure, especially in elderly patients with mild or no pulmonary abnormalities. In these cases, therapeutic consequences of a positive or negative biopsy outcome are minimal. Conjunctival tissue biopsy is less invasive than lung biopsy, but controversial results were reported on its diagnostic value. In the last few years, one study has reported on high efficacy of undirected conjunctival biopsy and recommended this procedure as a first biopsy attempt in patient suspected with sarcoidosis (Chung et al. 2006).

Previous reports on imaging in sarcoidosis show that CT scan is more sensitive than chest X-ray. Chest CT scan revealed pathology suggestive of sarcoidosis in 14/17 (82%) elderly white patients with uveitis of an unknown cause and a normal chest X-ray (Kaiser et al. 2002). In another study, chest CT showed parenchymal abnormalities and

mediastinal or hilar adenopathies in 23 (72%) of the 32 patients, while only 14 (38%) of the 37 patients with PMC had abnormal chest radiographs (Abad et al. 2004).
The choice and timing of radiological examination remains a matter for consideration, because it is not desirable to expose patients to high radiation doses. Further contributing investigations comprise angiotensin converting enzyme (ACE) and lysozyme levels in the serum (Gronhagen-Riska et al. 1979; Ferlitsch et al. 1980). However, ACE reflects all ACE-producing granulomas and is not specific for sarcoidosis (Thorne & Brucker 2000).
Overall, patients with PMC had frequent occurrence of CME (58%) and glaucoma (27%) and exhibited limited visual outcomes. In the total uveitis population, 4% developed bilateral VA of <0.1 and additional 6% had a bilateral visual acuity of <0.3, which is much better than our results for PMC (Rothova et al. 1996). PMC subjects had worse visual outcome than patients with other ocular manifestations of sarcoidosis (Lee et al. 2009). With the introduction of OCT, the associated disorders of vitreoretinal interface became evident, and the studies that included OCT showed a relatively high prevalence of epiretinal membrane formation (21%; 6/31 patients).
The systematic studies on efficacy and side effects of treatment used for this clinical entity are lacking. Ideally, the treatment of PMC should prevent visual loss and ocular complications and should have acceptable safety profile. The use of periocular steroids in PMC is limited by its frequent chronic and bilateral course as well as elderly age of patients (increased development of cataract and glaucoma). Prolonged use of systemic corticosteroids has significant side effects in the PMC population of predominantly elderly women and should be reserved for temporary needs or for situations when quick effect is essential. The use of intraocular devices with steroids in PMC was not yet been evaluated and might become useful. However, the associated cataract and glaucoma as well as bilateral involvement represent local limiting factors. MTX tended to prevent recurrent relapses of CME better than systemic steroids did (20% in non-MTX group and 75% in MTX-receiving patients, $p = 0.1$) (Abad et al. 2004). The role of vitrectomy was not extensively evaluated, but Nölle et al. reported no influence on the long-term visual acuity (n = 9) (Nölle & Eckardt 1993). Recently, a good effect of biological therapies was also reported (Baughman et al. 2008).
Our own policy is to approach PMC in the stepwise fashion, depending on clinical manifestations. When systemic treatment becomes necessary and a short course of steroids did not improve the inflammation sufficiently, we favour the combination of steroids with MTX (starting dosage: 20 mg prednisone per day and 10 mg MTX per week supplemented by folic acid).
In the following weeks, the steroids are decreased to 7.5 mg/day and if necessary MTX is increased up to 20 mg/week. We treat patients with this combination for several weeks, and laboratory tests are evaluated regularly. If the situation is abated, prednisone is entirely withdrawn. PPV is considered a good therapeutic option in cases with

epiretinal membranes and quiet uveitis. Owing to the retrospective character of the included studies, radiological examinations were not established for each patient and biopsy was lacking in the majority of patients. Therefore, the prevalence of proven or presumed sarcoidosis could be underestimated. This holds also for the prevalence of glaucoma and ERM.

Our review illustrates the poor visual outcome of patients with PMC among the patients with uveitis and points out the high prevalence of complications, such as CME, glaucoma and ERM. In nearly half of the patients with PMC, proven or presumed sarcoidosis was diagnosed. Randomized or controlled studies on the therapy for PMC are lacking, and therefore, the evidence-based considerations on treatment regimens are not as yet feasible.

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CHAPTER 7

Long-term visual prognosis of peripheral multifocal chorioretinitis

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Abstract

Purpose: To report on the clinical manifestations, complications, and long-term visual prognosis of patients with peripheral multifocal chorioretinitis and to search for predictors for a lower visual outcome.

Design: Retrospective consecutive observational case series.

Methods: Setting: Institutional. Patient population: 134 eyes in 69 patients with a minimum follow-up period of 5 years. Observation procedure: Clinical characteristics were recorded as well as the visual acuity (VA) at the onset of uveitis; after 1, 5, and 10 years, and at the end of the follow-up period. Main outcome measures: Visual acuity, clinical features and complications, required medications and surgeries.

Results: The majority of the patients were elderly females with chronic bilateral ocular involvement, who developed multiple ocular complications over time. Systemic sarcoidosis was present in 39% of patients. In addition to peripheral retinal lesions and vitritis, papillitis was present in 95% of cases. The major complications included macular edema (91%), cataract (93%), glaucoma (35%), and optic disc atrophy (25%). The treatment regimens included systemic corticosteroids and/or immunosuppressive drugs in 44% of patients, and 84% of patients required intra-ocular surgery. One third of the affected eyes developed VA < 20/40 at 5-10 years of follow-up. VA at 1 year was the most important predictor of visual outcome at 5 and 10 years ($P < .001$).

Conclusions: Peripheral multifocal chorioretinitis was associated with a high prevalence of cataract, macular edema, optic disc atrophy and glaucoma. Despite the chronic course of the disease, multiple complications and surgical interventions, the majority of patients achieved satisfactory long-term visual acuity.

Introduction

Peripheral multifocal chorioretinitis (PMC) is a distinct clinical entity within a larger family of multifocal chorioretinitis or choroiditis disorders.[1-4] The characteristic features of peripheral multifocal chorioretinitis include several "punched-out" chorioretinal lesions in the peripheral retina and chronic vitritis, which is often accompanied by mild inflammation of the anterior chamber. Peripheral multifocal chorioretinitis occurs primarily in white women aged 55 years[5] and older; in approximately one third of patients, peripheral multifocal chorioretinitis is associated with sarcoidosis.[6] In peripheral multifocal chorioretinitis, cystoid macular edema (CME) is the primary ocular complication underlying decreased visual acuity (VA). At present, the long-term visual outcome of peripheral multifocal chorioretinitis is not known.[6] Here, we report the clinical manifestations, complication rates, and long-term visual prognosis of 69 patients (134 eyes) with PMC who were followed for a minimum of 5 years.

Methods

We performed a retrospective consecutive observational case series of all 69 patients with peripheral multifocal chorioretinitis who were assessed at our hospital from 1992 through 2007 and who completed a follow-up course of at least 5 years; 39 of these patients were followed for at least 10 years. The Institutional Review Board of the University Medical Center Utrecht waived the need for approval of this retrospective chart review. The study adhered to the tenets of the Declaration of Helsinki.

We extracted each patient's demographics and each patient's clinical, laboratory, and imaging findings from the hospital records. We noted the development of complications, including macular edema, macular pucker, cataract, optic atrophy, ocular hypertension, and glaucoma, as well as all ocular surgical interventions. Ocular comorbidity was also noted, as well as any medications used during the entire follow-up period. Throughout the follow-up period, none of the 69 patients took any biological pharmaceutical agent. The data were collected at disease onset and again at 1 and 5 years after onset; where available, data were also recorded at the 10-year follow-up visit. Data regarding VA were available at all follow-up visits for 31 patients.

Peripheral multifocal chorioretinitis was defined as the combined presence of multiple (>10) small round "punched-out" lesions in the peripheral retina, an absence of central chorioretinal lesions, and the presence of associated intraocular inflammatory disease.[1] The diagnostic criteria for ocular sarcoidosis—as defined by the Scientific Committee of the First International Workshop on Ocular Sarcoidosis—were applied as well as was possible.[7] In brief, a diagnosis of definite sarcoidosis was given to biopsy- or bronchoalveolar lavage-confirmed cases, and a diagnosis of presumed sarcoidosis was given to patients who had radiographic signs characteristic of sarcoidosis but no available biopsy data. In this study, a diagnosis of probable sarcoidosis was given to patients

who did not have a positive chest radiograph or, if available, a positive chest computed tomography (CT) scan, but had classic signs of peripheral multifocal chorioretinitis and serum angiotensin-converting enzyme (ACE) levels >30 U/L; in our own laboratory, the diagnostic threshold for serum ACE is 20 U/L.

Macular edema was defined either as leakage in the macular area on fluorescein angiography or in accordance with the following optical coherence tomography (OCT) criteria. For Stratus Time-Domain OCT (Carl Zeiss Meditec AG, Jena, Germany), macular edema was defined as retinal thickness >249 μm (the mean thickness of nonaffected retinas plus 2 standard deviations) and/or the presence of retinal cysts. After 2008, Cirrus Spectral-Domain OCT (Carl Zeiss Meditec AG, Jena, Germany) was used; using this method, macular edema was defined as retinal thickness >304 μm and/or the presence of retinal cysts. Chronic macular edema was defined as macular edema that lasted longer than 1 year. In the data analysis, recurrent macular edema was also classified as chronic macular edema. Macular epiretinal membrane was diagnosed based on funduscopy and confirmed by OCT when possible.

Glaucoma was diagnosed based on the presence of an excavated optic disc, glaucomatous visual field loss, and concurrent elevated intraocular pressure. Papillitis was defined as optic disc edema and/or a leaking, hyperfluorescent optic disc on fluorescein angiography.

If available, the VA of each eye was obtained from the medical records at the onset of uveitis; 1, 5, and 10 years after onset; and at the end of the follow-up period (for patients who were followed for longer than 10 years). For analysis, VA was transformed to logMAR values. Amblyopic eyes were not included in the VA measurements.

The data were analyzed using SPSS 20.0 (IBM, Armonk, New York, USA). The Mann-Whitney U test was used to analyze continuous variables, and the Fisher exact test was used to analyze categorical variables. Prognostic factors for low VA at the 5-year and 10-year follow-up visit were studied using generalized estimated equations with statistical correction to test for correlations between the 2 eyes of 1 patient. Characteristics with a relevant effect on outcome in the univariate analyses were evaluated further using a multivariate analysis. All statistical tests were 2-sided, and differences were considered significant if $P < .05$.

Table 1. Demographics and clinical features of 69 patients with peripheral multifocal chorioretinitis

	N	%
Female sex	58/69	84
Median age at onset of uveitis, y (range)	64 (4-87)	n.a.
Systemic sarcoidosis, total (definite+presumed)[a]	26/67	39
Definite (confirmed by biopsy or BAL)	16/67	24
Presumed[b]	10/67	15
Probable[c]	6/67	9
No sign of systemic sarcoidosis	35/67	52
Diagnosis of definite/presumed sarcoidosis[d]		
Prior to onset of uveitis	1/25	4
During uveitis screening	17/25	68
After onset of uveitis	7/25	28
Co-morbidity		
Cardiovascular disorder[e]	28/69	41
Thyroid disorder	10/69	14

BAL= bronchoalveolar lavage; n.a. = not applicable.

[a] In 2 patients, imaging results were not available.

