

**INVESTIGATION OF INFLAMMATORY DISEASES BY
MODERN OPHTHALMOLOGICAL DIAGNOSTIC TOOLS**

Ph.D. Thesis

Lilla Smeller, M.D.

Szeged 2023

INVESTIGATION OF INFLAMMATORY DISEASES BY MODERN OPHTHALMOLOGICAL DIAGNOSTIC TOOLS

Ph.D. Thesis

Lilla Smeller, M.D.



Ph.D. program:

University of Szeged, Doctoral School of Clinical Medicine

Clinical and Experimental Research for Reconstructive and Organ-
sparing Surgery

Program director: **Prof. Lajos Kemény M.D., Ph.D., DSc, MHAS**

Supervisor:

Dr. Nicolette Sohar, M.D., Ph.D.

Department of Ophthalmology

Szeged

2023

Contents

1. Publications related to the subject of the thesis	4.
2. List of abbreviations	6.
3. Introduction	8.
4. Aims of the thesis	9.
5. Background	10.
5.1. Scleritis	10.
5.2. Uveitis	12.
5.2.1. Pediatric uveitis	14.
5.2.2. Uveitis in adults	15.
5.3. Rare bilateral uveitis in SARS CoV2 pandemic	16.
5.4. Modern ophthalmic imaging	17.
5.4.1. Optical coherence tomography (OCT)	17.
5.4.2. Ultra widefield fundus imaging (UWFI)	19.
5.4.3. Ultra widefield fundus autofluorescence (FAF)	19.
5.4.4. Ultra widefield fundus fluorescein angiography (FLAG)	19.
6. Patients and methods	21.
6.1. Patients	21.
6.1.1. Scleritis patients	21.
6.1.2. Juvenile uveitic patients	21.
6.1.3. Adult uveitic patients	22.
6.1.4. MEWDS patient	22.
6.2. Methods	22.
6.2.1. Ophthalmologic examinations	22.

6.2.2. Optical coherence tomography (OCT)	23.
6.2.3. Ultra widefield fundus imaging (UWFI)	23.
6.3 Ethics	23.
7. Results	24.
7.1. Scleritis patients	24.
7.2. Pediatric uveitic patients	28.
7.3. Adult uveitic patients	31.
7.4. MEWDS patient	34.
8. Discussion	38.
8.1. Examination of scleritic patients	38.
8.2. Examination of uveitic patients	41.
8.3. Examination of MEWDS patient	43.
9. Summary	45.
10. Acknowledgment	46.
11. Bibliography	47.

1. Publications related to the subject of the thesis

1. Lilla Smeller, Edit Toth-Molnar, and Nicolette Sohar

Optical Coherence Tomography: Focus on the Pathology of Macula in Scleritis Patients

Journal of Clinical. Medicine. 2023, 12 (14): 4825

<https://doi.org/10.3390/jcm12144825>

IF:3.9

Journal ranking Q1

2. Lilla Smeller, Edit Toth-Molnar, Nicolette Sohar

White Dot Syndrome Report in a SARS-CoV-2 Patient

Case Reports in Ophthalmology 2022; 13:744–750.

DOI: 10.1159/000526090

IF: 0.4

Journal ranking Q3

3. Smeller Lilla dr.1, Sümegi Viktória dr.2, Tóth-Molnár Edit dr.1, Sohar Nicolette dr.1

1Szegedi Tudományegyetem, Általános Orvostudományi Kar, Szemészeti Klinika, Szeged

2Szegedi Tudományegyetem, Általános Orvostudományi Kar, Reumatológiai és Immunológiai Klinika, Szeged

A biológiai terápia helye a gyermekkori uveitis ellátásában

Orvosi Hetilap [Biological therapy of uveitis in children]. 2022; 163 (35): 1402–1408.

doi.org/10.1556/650.2022.32578

IF: 0.6

Journal ranking Q3

2. List of abbreviations

AC anterior chamber

AMD age-related macular degeneration

ANA anti nuclear antibody

BCVA best corrected visual acuity

BRB blood–retina barrier

CME cystoid macular edema

CRT central retina thickness

DMARD disease-modifying antirheumatic drugs

DME diffuse macular edema

ERM epiretinal membrane

ETDRS early treatment of diabetic retinopathy study

FAF fundus autofluorescence

FLAG fluorescein angiography

IUSG International Uveitis Study Group

LE left eye

ME macular edema

MEWDS multiple evanescent white dot syndrome

MTX methotrexate

NDC non-differentiated collagenosis

NIH National Institution of Health

OCT optical coherence tomography

OCTA optical coherence tomography angiography

RE right eye

RPE retinal pigment epithelium

SARS-CoV-2 severe acute respiratory syndrome coronavirus

SLE Systemic Lupus Erythematosus

SRD serous retinal detachment

SS-OCT swept-source optical coherence tomography

TA triamcinolone-acetate

TNF tumor necrosis factor

UWI Ultra widefield imaging

VA visual acuity

3. Introduction

The global prevalence of inflammatory diseases is increasing. As a result, the number of eye complications related to these diseases has also increased, ranging from minor symptoms to vision-threatening complications. These ocular manifestations may result from the disease itself or from treatments that are used to treat the primary disease.