[b] Radiographic signs characteristic of sarcoidosis, but no biopsy data available. In 18 patients a chest computed tomography (CT) scan was available. No CT scan was available in 42 patients with a normal chest radiograph.

[c] Absence of positive imaging, but the presence of typical clinical features of peripheral multifocal chorioretinitis, with serum angiotensin-converting enzyme levels >30 U/L.

[d] Information was not available for 1 sarcoidosis patient.

[e] Includes hypertension, diabetes mellitus, and hypercholesterolemia.

Results

The 69 patients in this retrospective study had a median age at onset of peripheral multifocal chorioretinitis of 64 years (range: 4-87 years); 46 of the 69 patients (67%) were 60 years of age or older at the time of onset. The general clinical characteristics of our study cohort are summarized in Table 1. The majority of patients were female (58/69, 84%) and/or white (66/69, 96%). Twenty-six of 67 patients (39%) were diagnosed with definite or presumed sarcoidosis; of these, 17 patients (68%) were diagnosed while screening for uveitis. Thirteen of 63 patients had an abnormal chest radiograph and 14 of 18 patients had an abnormal CT scan. Associated thyroid disorders were noted in 10 of 69 patients (14%). The ophthalmic features that developed during the course of the disease (Figure) are summarized in Table 2. We found no significant difference between patients with systemic sarcoidosis and patients without systemic sarcoidosis with respect to the occurrence of clinical manifestations (for all clinical manifestations, $P > .05$). During the course of the disease, papillitis was observed in 61 of 64 patients (95%).

Table 2. Ophthalmic features of 69 patients with peripheral multifocal chorioretinitis

Ophthalmic feature	N[a]	%
Anatomical location of uveitis		
Posterior uveitis	9/66	14
Panuveitis	57/66	86
Bilateral PMC	65/69	94
Keratic precipitates	35/68	51
Inflammatory cells in anterior chamber	60/68	88
Iris nodules	9/69	13
Posterior synechiae	29/69	42
Snow balls	32/69	46
Papillitis	61/64	95
Periphlebitis	42/66	64
Retinal arterial macro-aneurysms	5/69	7

PMC= peripheral multifocal chorioretinitis.
[a] Some data were not available for some patients.

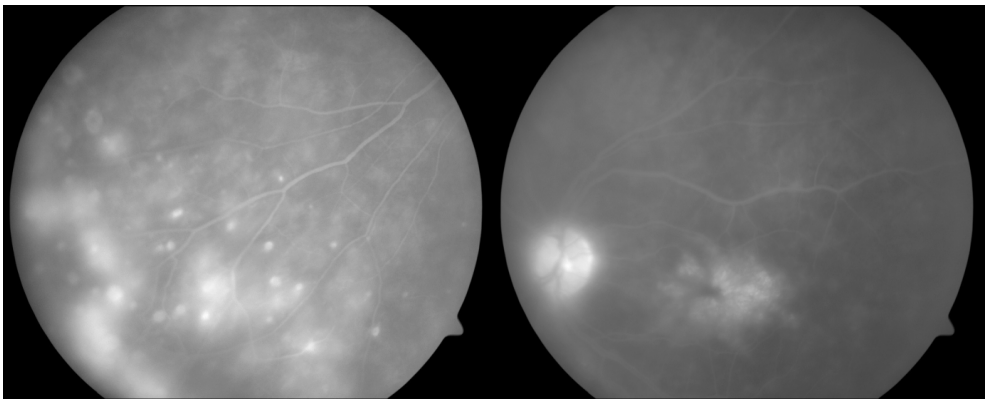

Figure. Fluorescein angiography of a patient with active peripheral multifocal chorioretinitis. The patient is a 67-year-old white woman with bilateral disease, 1 year after onset of the uveitis and prior to systemic treatment. (Left) The nasal-inferior periphery of the left eye contains several lesions leading to "punched-out" scars; (Right) fluorescein leakage from the posterior pole of this eye reveals the presence of cystoid macular edema and papillitis.

The development of ocular co-morbidity and complications is summarized in Table 3. Macular edema was the most prevalent complication of peripheral multifocal chorioretinitis, developing in at least 1 eye in 63 of 69 patients (91%) within the follow-up period. Further analysis per eye revealed that macular edema was present in 42 of

69 eyes (61%) at the onset of peripheral multifocal chorioretinitis (data were available in only 69 of 134 eyes), in 67 of 86 eyes (78%) at 1 year, in 34 of 74 eyes (46%) at 5 years, and in 19 of 43 eyes (44%) at 10 years. During the entire follow-up period, the cumulative incidence of macular edema was 81% (ie, 108 of 134 eyes had developed macular edema). The presence of systemic sarcoidosis had no influence on the risk of developing macular edema (P = .49).

Table 3. Ocular complications and comorbidity of 69 patients with peripheral multifocal chorioretinitis

Ocular complication and/or co-morbidity[a]	N[b]	%
Cystoid macular edema	63/69	91
Epiretinal membrane	32/68	47
Cataract	64/69	93
Corticosteroid-induced intraocular pressure ≥30 mmHg	7/69	10
Glaucoma	24/69	35
Optic atrophy (pallor + visual field loss)	17/64	25
Age-related macular degeneration	5/69	7
Retinal ischemia	8/66	12

[a] Present in at least one eye.
[b] Some data were not available for some patients.

Within the follow-up period, optic disc atrophy was observed in 17 of 64 patients (25%), glaucoma was observed in 24 of 69 patients (35%), and an epiretinal membrane was observed in 32 of 68 patients (47%). No optic atrophy was found in the 3 patients without papillitis and in 16 of 60 patients with papillitis (27%) optic disc atrophy occurred. In the group of patients with papillitis, the age at onset of uveitis and the duration of follow-up did not differ between the patients with or without optic disc atrophy (P = .11 and P = .89, respectively). Within the papillitis group, the prevalence of sarcoidosis did not differ between the patients with or without optic disc atrophy (P = .77); however, the prevalence of AMD differed between these two groups (4/16 vs. 1/44, respectively; P = .02).

The therapeutic interventions are listed in Table 4. One patient received eye drops as the sole treatment. Periocular corticosteroid injections were used to treat 56 of 69 patients (81%). Immunosuppressive drugs were given to 13 of 69 patients (19%), and 24 of 69 patients (35%) received a systemic course of prednisone; in total, 30 of 69 patients (44%) received systemic corticosteroids and/or immunosuppressive drugs. Fifty-eight of the 69 patients (84%) underwent a surgical intervention in at least 1 eye; the majority of surgical interventions were cataract surgeries. Although 24 patients developed glaucoma, only 3 of these patients required surgical intervention. Glaucoma

was not significantly associated with the use of periocular steroid injections (P = .52). In addition, the patients with peripheral multifocal chorioretinitis and systemic sarcoidosis did not differ significantly from the patients with peripheral multifocal chorioretinitis without systemic sarcoidosis with respect to their medical and/or surgical treatment modalities (P > .1). Sixteen patients underwent pars plana vitrectomy (PPV); however, PPV did not affect the need for local or systemic medical therapy.

Table 4. Medical treatment and surgical interventions in 69 patients with peripheral multifocal chorioretinitis

Treatment modality	N	%
Periocular steroids	56/69	81
Systemic treatment		
Corticosteroids	24/69	35
Immunosuppressive drugs[a]	13/69	19
Pars plana vitrectomy[b]	16/69	23
Cataract surgery	55/69	80
Glaucoma surgery	3/69	4
Total intra-ocular surgery[c]	58/69	84
Laser coagulation of ischemic retina	3/69	4
Ptosis surgery	6/69	9

[a] Includes methotrexate, cyclosporine, or azathioprine

[b] Pars plana vitrectomy was performed for diagnostic purposes in 6 patients, for persistent macular edema in 3 patients, for epiretinal membrane in 4 patients, and for retinal detachment, a macular hole, and vitreous opacities in 1 patient each. Three patients underwent vitrectomy in combination with a cataract extraction.

[c] Includes pars plana vitrectomy, cataract extraction, and/or glaucoma surgery

The time course of VA in the patient cohort is summarized in Table 5. At onset, the median VA of all affected eyes was 0.50. Median VA at the 1-year follow-up was 0.50; at the 5-year follow-up, median VA was 0.61 (P = .08 compared to the VA at onset), and median VA at 10 years was 0.68 (P = .23 compared to the VA at onset). At the 5-year follow-up, 25 of 66 patients (38%) had visual acuity of 20/63 or worse in at least 1 eye. At onset, 5 years, and 10 years, 7 of 112 affected eyes (6%), 11 of 126 affected eyes (13%), and 7 of 72 affected eyes (10%), respectively, had VA worse than 20/200. VA decreased to worse than 20/200 in 19 of 131 eyes (14%) at the end of follow-up, with a median follow-up period of 10 years (range: 5-21 years). Approximately one third of affected eyes had VA worse than 20/40 at both 5 and 10 years of follow-up, which was significantly lower than at onset, in which 43% of affected eyes had VA worse than

20/40 (P < .005 for both the 5-year and 10-year follow-up times). Bilateral loss of VA to worse than 20/200 occurred in 4 of 69 patients (6%) at the end of follow-up.
Macular edema was the principal cause of a decreased VA to worse than 20/40 in 22 of the 40 affected eyes (55%). Macular edema occurred during follow-up in 108 of 134 eyes (81%). Chronic macular edema occurred in 67 of 134 eyes (50%). Eyes that experienced macular edema during follow up had a lower median VA at 5 years (0.58, n=105) than eyes without (a history of) macular edema (0.86, n=24, P < .001). At the 10-year follow-up visit, the median VA of eyes with (a history of) macular edema was 0.56 (n=57), which was poorer than that of patients without macular edema (0.99, n=16, P < .001).

Table 5. Progression of visual acuity (VA) in eyes with peripheral multifocal chorioretinitis[a]

Visual acuity	Onset	1 year	5 years	10 years
≥20/40	64/112 (57%)	67/123 (54%)	82/126 (65%)	52/72 (72%)
20/63≤ VA <20/40	15/113 (13%)	18/122 (15%)	12/126 (10%)	7/72 (10%)
20/200≤ VA <20/63	26/112 (23%)	32/123 (26%)	21/126 (17%)	6/72 (8%)
<20/200	7/112[b] (6%)	6/123 (5%)	11/126 (9%)	7/72[b] (10%)

[a] Three amblyopic eyes were excluded.
[b] Out of 7 non-amblyopic eyes with visual acuity at onset <20/200, macular edema was present in 2 eyes, and both eyes improved after therapy. Two eyes had a subretinal neovascularization, 1 eye had dry age-related macular degeneration, 1 eye had a macroaneurysm with foveal exudates, and 1 eye had a venous occlusion. At the 10-year follow-up, 7 eyes had visual acuity <20/200. Five of these 7 eyes had macular edema; the sixth patient had a retinal detachment and cataract, and the seventh patient developed end-stage glaucoma.

VA at the onset of peripheral multifocal chorioretinitis and at the 5-year follow-up did not differ significantly between the group with systemic sarcoidosis and the group without systemic sarcoidosis (at onset: P = .91; at 5 years: P = .55); however, VA was slightly but significantly better at the 10-year follow-up in the group with systemic sarcoidosis (n=19 eyes, median VA: 0.80) compared to the group without systemic sarcoidosis (n=50 eyes, median VA: 0.69; P = .02). Considering the 16 patients (32 eyes) with definite sarcoidosis, the median VA was 0.78 at 5-year follow-up (n=26 eyes) and 0.82 at 10-year follow-up (n=14 eyes). In this group, the cumulative incidence of macular edema was 22 of 32 eyes (69%).
The presence of an epiretinal membrane did not affect VA at either the 5-year follow-up (P = .93) or the 10-year follow-up (P = .80). With respect to the 15 eyes that underwent PPV, the median pre-PPV VA was 0.20 (range: light perception to 0.55); 6 months after PPV, the median visual acuity was 0.25 (range: 0.01-0.6) (P = .13 compared with pre-PPV VA). With respect to the 7 patients who had macular edema and/or an epiretinal

membrane, post-PPV visual acuity improved, with an increase in median VA from 0.22 to 0.40 (P = .03).

We next investigated whether any factors were predictors of VA at the 5-year and 10-year follow-up times. Univariate analyses revealed that sex (P = .002), the age at onset of the uveitis (P = .008), VA at the onset of peripheral multifocal chorioretinitis (P < .001) and at 1 year (P < .001), macular edema at onset (P = .007) and age- related macular degeneration (P = .028) were the predictors of VA at 5 years. In contrast, the presence of macular edema at 1 year, chronic macular edema, the presence of an epiretinal membrane and the presence/absence of definitive or presumed sarcoidosis were not associated with future VA. Following multivariate analysis with these parameters, except for the VA at onset (because of the high correlation with VA at one year), only VA at 1 year remained a significant predictor of VA at 5 years (P < .001). The significant predictors for VA at 10 years (based on the 37 patients in the cohort with 10-year follow-up data) included sex (P = .036), age at onset of the uveitis (P = .017), VA at onset (P = .002) and at 1-year follow-up (P < .001), macular edema at 1 year (P = .008), age-related macular degeneration (AMD) (P < .001, but only 1 eye with AMD was available in the evaluation of VA at 10 years), and the presence/absence of definitive or presumed sarcoidosis (P = .018). A multivariate analysis using these 5 variables (excluding VA at onset because of the high correlation with VA at 1 year and excluding AMD) revealed that a better VA at 1 year (P < .001) and the presence of definitive or presumed systemic sarcoidosis (P = .033) were predictors of a better VA at 10 years. With respect to the clinical signs of uveitis (Table 2), the only predictive factors for VA were papillitis and iris granulomas in the uni- and multivariate analyses. Papillitis was negatively associated with the VA at 10 years (P < .001), but the presence of iris granulomas was a predictor for a good VA at 10 years (P = .01).

Discussion

We report that the majority of patients with peripheral multifocal chorioretinitis in our study cohort had chronic bilateral ocular involvement with associated papillitis. These patients also developed multiple ocular complications during the follow-up period, the most common of which were cataract and macular edema. The majority of our patients with peripheral multifocal chorioretinitis were elderly women, and 39% of patients had sarcoidosis. Peripheral multifocal chorioretinitis was also associated with high morbidity: intraocular surgery was required for 84% of patients, and approximately half of all patients required systemic prednisone and/or immunosuppressive drugs. In one third of the eyes, VA was worse than 20/40 at 5 and 10 years of follow-up, and macular edema was the principal cause of decreased VA. The most important predictor of poor visual outcome was VA at 1 year.

A large-scale study of uveitis revealed that sarcoidosis represents approximately 7-11% of panuveitis patients.[8,9] Although multifocal choroiditis accounts for 10-50% of all forms

of ocular sarcoidosis,[10,5] the precise prevalence of peripheral multifocal chorioretinitis among patients with ocular sarcoidosis is not known. Our finding that peripheral multifocal chorioretinitis and sarcoidosis are associated in elderly women is consistent with previous reports.[11] In a population of elderly uveitis patients (over the age of 60), 37% of patients had sarcoidosis.[12] In addition, 3 previous studies of peripheral multifocal chorioretinitis found that 24-68% of patients had definitive or presumed sarcoidosis.[1,2,4] In our cohort of patients with peripheral multifocal chorioretinitis, we found evidence of systemic sarcoidosis in 39% of patients, which is lower than the prevalence reported by Abad and associates.[4] Differences in inclusion criteria and/or the method of identifying sarcoidosis might explain this difference in prevalence. In Abad and associates' study, 62% of patients received a chest CT scan; in contrast, only 26% of patients in our cohort received a chest CT.

In our cohort, the patients with systemic sarcoidosis were similar to the patients without sarcoidosis with respect to their clinical manifestations of peripheral multifocal chorioretinitis in terms of the prevalence of ocular complications. Their visual prognoses were also similar; however, at the 10-year follow-up, median VA was slightly better in the patients with systemic sarcoidosis, although the clinical significance of this relatively small difference is uncertain. Our results are consistent with a previous study of visual outcome among patients with peripheral multifocal chorioretinitis with and without sarcoidosis.[1] On the other hand, another study reported poorer visual outcome among patients with peripheral multifocal chorioretinitis with systemic sarcoidosis; however, this study included fewer patients (37 patients) and shorter follow-up times.[4] Another study found that the visual prognosis of sarcoidosis-related uveitis was independent of the magnitude of systemic sarcoidosis at the time of onset.[13]

A previous study[14] reported that the presence of peripheral multifocal chorioretinitis and posterior synechiae in elderly patients with uveitis was associated with positive findings for sarcoidosis on a high-resolution computed tomography scan. In contrast, we found no association between posterior synechiae and systemic sarcoidosis; this difference might be explained by differences in inclusion criteria.

The percentage of patients with peripheral multifocal chorioretinitis and macular edema (81%) is somewhat higher than reported for patients with peripheral multifocal chorioretinitis (72%), possibly because of the availability of the OCT and our longer follow-up time.[1] At the time of presentation, the prevalence of macular edema in our cohort (61%) is somewhat higher than a previous report by Abad and associates (46%), possibly because of missing data in our study.[4]

The reported prevalence of macular edema in ocular sarcoidosis varies widely and might be due to the differences in the diagnosis of sarcoidosis. The cumulative incidence of macular edema in the patients with peripheral multifocal chorioretinitis and definite sarcoidosis in our study (69%)) is higher than reported for 44 patients with biopsy-proven ocular sarcoidosis (57%).[15] Their median follow-up time (3 years) was much

lower and a minimum follow-up time was not present in their inclusion criteria. Until several years after onset of the uveitis, macular edema may arise.

Khalatbari and associates studied a cohort of 76 patients with biopsy-proven or presumed (ie positive radiograph) ocular sarcoidosis and posterior segment involvement and reported that white female patients had the highest prevalence of macular edema (61%, n=18).[5] Their inclusion criterion of posterior segment involvement was wider than our inclusion criteria.

The formation of an epiretinal membrane is a relatively common complication in ocular sarcoidosis, occurring in approximately 30% of cases.[15,5,16] In our study, nearly half of the peripheral multifocal chorioretinitis patients (representing one third of the eyes) developed an epiretinal membrane. The clinically beneficial effect of performing pars plana vitrectomy that we observed in eyes with macular edema and/or an epiretinal membrane, as well as in eyes with vitritis and/or vitreous opacities, is consistent with previous reports.[16-21]

Glaucoma is a relatively common severe complication of uveitis, affecting approximately 20% of uveitis patients.[22-26] The prevalence of glaucoma in sarcoidosis-related uveitis ranges from 4 to 33% of affected eyes.[27] In our study of patients with peripheral multifocal chorioretinitis, glaucoma developed in 35% of patients, which is similar to the rate reported by other groups.[6] Our study found no association between glaucoma and the use of periocular steroids, which can be explained by the screening of our patients on the risk of developing glaucoma: all patients who experienced a substantial rise in intraocular pressure attributable to topical steroid administration were excluded from periocular steroid injections. If unexpectedly, the intraocular pressure still rose owing to periocular steroids and could not be normalized by maximum topical anti-glaucoma medication, the subconjunctival depot was surgically removed.

Papillitis and optic disc atrophy have been studied only rarely among uveitis patients. With respect to ocular sarcoidosis, the prevalence of optic nerve involvement varies widely (from approximately 7% up to 34%).[27-30,15]In our cohort, we found a surprisingly high prevalence of papillitis (it was present in nearly all patients), and 25% of our patients developed optic disc atrophy.

Very few studies have reported long-term visual outcome in uveitis patients.[26] Our results suggest that the majority of our patients with peripheral multifocal chorioretinitis had long-term VA that was 20/40 or better, which is consistent with previous reports of patients with ocular sarcoidosis.[10,31] We also found that macular edema was the principal cause of decreased VA. Long-lasting (ie, chronic) macular edema can result in an atrophic retina,[32] a finding that we also observed in our cohort.

The rates of resolved macular edema after 5 and 10 years were similar to previous findings in a population of patients in Greece with general uveitis and macular edema.[33] However, unlike the previous report, our cohort of patients with peripheral multifocal chorioretinitis did not improve further during follow-up; this difference might be

explained by the relatively high prevalence of intermediate uveitis (in 40 of 58 patients) in the Greek cohort. In our study, the strongest predictor of visual outcome was VA at the 1-year follow-up visit. Thus, optimum VA reached after 1 year of treatment was indicative of the best VA over the long run.

Because our study was retrospective, it might have included a potential selection bias towards severe and/or chronic patients in our tertiary care center. In addition, some patients were not examined systematically, and some of our findings (for example, the prevalence of optic nerve atrophy) might have been underestimated. Moreover, in the past, a chest CT scan was not routinely performed in case of a normal chest radiograph when searching for the diagnosis of sarcoidosis and the prevalence of sarcoidosis might have been underestimated. Because the prognosis and treatment of patients with peripheral multifocal chorioretinitis were similar regardless of the presence of sarcoidosis, one might question whether testing for systemic sarcoidosis is clinically valuable in patients who do not present with nonocular complaints. Nevertheless, testing for the presence of an associated systemic disease has merit. For example, primary vitreoretinal lymphoma can present with clinical features that are reminiscent of peripheral multifocal chorioretinitis, and distinguishing between the 2 conditions based solely on ocular manifestations may not be reliable. Moreover, systemic sarcoidosis might cause complications that are subclinical yet potentially dangerous, including cardiac arrhythmia.

In conclusion, our results suggest that peripheral multifocal chorioretinitis manifests primarily in elderly female patients, is closely associated with sarcoidosis, and follows a chronic course that frequently includes multiple ocular complications. In our cohort, the treatment regimen often included the chronic use of immunosuppressive drugs and/or surgical intervention, and these treatments provided improved long-term visual acuity. Nevertheless, the most effective and safe treatment for elderly patients with peripheral multifocal chorioretinitis has not been determined. The advanced age of most patients with peripheral multifocal chorioretinitis raises the question of whether exposing this relatively vulnerable group of patients to chronic systemic immunosuppressive therapy constitutes reasonable care; moreover, it remains unclear whether surgical options such as PPV can provide improved visual outcome in this patient population. Therefore, a randomized trial comparing both the efficacy and complications associated with surgical and medical approaches for treating peripheral multifocal chorioretinitis in elderly patients would help address these important questions.

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CHAPTER 8

Soluble IL-2 receptor and angiotensin-converting enzyme in aqueous humor of sarcoidosis patients

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Abstract

Aims: To investigate the applicability of measurements of soluble interleukin-2 receptor (sIL-2R) and angiotensin converting enzyme (ACE) levels in aqueous humour to confirm the diagnosis of ocular sarcoidosis.

Methods: sIL-2R and ACE levels were determined in 27 paired aqueous humour (AqH) and serum samples from uveitis patients with sarcoidosis and were compared to the results obtained with samples of 20 patients with infectious uveitis and of 17 non-inflammatory controls.

Results: Intraocular sIL-2R and ACE levels were increased in ocular sarcoidosis compared to the non-inflammatory controls (P <.001). No significant difference was found in the intraocular sIL-2R and ACE levels between ocular sarcoidosis and infectious uveitis (P = 1.00).

In ocular sarcoidosis, AqH sIL-2R and ACE levels were higher in the eyes with an active uveitis than in the eyes with an inactive uveitis (P = .006 and P =.002, respectively). Moreover, sarcoidosis eyes with an active uveitis had higher AqH ACE levels than eyes with an active infectious uveitis (P = .03).

In treatment-naive patients the median AqH ACE was higher in ocular sarcoidosis than in infectious uveitis (1364 pg/ml vs. 544 pg/ml, respectively, P = .02). The AqH-serum ratio proofed not to be useful for the diagnosis of ocular sarcoidosis.

Conclusions: AqH sIL-2R and ACE levels were increased in patients with uveitis associated with sarcoidosis, but do not differ from those with infectious causes. The elevated AqH sIL-2R and ACE-levels are typical for active and treatment-naive uveitis. Our findings suggest an intraocular release of sIL-2R and ACE due to an inflammatory process irrespective of its cause.

Introduction

Sarcoidosis is a common cause of uveitis and may manifest in all parts of the eye.
A definite diagnosis of sarcoidosis is made on histological changes of affected tissues, which in ocular disorders often is impossible. In case of a uveitis with clinical signs compatible with ocular sarcoidosis, ocular sarcoidosis is assumed when a diagnosis of systemic sarcoidosis is made.[1] In patients with suspected ocular sarcoidosis usually a chest X-ray or CT-scan is performed as well as serum levels of soluble interleukin-2 receptor (sIL-2R) and angiotensin-converting enzyme (ACE) are measured. However, the sensitivity and specificity of these serum markers for systemic or ocular sarcoidosis are low.[2-4] Ocular sarcoidosis is suspected in many cases of unexplained uveitis, but the confirmation of the diagnosis often cannot be made. Whether sarcoidosis can become manifest only with ocular involvement, is debated.[5] It has been noted however, that ocular disease is commonly the first manifestation of sarcoidosis.[6] Currently, no tests are available to establish the diagnosis of ocular sarcoidosis in the absence of systemic manifestations.
Therefore, we studied the sensitivity and specificity of intraocular sIL-2R and ACE as diagnostic markers for ocular sarcoidosis. For this purpose, sIL-2R and ACE levels were determined in 27 paired aqueous humour (AqH) and serum samples from uveitis patients with sarcoidosis, and compared to levels in patients with infectious uveitis and non-inflammatory controls.

Methods

Patients and samples

Paired AqH and serum samples were obtained from patients with uveitis who visited the University Medical Center Utrecht (UMCU) between January 2007 and November 2013 and who had undergone a diagnostic aqueous tap. AqH and blood samples were also collected during cataract extractions, provided the patients had given informed consent. The AqH samples were stored at -80°C and had been frozen-thawed no more than twice prior to analysis for this study, because of known instability of some cytokines upon freeze-thawing cycles.[7,8,13]
This study was conducted according to the declaration of Helsinki and with approval from the institutional review board of the UMCU. All patients consented to the use of their material for this study.
Patients were categorized by using the criteria from the international workshop on ocular sarcoidosis.[1] Definite ocular sarcoidosis was defined as a biopsy-supported diagnosis with a compatible uveitis.[1] Presumed ocular sarcoidosis was defined as a sarcoidosis-compatible uveitis in the presence of a bilateral hilar lymphadenopathy in the absence of a biopsy. In this report the term sarcoidosis is used for all patients with definite or presumed sarcoidosis.

An overview of included patients and their diagnoses is given in Table 1. Thirty-one patients with sarcoidosis were included (27 with paired serum and AqH-samples and 4 with AqH-samples only). As inflammatory controls we included AqH/serum pairs of 20 patients with an infectious uveitis that was laboratory-proven on intraocular fluid (including eight patients with toxoplasmosis, six with varicella zoster virus and six with herpes simplex virus). As non-inflammatory controls, AqH/serum samples from 17 patients with age-related cataract or cataract secondary to a previous pars plana vitrectomy were included. In two control patients, the serum was hemolytic and the serum levels of sIL-2R and ACE were excluded. The infectious and non-inflammatory controls were matched to the sarcoidosis group for gender and age to the extent possible (Table 1).

Intra-ocular and systemic signs and medication were recorded. The uveitic eyes were classified as active or inactive, based on clinical manifestations (presence or absence of cells in the AqH, fresh keratic precipitates, vitreous cells and angiographic findings of retinal vasculitis, active chorioretinal lesions, fluorescein leakage in the (extra)macular area and/or papillitis). This resulted in 14 active eyes of patients with sarcoidosis and 15 active eyes with infectious uveitis. A subsequent analysis was done for the 10 patients with sarcoidosis and the 4 infectious controls that were treatment-naive at the time of AqH sampling.

sIL-2R and ACE measurement

Multiplex immunoassays for sIL-2R and ACE were performed at the MultiPlex Core Facility of the Laboratory of Translational Immunology (UMCU, the Netherlands) using in-house validated tests essentially as described previously.[7,8] Uniquely color-coded magnetic beads (MagPlex Microsperes, Luminex, Austin, Texas) were conjugated to antibodies specific for the reported analytes and incubated with 60 μL of standard dilutions of AqH or serum for 1 h with continuous shaking in the dark. If necessary, sample diluent (Bio-Rad, Hercules California, USA) was added to obtain the correct volume and results were corrected for this. Plates were washed (Bio-Plex Pro II Wash Station; Bio-Rad, Hercules, California, USA) and a corresponding cocktail of biotinylated detection antibodies was added for 1 h. Repeated washings were followed by a 10 min streptavidin-phycoerythrin (PE) incubation. Fluorescence intensity of PE was measured using a Flexmap 3D system (Luminex) and analyzed with the BioPlex Manager software (version 6.1; Bio-Rad) using 5-parameter curve fitting. In two patients, the sIL-2R bead counts in AqH were too low and were excluded from analysis.

To assess whether sIL-2R and ACE was induced intraocular, the ratio between the intraocular concentration and the serum concentration was calculated.

For statistical analyses, the non-parametric Kruskal-Wallis and Mann-Whitney *U* tests were used for continuous data and the Fisher exact test for categorical data. Post-hoc tests (when the null-hypothesis on equal medians in the three patient groups was rejected)

Table 1. General characteristics of patients and controls

	Sarcoidosis	Infectious uveitis	Non-inflammatory controls	*P***
Number of patients	31	20	17	
Median age (years, range)	67 (34-83)	58 (34-86)	64 (45-91)	0.053
Gender (male/female)	8/23	7/13	8/9	0.33
Anatomical location of uveitis				0.000
- Anterior	0	10	n.a.	
- Intermediate	0	0		
- Posterior	2	0		
- Pan	29	10		
Uveitis uni-/bilateral	4/27	19/1	n.a.	0.000
Ocular active/inactive	14/17	15/5	n.a.	0.046
Medication				0.002
- None	10	4	17	
- Local*	11	9	0	
- Systemic immunosuppressive +/- local	10	1	0	
- Systemic antiviral/ anti-toxoplasmosis +/-local	0	6	0	

* includes eye drops and peri-ocular injections
** all Fisher exact test, except for age: Kruskal-Wallis test
n.a.: not applicable

were performed by pair wise comparisons including Dunn-Bonferroni correction. Non-parametric Spearman correlation analyses were performed for the sIL-2R and ACE concentrations in serum and aqueous humour. All statistical analyses were performed using the SPSS software version 22 (SPSS, Chicago, Il, USA).

Results

sIL-2R analysis

In serum the sarcoidosis patients had significantly higher levels than the non-inflammatory controls, but no difference was observed between the sarcoidosis patients and the infectious controls ($P < .001$ and .22, respectively; Table 2).

Intraocular sIL-2R was significantly increased in ocular sarcoidosis compared to the non-inflammatory controls ($P < .001$, Table 2 and Figure 1A), but no significant difference was found with the infectious controls ($P = 1.00$).
Intraocular sIL-2R levels did not correlate with the serum levels in the non-inflammatory and infectious controls ($P \geq .056$), but correlated weakly in the sarcoidosis eyes (R = 0.43, $P = .032$).
In the sarcoidosis group, AqH sIL-2R levels were significantly higher in the 12 patients with active uveitis than in the 17 with inactive uveitis (median 697 vs 89 pg/ml, respectively, $P = .006$, Figure 2A). In the infectious controls group, no significant difference was seen between the 15 patients with active uveitis versus those with inactive uveitis ($P = .098$). No difference of AqH levels of sIL-2R was observed in active ocular sarcoidosis and active infectious uveitis ($P = .37$).
In the sarcoidosis group, the two highest AqH sIL-2R values (6350 and 3230 pg/ml) were of two eyes with a severe uveitis at presentation. Similarly in the infectious control group two eyes with acute retinal necrosis (ARN) had the highest levels of sIL-2R in the AqH (2808 and 2389 pg/ml).
After excluding patients with systemic antiviral or anti-inflammatory medications, the serum slL2-R levels in sarcoidosis patients were significantly higher than in patients with infectious uveitis (520 pg/ml (n=20) vs. 262 pg/ml (n=12), respectively, $P = .015$).
In treatment-naive patients, the AqH sIL-2R was higher in ocular sarcoidosis than in infectious uveitis, but this difference did not reach significance (777 pg/ml (n=9) vs. 180 pg/ml (n=4), $P = .11$).
An analysis of the sarcoidosis group showed that AqH or serum sIL-2R levels did not differ between patients receiving no medication, local medication or systemic medication ($P = .068$ and .086, respectively).
No significant differences were found in the AqH sIL-2R levels when the uveitis patients were stratified by anatomic classification ($P = .61$).
The AqH/serum-ratio was calculated for sIL-2R in the three patient groups. A ratio above 1 was more commonly found in the two uveitis groups than in the non-inflammatory controls, but this was not significant (Table 3).

ACE analysis

Serum ACE levels were similar in all three groups (Table 2).
In AqH median ACE levels were increased in ocular sarcoidosis compared to the non-inflammatory controls ($P < .001$, Table 2 and Figure 1B), but no significant difference was found between ocular sarcoidosis and infectious uveitis ($P = 1.000$).
In all three groups, AqH ACE did not correlate with the serum levels ($P > .09$).
In ocular sarcoidosis AqH ACE was higher in active uveitis than in inactive uveitis ($P = .002$, Figure 2B). In infectious uveitis, ($P = .31$, Figure 2B) no difference in AqH ACE

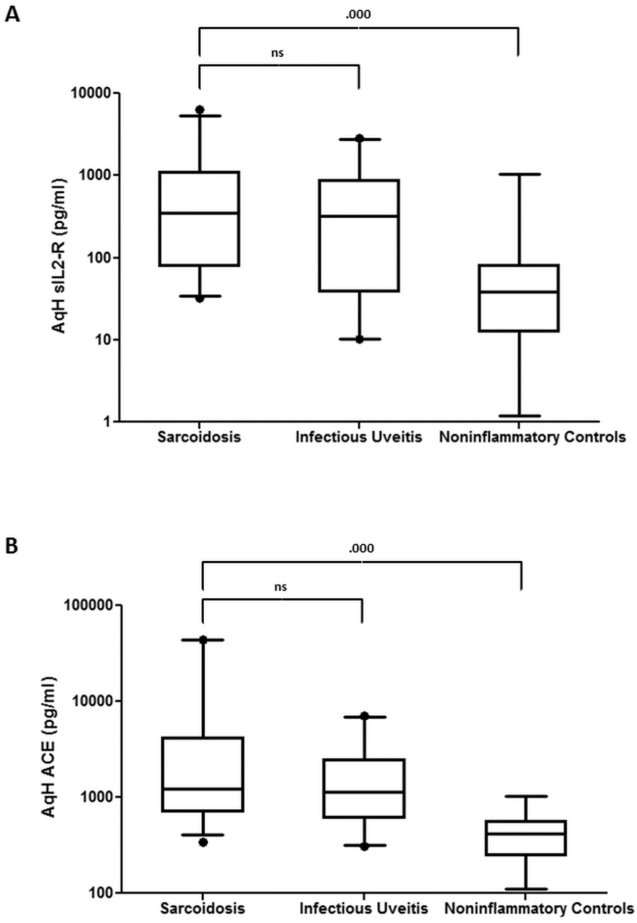

Figure 1. Intraocular sIL-2R (A) and ACE (B) concentrations in sarcoidosis patients, infectious uveitis patients and non-inflammatory controls. The data are presented as median-based boxplots indicating the 5-95 percentiles. Outliers are represented as dots. Statistical values are given (Mann-Whitney U test with Dunn-Bonferroni correction), ns: not significant.

was noted between active and inactive uveitis. Moreover, active ocular sarcoidosis had significantly higher AqH ACE levels than active infectious uveitis (P = .03, Figure 2B).
After excluding patients with systemic antiviral or anti-inflammatory medications, the serum ACE levels in sarcoidosis patients were significantly higher than in patients with infectious uveitis (213626 pg/ml (n=20) vs.154150 pg/ml (n=12), P = .027).
In the sarcoidosis group neither in AqH nor in serum differences were seen in ACE levels between treated (local or systemic), and untreated patients (P = .24 and .11, respectively).
In treatment-naive patients the median AqH ACE was higher in ocular sarcoidosis than in infectious uveitis (1364 pg/ml (n=10) vs. 544 pg/ml (n=4), P =.024).
The anatomical location of uveitis had no influence on AqH ACE levels (P = .13).

Table 2. sIL-2R and ACE concentrations in aqueous humor and serum

	Sarcoidosis	Infectious uveitis	Non-inflammatory controls
sIL-2R Serum			
n=	27	20	17
median concentration (pg/ml)	460	277	108
range (pg/ml)	36-2128	13-1331	0-370
*P***=		0.22	0.000
sIL-2R AqH			
n=	29	20	17
median concentration (pg/ml)	349	324	38
range (pg/ml)	33-6350	10-2809	1-1042
*P*** =		1.000	.000
active uveitis			
n=	12	15	
median concentration (pg/ml)	697	583	
range (pg/ml)	99-6350	10-2809	
*P**=	0.37		
ACE Serum			
n=	27	19	16
median concentration (pg/ml)	198435	157727	193256
range (pg/ml)	65102-624141	68011-277713	93327-339053
*P****=	0.25		
ACE AqH			
n=	31	20	17
median concentration (pg/ml)	1225	1136	413
range (pg/ml)	338-44061	313-7089	111-1032
*P***=		1.000	.000
active uveitis			
n=	14	15	
median concentration (pg/ml)	4434	1212	
range (pg/ml)	450-44061	422-7089	
P* =	.029		

sIL-2R: soluble interleukin-2 receptor; ACE: angiotensin converting enzyme; AqH: aqueous humour.
* Mann-Whitney *U* test, to compare within the active eyes between sarcoidosis and infectious uveitis.
** Mann-Whitney *U* test; post-hoc pair-wise comparison with the sarcoidosis group including Dunn-Bonferroni-correction.
*** Kruskal-Wallis test.

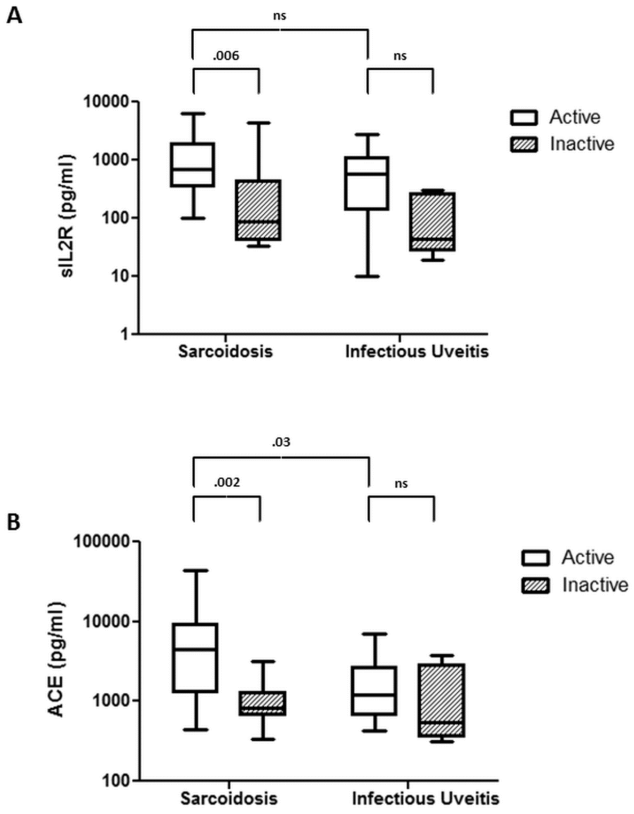

Figure 2. Intraocular sIL-2R (A) and ACE (B) concentrations in patients with active and inactive uveitis. The data are presented as median-based boxplots indicating the 5-95 percentiles. Statistical values are given (Mann-Whitney U test), ns: not significant.

The AqH/serum-ratio was calculated for ACE, but a value above 1 was not observed (Table 3). No significant differences were found in the AqH/serum-ratios between ocular sarcoidosis and infectious uveitis (P = 1.000).

Relation sIL-2R and ACE

No correlation between sIL-2R and ACE was found in the AqH or serum in the non-inflammatory controls. In the uveitis eyes, a moderate correlation between sIL-2R and ACE was found in AqH (sarcoidosis R = 0.57 and infectious controls R = 0.71, $P \leq .001$) and in serum (sarcoidosis R = 0.47 and infectious controls R = 0.48, $P \leq .04$). To determine whether the combination of sIL-2R and ACE was discriminatory, elevated levels, that is concentrations higher than the 97.5th-percentile of the non-inflammatory controls, were determined. In 5/29 of the sarcoidosis patients and 3/20 of the infectious controls both sIL-2R and ACE levels in AqH were elevated and in none of the 17 non-inflammatory

Table 3. Ratio Aqueous humor/serum of sIL-2R- and ACE-concentrations

	Sarcoidosis (n = 25)	Infectious uveitis (n = 19)	Non-inflammatory controls (n = 15)
sIL-2R			
median ratio	0.742	0.757	0.203
range	0.10-9.44	0.04-11.35	0.01-2.78
*P** =	0.094		
ratio >1	11/25 (44%)	8/19 (42%)	4/15 (27%)
*P*** =	.55		
no therapy			
median ratio	2.240	0.998	na
range	(0.12-9.44)	(0.09-2.96)	
*P**** =	0.50		
ACE			
median ratio	0.00724	0.0081	0.0024
range	0.0015-0.4140	0.0011-0.0469	0.0005- 0.0053
*P** =	0.000		
*P*****=		1.000	
ratio >1	0	0	0
no therapy			
median ratio	0.0078	0.0032	na
range	0.0015-0.414	0.0028-0.0071	
*P**** =	0.08		

na: not applicable
* Kruskal-Wallis test
** Fisher's exact test
*** Mann-Whitney U test
**** Mann-Whitney U test, post-hoc pair-wise comparison with the sarcoidosis group including Dunn-Bonferroni-correction

controls, however, no significant differences between the two uveitis groups were found (P = 1.0). This indicates that the combination of elevated AqH sIL-2R and ACE is not discriminatory for sarcoidosis either.

Discussion

In this study, we report on increased intraocular levels of sIL-2R and ACE in patients with ocular sarcoidosis and with infectious uveitis compared to non-inflammatory controls, but

no significant differences were observed between ocular sarcoidosis and infectious uveitis. Our findings suggest a non-specific release of sIL-2R and ACE due to an intraocular inflammatory process and indicate that intraocular sIL-2R and ACE measurement does not discriminate between uveitis entities. Measurements of AqH sIL-2R and ACE levels in addition to serum measurements do not contribute to a more sensitive method to diagnose ocular sarcoidosis.

sIL-2R is part of the receptor of IL-2. Interleukin-2, a T-helper cell cytokine, is essential for the regulation of proliferation and survival of different T-cell subsets. The IL-2-receptor is composed of three subunits (alpha, beta and gamma). The alpha-chain (CD25) is strongly expressed on activated T-cells and is secreted in a soluble form, called sIL-2R. Therefore, serum sIL-2R is a marker of T-cell activation.[9,10] In sarcoidosis, the sIL-2R level is correlated with the extent of T-lymphocyte alveolitis.[11] However, in extrapulmonary sarcoidosis, sIL-2R levels can even be higher than in patients with exclusively pulmonary sarcoidosis.

ACE is produced by endothelial cells (mainly in the lungs) and activated monocytes. In sarcoidosis patients it is produced by the epithelioid cells and macrophages in granulomas. The serum levels are an indication for the extent of granulomatous burden in a patient.[12]

Our findings on increased AqH sIL-2R levels are in concordance with the sIL-2R levels in spinal fluid of neurosarcoidosis patients, which were also increased compared to the controls.[13] Similar to our study, spinal fluids in neurosarcoidosis and bacterial/viral meningitis had a large overlap in the sIL-2R concentration range and sIL-2R did not discriminate between these two groups.

Our results on ACE measurements are partly in concordance with the data of Weinreb and colleagues.[14] They measured ACE activity in the aqueous humour of 16 sarcoidosis patients and found higher levels compared to normal controls. Contrary to our findings, however, they detected higher AqH ACE levels in sarcoidosis patients than in other uveitis syndromes, although we did find higher AqH ACE levels in ocular sarcoidosis compared to infectious uveitis in the group of treatment-naïve patients. The study by Weinreb and associates showed that in patients with sarcoidosis with normal serum ACE levels, AqH ACE levels can be elevated,[14] suggesting that AqH ACE measurements may render the diagnosis of ocular sarcoidosis more likely. Our study demonstrates that increased levels of AqH ACE are not specific for sarcoidosis, and may also be found in infectious uveitis.

Intraocular levels of sIL-2R and ACE correlated with activity of uveitis. The high levels in ARN and severely inflamed sarcoidosis eyes may suggest massive Th1-cell and monocyte activation.

In previous studies, contradictory results on the correlation between sIL-2R and ACE in serum were reported.[15,16,3] We measured ACE concentrations in contrary to most studies, which measured ACE activity. In our study, sIL-2R and ACE concentrations correlated moderately in uveitis, both in serum and AqH.

The wide range of sIL-2R and ACE concentrations among the sarcoidosis patients might be explained by the enormous diversity of the disease. Sarcoidosis is a collective term for many

diseases with diverse genetic constitution, diverse presentations and diverse prognosis. In the eye, sarcoidosis can present as a granulomatous or as a non-granulomatous uveitis, varying from an anterior uveitis to a panuveitis with a retinal vasculitis or a peripheral multifocal chorioretinitis, confirming the heterogeneity of the disease.

One of the questions was whether AqH sIL-2R and ACE was produced intraocular or diffused from the peripheral blood into the eye. The elevated levels of sIL-2R in the eye compared to serum are indicative for intraocular production. In contrast, the intraocular ACE levels were lower than in serum and therefore, in addition to intraocular production, ACE might have leaked from the blood into the eye in the uveitis patients, due to a breakdown of the blood-retina barrier.

A few remarks can be made on this study. First, the topical and systemic anti-inflammatory medication influences the levels of cytokines. Ideally, this study should be conducted in treatment-naive eyes, but their numbers in this study were low. The trend towards higher intraocular levels of sIL-2R and ACE in ocular sarcoidosis requires further investigation.

Second, this study raises the question how the results would be in non-infectious uveitis. If intraocular levels of sIL-2R and ACE are significantly higher in ocular sarcoidosis than in non-infectious uveitis, sIL-2R and ACE measurement could be used to diagnose ocular sarcoidosis, as infectious causes can be excluded by using Polymerase Chain Reaction and Goldmann-Witmer Coefficients. Petereit et al indeed demonstrated higher levels of sIL-2R in neurosarcoidosis than in multiple sclerosis or CNS-vasculitis and were even able to define a discriminatory cut-off point.[13]

In conclusion, we showed that elevated aqueous sIL-2R and ACE levels occur in patients with uveitis, but do not discriminate between ocular sarcoidosis and infectious uveitis. The elevated levels were typical for active and treatment-naive uveitis. Future studies, including analysis of additional immune mediators, are needed to investigate the possibility of diagnosing ocular sarcoidosis based on a specific cytokine profile that could discriminate sarcoidosis from other uveitis entities.

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CHAPTER 9

Summary and conclusions

Summary

This thesis investigates macular edema (ME) in uveitis, especially its diagnosis by diverse imaging techniques and puts emphasis on (its occurrence in) ocular sarcoidosis. ME is a condition characterized by the accumulation of fluid in the central area of the retina, called the macula, which serves the detailed vision. ME is one of the major complications in ocular inflammation, named uveitis, and may result in definitive loss of vision.

Chapter 1 presents a general introduction on the prevalence and risk factors of developing ME in uveitis and summarizes its pathophysiology. Despite new treatment strategies, ME still represents a major problem in uveitis, and may result in permanent blindness and/or visual impairment. The two methods of imaging are introduced, fluorescein angiography (FA) and optical coherence tomography (OCT). In the past, FA was the golden standard for assessment of ME. In addition, on the angiogram all other signs of active uveitis can be evaluated, such as vasculitis and papillitis. In the nineties, the time-domain OCT (TD-OCT) was introduced, with the major advantage of being non-invasive and providing quantitative information. A major improvement in the resolution and image acquisition speed occurred with the introduction of the spectral domain OCT (SD-OCT). Microcysts were discovered and the integrity of the inner-/outer segment junction (IS/OS line) can be assessed with SD-OCT. Recent research on the pathophysiology of ME revealed that the breakdown of the blood retinal barrier in uveitis is not a static phenomenon, but a dynamic one. In addition to a breakdown of the tight junctions, also an enhanced transcellular transport is involved. ME develops due to water accumulation in interstitial spaces or within cells. Extracellular edema is the result of protein leakage into the retinal interstitium. Intracellular edema is the result of swelling of the Muller cells. The relationship between macular ME and visual acuity is not simple and depends on multiple factors including the degree and duration of ME. Visual acuity and microperimetry are the main methods that evaluate the visual function of a patient with macular edema. In the last part of the introduction, systemic and ocular sarcoidosis are introduced. Sarcoidosis-associated uveitis is quite common in the Netherlands involving 7-11% of all with uveitis and is frequently complicated by ME and epiretinal membranes. The diagnostic approaches for systemic and ocular sarcoidosis as well their shortcomings are summarized. The diagnosis of ocular sarcoidosis is commonly difficult and screening in uveitis patients for sarcoidosis includes blood testing and imaging techniques of the lungs. Serum soluble IL-2 receptor and angiotensin converting enzyme are introduced as markers of systemic sarcoidosis.

Chapter 2 designates the imaging methods useful for diagnosis and follow-up of uveitic ME. FA offers the possibility to discriminate between ME due to uveitis activity and ME in a quiescent eye, which asks for different treatment regimes. Although several grading systems are available to assess the severity of ME, FA remains a qualitative investigation.

The OCT offers a non-invasive way of imaging and can be used in monitoring the activity during treatment. It is emphasized that the different OCT-systems cannot be easily compared, because of differences in the definition of the outer retinal border. The OCT made it possible to divide the ME in a diffuse type, a cystoid type, the presence of subretinal fluid and ME due to vitreoretinal adhesions. The integrity of the IS/OS line is of prognostic significance for visual acuity. An epiretinal membrane is easily seen on the OCT and has been proven to represent a negative prognostic factor for outcome of medical treatment. FA and OCT are complementary investigations, because fluorescein leakage, as a sign of the disturbed blood retinal barrier, provides different information from the anatomical changes such as retinal thickening seen on OCT. For the diagnosis of uveitis and assessing its inflammatory activity, FA is the first choice. For monitoring, OCT is suitable and recommended.

Chapter 3 investigates the impact and importance of a frequently encountered phenomenon of a subfoveal serous retinal detachment (SRD) in 98 patients with uveitic ME. The 37 patients with a SRD had a shorter history of uveitis and ME than the 61 patients with ME but without SRD. Although the total retinal thickness was higher in the ME with SRD group, the neuroretinal thickness was equal in both groups. At onset, the visual acuity was worse in the ME with SRD group, but the prognosis was favorable: the ME with SRF improved even better than the patients with ME without SRD. Both groups had similar results in visual acuity and total retinal thickness. About 80% of the SRDs had disappeared at 3-month follow-up. We conclude that SRD develops in the early stages of ME and uveitis but responds well to medical treatment.

Chapter 4 compares the usefulness, similarities and discrepancies of FA and OCT imaging in patients with ME in uveitis. We performed a study on 112 uveitis eyes (of 78 patients) that had ME and underwent simultaneously time domain OCT (TD-OCT) and FA. Comparison of FA and OCT images revealed that nearly half of the eyes had discrepant findings. Similar findings on FA and OCT were found in cases with more severe macular leakage on FA and larger central retinal thickness on OCT. In 30% of the eyes a mild fluorescein leakage was found but no retinal thickening or retinal cysts were seen on OCT. Half of the 14 birdshot patients had this discrepancy. We speculate that in a thin retina a retinal thickening is not easily recognized. OCT revealed ME in 15% of the eyes with no leakage on FA. This discrepancy was common in inactive uveitis and also occurred more often in young patients with an intermediate uveitis. Possible explanations are that this type of edema is intracellularly located or that this edema represents the remains of accumulated fluid after the uveitis subsided and the active leakage had stopped. We emphasize the importance of performing both investigations, because they illustrate different aspects of uveitic ME: FA showing the

macular vasculature and the integrity of the blood retinal barrier and OCT revealing the anatomical presence of and changes due to intra-/subretinal fluid.

Chapter 5 summarizes the current treatment options for inflammatory ME. The effects of nonsteroidal anti-inflammatory drugs administered locally or systemically, were disappointing in their effect on uveitic ME. Local or systemic corticosteroids are recommended in the initial phase of ME, because of their quick effect, but prolonged use is not attractive because of the severe side-effects. Immunomodulatory drugs can be given as steroid sparing therapy: methotrexate, cyclosporin, azathioprine and mycophenolate mofetil are commonly used. Interferons are not frequently used because of their serious side effects such as depression. In severe cases, anti-TNF medications can be prescribed. Intravitreal steroid implants are effective and especially the biodegradable dexamethason implant is useful, although an elevated intraocular pressure can occur. Intravitreal administration of anti-VEGF medication can be (temporarily) effective in uveitic ME as long as the inflammation is under control. In selected cases, pars plana vitrectomy can be useful. We propose a treatment algorithm where we suggest starting with periocular steroid injections (especially in those with unilateral ME) and if this is insufficient or in bilateral cases, immunomodulatory drugs are recommended. When inflammation is under control, but ME persists, the pump function of the retinal pigment epithelium can be stimulated by oral acetazolamide or somatostatin analogues.

Chapter 6 concerns a review article on peripheral multifocal chorioretinitis (PMC). PMC is a chronic bilateral uveitis with vitritis and multiple punched out lesions in the retinal periphery in the absence of central chorioretinal lesions. Only 8 articles fulfilled the diagnostic criteria of PMC, totaling 85 patients. This type of uveitis concerns predominantly elderly women and in almost half the PMC cases, evidence of systemic sarcoidosis was found. ME was present in 60% of the patients, glaucoma in 27% and an epiretinal membrane in 21%. Periocular or systemic steroids were the first choice of treatment and less than one fifth used immunosuppressive medication (methotrexate or cyclosporine). The best therapeutic approach for PMC is not yet clear. The mean visual acuity for the better eye was 0.47 and for the worse eye 0.29, which suggests a rather poor visual outcome in the spectrum of diverse uveitic entities.

Chapter 7 reveals the long term prognosis of 69 patients with PMC consulting the University Medical Center of Utrecht. The association with sarcoidosis was found in 39%. This is likely to be an underestimation, because only 26% of patients received a chest CT-scan, which is more sensitive than the chest radiograph. We found no differences in clinical manifestations and/or complications between the patients with and without sarcoidosis. Moreover, the visual acuity was similar in the two groups. A high cumulative incidence of ME of 81% was found and a prevalence of glaucoma of

35%, which is higher than in the general uveitis population. Strength of this study is that only patients with at least 5 year follow-up were included. In addition, we report on a new characteristic of PMC, specifically papillitis, which was experienced by 95% of all PMC patients, resulting in 25% of the patients with optic atrophy. Despite many medical and surgical interventions, about 70% of the eyes had a visual acuity of at least 0.5 at ten years follow-up. Our study shows that the visual results can be better than previously reported.

Chapter 8 investigates the usefulness of the assessment of two biomarkers for sarcoidosis in ocular fluid. The diagnosis of ocular sarcoidosis is difficult to prove and it frequently occurs that a uveitis is suspected to be related to sarcoidosis, but cannot be proven. Soluble interleukin-2 receptor (sIL-2R) and angiotensin-converting enzyme (ACE) are two markers that are used for the follow-up of systemic sarcoidosis patients but which have a low diagnostic sensitivity and specificity in the setting of uveitis. We describe the measurements of sIL-2R and ACE in the aqueous humor and serum of 27 patients with sarcoidosis. The results were compared to 20 controls with infectious uveitis and 17 non-inflammatory cataract controls. Although elevated intraocular levels of ACE or sIL-2R were found in sarcoidosis patients compared to non-inflammatory controls, a large overlap existed between the sarcoidosis-associated uveitis and the controls with infectious uveitis. The median ACE concentration in the aqueous humor of treatment-naïve patients was higher in ocular sarcoidosis than in infectious uveitis. The aqueous humor-to-serum ratio was not specific and therefore not useful for the diagnosis of ocular sarcoidosis. We conclude that measurement of ACE and sIL-2R in aqueous humor in patients with uveitis did not represent a sensitive method for diagnosis of ocular sarcoidosis.

Closing remarks and future perspectives

This thesis focused on the imaging of macular edema (ME) and vitreoretinal interface in uveitis with the purpose of a better understanding of the characteristics that we observe during fluorescein angiography (FA) and optical coherence tomography (OCT). Because of the large impact of ME on the visual prognosis and because of better treatment possibilities, we treat ME earlier and more aggressively. The use of a more aggressive treatment (with its potential side-effects) also asks for a more accurate evaluation of the therapy effects. The better understanding of the disturbances in the blood retinal barrier in uveitis on a molecular level will help us to interpret the imaging results and to formulate or verify hypotheses on the pathophysiology of uveitic ME.

First finding described in this thesis is that the appearance of subretinal fluid (SRF) in uveitic macular edema is not a poor prognostic sign for the visual prognosis. On the contrary, our study showed that the SRF in uveitic ME responds well to treatment. This is contradictory to the findings on SRF in ME in a branched retinal vein occlusion

or in diabetic retinopathy. Our results on a good treatment response of SRF and ME in uveitis have been confirmed by another study.[1] The published series on uveitic ME-associated SRF now totals over 300 patients, with an overall estimate of 40% of patients with uveitic ME having SRF. The exact mechanism of this fluid accumulation at the subretinal level, is unknown. It seems to occur most often in severe ME, suggesting that SRF is a consequence of an overload of fluid from the intraretinal cysts in its way towards the retinal pigment epithelium. In our study, the thickness of the neurosensory layer in ME with SRF was similar to the ME without SRF, which does not support the assumption that SRF is a mere consequence of a more severe ME. The tissue resistance might also play a role in the setting of exceeding the pump capacity of the RPE. It is also suggested that uveitis might lower the pump capacity. On the other hand, in uveitis, the outer blood retinal barrier might also be damaged, which would imply that SRF might also originate from the choroidal capillaries. More research is needed to investigate the exact origin of the SRF associated with ME.

In this thesis on uveitic ME, FA and OCT images were compared and published in 2012. In 2013, a new paper on the same topic, appeared.[2] Also in this report, macular leakage on FA was present in 40% of cases free of macular thickening on OCT and further macular thickening on OCT was present in 34% of cases without macular leakage on FA. Both studies reported a very high number of discrepancies. The FA-/OCT+ discrepancy is intriguing phenomenon and a longitudinal follow-up of these patients is necessary to find out the visual prognosis of affected patients. Our results indicate that imaging might be of value in making the correct diagnosis in patients with non-leaking ME. We have recently learned that it might occur in patients with toxic ME or in some tapetoretinal dystrophies. Intracellular edema seems to be the best explanation for the FA-/OCT+ discrepancy, but this discrepancy might also be the result of vascular leakage that occurred in the past, with fluid remaining in the retina that cannot be transported away by the glial cells or the RPE-cells. If this hypothesis of residual water accumulation is correct, than treatment with systemic acetazolamide or somatostatin analogs in such cases could be beneficial. In this thesis, we emphasized that the thin and atrophic retinas can also contain diffuse ME, without being recognized as ME. The FA+/OCT- discrepancy might also reflect the leakage of fluorescein (in a retina of normal thickness), as a marker for extracellular water movement, without the accumulation of proteins. Further research is needed to determine whether this condition could be harmful for the retina. This thesis also points out the possibility of anti-vascular endothelial growth factor (VEGF) therapy in cases with macular leakage in a non-active uveitis, which might help to minimize the edema and improve the barrier function. Because of the absence of VEGF-receptors on the RPE-cells, the outer barrier function or its pump function probably will not improve, but the anti-VEGF therapy might have effect on the choroidal permeability.

Future research is needed to explore the hypothesis that diffuse ME is in fact the initital stage of ME and cystoid ME is its more severe form. However, part of cases with the diffuse ME evolves to a macular epiretinal membrane. Whether aggressive treatment of the diffuse ME will help to reduce the formation of epiretinal membranes, needs to be investigated.

The second part of the thesis focused on sarcoidosis. We concluded that it is likely that most of the cases of peripheral multifocal chorioretinitis are related to sarcoidosis. Future research is needed to determine whether a CT-scan of the chest in PMC patients would reveal subclinical sarcoidosis. It is known that sarcoidosis with onset at older age is more frequently associated with extrapulmonary manifestations. Our findings of the frequent occurrence of opticopathy in PMC raised the hypothesis that a chronic inflammation of the optic nerve might result in an optic atrophy in susceptible patients. Better awareness of the chronic optic disc leakage on FA and appropriate visual field testing in PMC are indicated. The favorable visual results in our PMC-patients suggest that the stepwise approach in treatment of elderly PMC-patients might be reasonable.

As shown in patients with PMC, the diagnosis of ocular sarcoidosis in uveitis is often suspected, but cannot be proven. In case of a clinical suspicion of ocular sarcoidosis, we addressed the hypothesis that measurements of the biomarkers ACE and sIL-2R in the aqueous humor could become a more sensitive test for ocular sarcoidosis than serum measurements. Unfortunately, our findings have shown that this is not the case. The elevated levels of ACE and sIL-2R in aqueous humor in uveitis patients are not specific for sarcoidosis, but occur also in infectious uveitis. Future research is needed to identify a cytokine profile that would be specific for the diagnosis of ocular sarcoidosis.

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CHAPTER 10

Samenvatting en conclusies

Samenvatting

Dit proefschrift onderzoekt macula-oedeem (ME) bij uveïtis, met name de diagnosevorming door middel van beeldvorming en legt nadruk op (zijn voorkomen bij) oculaire sarcoïdose. ME is een conditie die gekenmerkt wordt door vochtophoping in het centrale deel van het netvlies, de gele vlek, waarmee het scherptezicht wordt verkregen. ME is een van de belangrijkste complicaties bij oogontstekingen, genaamd uveïtis, en kan tot definitief visusverlies leiden.

Hoofdstuk 1 geeft een algemene introductie over de prevalentie en risicofactoren van het ontwikkelen van ME bij uveïtis en vat de pathofysiologie samen. Ondanks nieuwe behandelstrategieën is ME nog steeds een groot probleem bij uveïtis en kan resulteren in blindheid en/of slechtziendheid in tenminste 1 oog bij 35% van alle uveïtispatienten. De twee beeldvormingstechnieken fluoresceïne angiografie (FA) en optische coherentie tomografie (OCT) worden beschreven. In het verleden was de FA de gouden standaard om ME vast te stellen. Bovendien kunnen alle andere aspecten van een actieve uveïtis worden gezien, zoals vasculitis en papillitis. In de jaren negentig werd de time-domain OCT geintroduceerd met het grote voordeel dat het niet-invasief is en kwantitatieve informatie geeft. Een belangrijke verbetering van de resolutie en de beeldopnamesnelheid ontstond met de introductie van de spectral domain OCT (SD-OCT). Microcysten werden ontdekt en ook kan de integriteit van de overgang van de binnen- naar de buitensegmenten van de fotoreceptoren (IS/OS-lijn) met SD-OCT worden beoordeeld. Recent onderzoek over de pathofysiologie van ME liet zien dat de afbraak van de bloed-retina barriere bij uveïtis niet een statisch verschijnsel is, maar dynamisch. Naast de afbraak van de tight junctions blijkt ook een versterkt transport transcellulair op te treden. ME ontstaat a.g.v. waterophoping in de interstitiële ruimte of binnen in de celllen. Extracellulair oedeem is het gevolg van zwelling van de Müllercellen. De relatie tussen ME en visus is niet eenvoudig en hangt van vele factoren af, zoals de mate en de duur van het ME. Visus en microperimetrie zijn de belangrijkste methoden om het visueel functioneren van een patient met ME te evalueren. In het laatste deel van de introductie worden systemische en oculaire sarcoïdose geïntroduceerd. Sarcoïdose-gerelateerde uveïtis komt geregeld voor in Nederland en vormt 7-11% van alle uveïtiden en wordt frequent gecompliceerd door ME en epiretinale membranen. Het diagnostische traject voor systemische en oculaire sarcoïdose als ook de beperkingen worden samengevat. De diagnose oculaire sarcoïdose is geregeld lastig te stellen en screening van uveïtispatienten op sarcoïdose omvat bloedbepalingen en beeldvorming van de longen. Soluble Il-2 receptor en angiotensin converting enzyme worden geïntroduceerd als markers voor systemische sarcoïdose.

Hoofdstuk 2 beschrijft de beeldvormingsmethoden die nuttig zijn voor diagnose en follow-up van voor inflammatoir ME. FA geeft de mogelijkheid om ME a.g.v.

uveïtisaktiviteit te onderscheiden van ME in een rustig oog, wat om verschillende behandelingen vraagt. Alhoewel verschillende graderingssystemen bestaan om de ernstig van ME vast te stellen, blijft FA een kwalitatief onderzoek. De OCT biedt een niet-invasieve manier van beeldvorming en kan worden gebruikt voor het monitoren van activiteit tijdens behandeling. Benadrukt wordt dat verschillende OCT-systemen niet gemakkelijk met elkaar te vergelijken zijn door verschillen in de definitie van de buitenste retinabegrenzing. De OCT heeft het mogelijk gemaakt om ME te onderscheiden in een diffuus type, een cystoïd type, de aanwezigheid van subretinaal vocht en ME a.g.v. vitreoretinale adhesies. De integriteit van de IS/OS-lijn is van prognostisch belang voor de gezichtsscherpte. Een epiretinale membraan is gemakkelijk herkenbaar op de OCT en blijkt een negatief voorspellende factor van de resultaten van medicamenteuze behandeling te zijn. FA en OCT zijn complementaire onderzoeken, omdat fluoresceïne lekkage, als teken van een verstoorde bloed retina barrière, andere informatie verschaft dan de anatomische veranderingen zoals retinale verdikking wat op OCT wordt gezien. Voor de diagnosevorming van uveïtis en bepaling van de ernst van de ontstekingsaktiviteit, FA is de eerste keuze. Voor het monitoren is de OCT geschikt en wordt aanbevolen.

Hoofdstuk 3 onderzoekt het effect en het belang van een frequent gevonden fenomeen van een subfoveale sereuze netvliesloslating (SRD) bij 98 uveïtispatiënten met ME. De 37 patiënten met ME en een SRD hadden een kortere duur van de uveïtis en van het ME dan de 61 patiënten met ME zonder SRD. Alhoewel de totale retinale dikte groter was in de ME met SRD groep, was de neuroretinale dikte in beide groepen gelijk. In het begin was de gezichtsscherpte slechter in de groep van ME met SRD, maar de prognose was gunstig: de groep van ME met SRD verbeterde zelfs beter dan de patiënten zonder SRD en beide groepen hadden gelijke uitkomsten wat betreft gezichtsscherpte en totale retinadikte. Ongeveer 80% van de SRDs was na 3 maanden follow-up verdwenen. We concluderen dat SRD in de vroege stadia van ME en uveïtis ontwikkelt en dat het goed reageert op medische behandeling.

Hoofdstuk 4 vergelijkt het nut, de overeenkomsten en de discrepanties van FA en OCT bij uveïtispatienten met ME. We beschrijven een studie van 112 uveïtisogen (van 78 patiënten) die ME hadden en gelijktijdig time-domain OCT (TD-OCT) en FA ondergingen. Vergelijking van de FA en OCT beelden liet zien dat bijna de helft van de patiënten discrepante bevindingen had. Overeenkomstige bevindingen op FA en OCT werden gevonden in geval van forsere fluoresceïne lekkage en een grotere centrale retinadikte op OCT. In 30% van de ogen werd een milde fluoresceïne lekkage gevonden maar geen retinale verdikking of retinale cystes op OCT. De helft van de 14 birdshotpatienten had deze discrepantie. We speculeren dat in een dunne retina een retinale verdikking niet gemakkelijk herkend wordt. OCT liet ME zien in 15% van de

ogen zonder fluoresceïne-lekkage op FA. Deze vorm van discrepantie zagen we vaak bij inactieve uveïtis en kwam ook vaker voor bij jongere patiënten met een intermediaire uveïtis. Mogelijke verklaringen zijn dat dit type oedeem intracellulair gelokaliseerd is of dat het oedeem achtergebleven, opgehoopte vloeistof is nadat de uveïtis tot rust is gekeerd en dat aktieve lekkage gestopt was. We benadrukken het belang van het doen van beide onderzoeken, omdat ze verschillende aspecten van het inflammatoire ME laten zien: FA dat de maculaire vasculatuur en de integriteit van de bloed-retina barrière laat zien en OCT de anatomische aanwezigheid van of veranderingen a.g.v. het intra- of subretinale vocht.

Hoofdstuk 5 vat de huidige behandelmogelijkheden voor inflammatoir ME samen. De effecten van niet-steroïdale anti-inflammatoire medicatie (NSAID's), lokaal of systemisch toegediend, vielen tegen w.b. hun effect op het inflammatoire ME. Lokale of systemische corticosteroïden worden aanbevolen in het begin van het ME, vanwege het snelle effect, maar langdurig gebruik is onaantrekkelijk i.v.m. ernstige bijwerkingen. Immunomodulerende medicijnen worden gegeven als steroïd-sparende medicatie: methotrexaat, ciclosporine, azathioprine en mycofenolaat mofetil worden geregeld gebruikt. Interferonen worden niet vaak gebruikt vanwege ernstige bijwerkingen als depressie. In ernstige gevallen kan anti-TNF medicatie voorgeschreven worden. Intravitreale steroïdimplantaten zijn effectief en m.n. het afbreekbare dexamethasonimplantaat is nuttig, maar een verhoogde oogdruk kan optreden. Intravitreaal toedienen van een anti-VEGF middel kan (tijdelijk) effectief zijn bij inflammatoir ME mits de ontsteking onder controle is. Bij geselecteerde patiënten kan een pars plana vitrectomie nuttig zijn. We stellen een behandelingsalgoritme voor waarin we suggereren om te starten met peri-oculaire steroïd injecties (m.n. bij de patiënten met een unilateraal ME) en als dit onvoldoende is of in geval van bilateraliteit, zijn immunomodulerende medicijnen aan te bevelen. Wanneer de ontsteking onder controle is, maar het ME persisteert, kan de pompfunctie van het retinale pigmentblad worden gestimuleerd door orale acetazolamide of somatostatine analoog.

Hoofdstuk 6 betreft een reviewartikel over perifere multifocale chorioretinitis (PMC). PMC is een chronische, bilaterale uveïtis met vitritis en multipele uitgeponste laesies in de retinale periferie met afwezigheid van centrale chorioretinale laesies. Slechts 8 artikelen voldeden aan de diagnostische criteria van PMC met in totaal 85 patiënten. Dit type uveïtis treft m.n. oudere vrouwen en bij bijna de helft van de patiënten werd sarcoïdose gevonden. ME was bij 60% van de patiënten aanwezig, glaucoom bij 27% en een epiretinale membraan bij 21%. Peri-oculaire of systemische steroïden waren de eerste keuze behandelingen en minder dan een vijfde gebruikte immunosuppressieve medicatie (methotrexaat of ciclosporine). De beste therapeutische benadering van PMC is nog niet duidelijk. De gemiddelde gezichtsscherpte van het beste oog was 0.46 en van

het slechtste oog 0.29, wat een redelijk beperkte visuele uitkomst suggereert in het licht van andere uveïtisentiteiten.

Hoofdstuk 7 laat de lange termijn prognose van 69 patiënten met PMC zien, die het Universitair Medisch Centrum Utrecht consulteerden. De associatie met sarcoïdose was gevonden bij 39%. Dit is waarschijnlijk een onderschatting, omdat slechts 26% van de patiënten een CT-scan van de thorax had ondergaan, wat gevoeliger is dan een röntgenfoto van de thorax. We vonden geen verschillen in klinische manifestaties en/of complicaties tussen de patiënten met en zonder sarcoïdose. Bovendien was de gezichtsscherpte gelijk in beide groepen. Een hoge cumulatieve incidentie van ME van 81% werd gevonden en een prevalentie van glaucoom van 35%, wat hoger is dan in de totale uveïtispopulatie. Sterkte van deze studie is dat alleen patiënten met een follow-up duur van tenminste 5 jaar zijn geïncludeerd. Bovendien melden we een nieuwe karakteristiek van PMC, te weten papillitis, wat 95% van de patiënten had doorgemaakt, en wat in 25% van de patiënten tot opticus atrofie heeft geleid. Ondanks de vele medicamenteuze en chirurgische interventies, had ongeveer 70% van de ogen een gezichtsscherpte van tenminste 0.5 na 10 jaar follow-up. Onze studie laat zien dat de resultaten gunstiger kunnen zijn dan in de literatuur gerapporteerd was.

Hoofdstuk 8 onderzoekt het nut van bepaling van twee biomarkers voor sarcoïdose in oogvocht. De diagnose oculaire sarcoïdose is moeilijk te stellen en het komt frequent voor dat een uveïtis suspect wordt bevonden voor sarcoïdose, maar niet kan worden aangetoond. Soluble interleukine-2 receptor (sIL-2R) en angiotensin-converting enzyme (ACE) zijn 2 markers die voor de follow-up van systemische sarcoïdose patienten wordt gebruikt, maar een lage diagnostische sensitiviteit en specificiteit hebben in geval van een uveïtis. We beschrijven de metingen van sIL-2R en ACE in het voorste oogkamervocht en serum van 27 sarcoïdosepatiënten. De resultaten werden vergeleken met 20 controles met infectieuze uveïtis en 17 niet-inflammatoire cataractcontroles. Alhoewel verhoogde intra-oculaire concentraties van ACE en sIL-2R werden gevonden in sarcoïdosepatiënten vergeleken met de niet-inflammatoire controles, bestond een grote overlap tussen de sarcoïdose-gerelateerde uveïtis en de controles met infectieuze uveïtis. De mediane ACE-concentratie in het voorste oogkamervocht in de onbehandelde patienten was hoger in oculaire sarcoïdose dan in infectieuze uveïtis. De ratio tussen voorste oogkamervocht en serum was niet specifiek en daarom niet nuttig voor de diagnose van oculaire sarcoïdose. We concluderen dat metingen van ACE en sIL-2R in voorste oogkamervocht bij patiënten met uveïtis geen sensitieve methode is om oculaire sarcoïdose te diagnostiseren.

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zal een van mijn volgende wetenschappelijke uitdagingen zijn. Mary van Schooneveld wil ik hier ook graag bedanken: dank voor je lieve betrokkenheid bij mijn wel en wee (en die van ons gezin) en ook voor me al vroeg introduceren in de leuke en leerzame fluorescentie-angiografie-avonden en -zaterdagen. Jouw enorme kennis, je liefde voor fluorescentie-angiografie, je strijd tegen zaken die de kwaliteit van de zorg bedreigen en je oog voor de hele patiënt zijn niet te evenaren en moet nog steeds het voorbeeld zijn voor alle oogartsen in opleiding, zoals je ook voor mij was en nog steeds bent.
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Curriculum vitae

De auteur van dit proefschrift werd geboren op 19 maart 1973 in Gouda. Op jonge leeftijd verhuisde ze naar Coevorden (Drenthe). Na het VWO-examen ging ze in 1991 geneeskunde studeren aan de Rijksuniversiteit van Groningen. De wetenschappelijke stage deed ze daar in het laboratorium voor experimentele oogheelkunde onder leiding van Prof. A. Kooijman. Begeleider van dit onderzoek naar contrastgevoeligheid bij oculaire hypertensie was dr. N. Jansonius. In augustus 1997 behaalde ze cum laude het artsexamen. In september 1997 begon ze als arts-onderzoeker bij de oogheelkundige fysica in het Academisch Ziekenhuis Utrecht. Doel van dit promotie-onderzoek was om de fluorescentie-angiografie te kwantificeren, onder leiding van Prof. D. van Norren en dr. P. van der Biesen. Dr. J. van der Kraats en dr. T. Berendschot en begeleidden het technische en fysische deel. Het onderzoek werd gesubsidieerd door de Fischer Stichting. De traditie van de werkgroep was om fundus reflectometrie en densitometrie te verrichten met door Van de Kraats ontwikkelde apparatuur. Een door hem gebouwde Scanning Laser Ophthalmoscope (SLO) was ook succesvol gebleken voor deze toepassing. Dit kreeg zijn vervolg in een nieuw-gebouwde 'Breed-Beeld SLO' met o.a. toevoeging van een blauwe argonlaser en een filter om alleen het groene fluorescentielicht op te vangen. Allereerst heeft Annette samen met haar collega's de meetopstelling uitgebreid getest, aangepast en geijkt om vervolgens fluorescentie-metingen in vitro, bij proefpersonen en bij patiënten te verrichten en te analyseren. Ad hoc door Van de Kraats geschreven software maakte het mogelijk om de fluorescentiebeelden te 'alignen' en hier fluorescentie-intensiteitsmetingen in te doen om fluoresceïne lekkage te kwantificeren. Helaas bleek de materie van fluorescenties afkomstig uit meerdere lagen in het oog te complex om met de bestaande middelen en resterende tijd goed te kunnen modelleren. Na 5 jaar is besloten om het project te beëindigen en is Annette in opleiding tot oogarts gegaan in het UMC Utrecht bij Prof. J. Stilma (opleider) en Prof. F. Treffers (medisch manager). De interesse voor de fluorescentie-angiografie en het netvlies bleef bestaan en i.h.b. voor de beeldvorming, die inmiddels gelukkig was uitgebreid met de OCT. In januari 2008 is ze oogarts geworden en heeft ze een vaste aanstelling mogen aanvaarden in het UMCU. In 2009 is Prof. S. Imhof als huidig afdelingshoofd gekomen. Annette's specialisaties zijn uveïtis, medische retina en glaucoom. De onderzoeksvraagstellingen in het huidige proefschrift komen direct voort uit de dagelijkse praktijk van de zorg voor uveïtispatiënten. Vanaf 2008 heeft ze naast haar klinische aanstelling van 3 dagen/wk een onderzoeksaanstelling van 1 dag/wk gekregen die is gesubsidieerd door de Fischer Stichting. Na beëindiging van deze aanstelling is de stafaanstelling uitgebreid naar 4 dagen/wk. Annette is in 2000 getrouwd met Tjaco Ossewaarde en samen hebben ze 2 kinderen: Vivianne (2001) en Stephan (2003).

List of publications

- Ossewaarde-van Norel A, Rothova A. Clinical review: Update on treatment of inflammatory macular edema. Ocul Immunol Inflamm. 2011;19(1):75-83.

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