The field of ophthalmic imaging has been revolutionized over the past 30 years, particularly with the introduction of optical coherence tomography (OCT), which has since become the standard of care for many diseases. Significant advances in both hardware and software have enabled the emergence of multiple imaging techniques for increasingly high-resolution and high-contrast imaging of both anterior and posterior part of the eye. New-generation optical imaging modalities include OCT angiography (OCTA).

Ultra widefield imaging (UWFI) systems can produce up to 200-degree images. It is a non-contact diagnostic tool for taking fundus photographs, autofluorescent photos, and making fluorescent angiography or indocyanine-green angiography.

All of these ophthalmic imaging methods are increasingly being used and translated into the clinical setting, where initial results are promising to use them in patient care. By revealing the pathophysiological structures and functions of the eye's complex neurovascular network, the development of imaging technology can lead to earlier detection of diseases, more accurate diagnosis and treatment monitoring, and better treatment of many ophthalmic diseases, among them uveitis. The prognosis in cases of uveitis could be good for those who receive prompt diagnosis and treatment, but serious complications may result permanent vision loss if left untreated. Diagnostic tools like OCT, OCTA, UWFI can play an important role in the diagnosis and management of the uveitis.

4. Aims of the thesis

The aims of the thesis were:

1. To examine patients with anterior scleritis and to investigate the changes of their macula using OCT: to find correlation between the images and the clinical symptom, too.
2. To determine whether the macular complications would affect the prognosis and the treatment of scleritis, and wheather the OCT results might be applied as biomarkers in ophthalmology.
3. To present the results of ophthalmic examinations of pediatric and adult uveitic patients treated at our Department with the newest treatments and to find possible correlations between their therapy and the prognosis of the disease. In addition, to determine the visual acuity of juvenile uveitic patients treated with adalimumab.
4. To find out how the macular complications could affect the prognosis and the treatment to be applied in uveitic patients (children and adults).
5. To present a bilateral multiple evanescent white dot syndrome (MEWDS) case caused by severe acut respiratory syndrome coronavirus (SARS CoV2) and to prove that modern imaging procedures are irreplaceable in time of SARS CoV2 pandemic.

5. Background

5.1. Scleritis

Scleritis is a chronic, painful, vision-threatening inflamed disease that is characterized by edema and cellular infiltration of the scleral and episcleral tissues. The most common etiology is inflammatory (noninfectious in 90% of all scleritis patients), either idiopathic or in the context of a systemic disease. Scleritis is commonly associated with systemic autoimmune disorders [1], including rheumatoid arthritis, systemic lupus erythematosus, relapsing polychondritis, spondylarthropathies, granulomatosis with polyangiitis, formerly known as Wegener granulomatosis, polyarteritis nodosa, and giant cell arteritis [1–3].

Based on the anatomical location of the inflammation, scleritis may be classified as anterior and posterior ones. Anterior scleritis usually creates symptoms of continuous deep, boring pain in the eye, associated with intense redness. Posterior scleritis is characterized by flattening of the posterior aspect of the globe, thickening of the posterior coats of the eye, and retrobulbar edema [4, 5].

The most common clinical forms are diffuse and nodular scleritis [3] (Figure 1). Necrotizing scleritis is much less frequent and associated with systemic autoimmune disorders [6]. The onset is usually with inflammatory cells infiltration of the sclera and episclera, mediated by proinflammatory cytokines and intercellular adhesion molecules. [7].

In nonnecrotizing type of scleritis, the autoimmune process starts from the structural part of the sclera. The inflammation is driven by the innate immune system and responds to antigen-presenting cells, macrophages, granulocytes and resident tissue macrophages. The necrotizing scleritis shows a predominance of B-cells and macrophages, that induces the changes in the stromal part and activates acquired immunity [7].

Scleritis is a rare disease. Although well-defined incidence rates are hard to find, the prevalence is estimated to be six cases per 10,000 people. Anterior scleritis is demonstrated in 94% of the cases, and posterior scleritis is diagnosed only in 6% of the patients [3, 5, 6, 8].

In differential diagnosis, episcleritis is the most important one as it refers to the inflammation of the superficial episcleral tissue. Episcleritis is usually idiopathic, poses no

serious threat to vision, and does not affect the adjacent tissues in the eye. Vessels have a reddish hue compared to the deeper-bluish hue in scleritis [3, 5, 6, 8].

Scleritis is usually painful and can lead to vision loss due to progressive inflammation and destruction of the ocular tissues or even to morbidity and mortality due to an underlying collagen vascular disease [1–3].

Immunohistochemistry studies reveal that there is a localized scleral vasculitis, most likely secondary to the deposition of circulating immune complexes, in patients with necrotizing scleritis [9–11].

Scleritis may often pose a diagnostic challenge since the clinical features are subtle and diagnostic modalities are limited [1, 2]. The diagnosis of scleritis is usually based on clinical assessment and ultrasonography. B-scan ultrasound is the most useful confirmatory analysis method for the diagnosis of posterior scleritis [12]. It can show diffuse thickness of the choroid because of the increased amount of fluid in subtenon space and around the optic nerve, the so-called T sign [3]. The variability in clinical presentations, also in ultrasonography findings, as well as unfamiliarity with the diagnosis account for the fact that scleritis is one of the most underdiagnosed conditions in ophthalmology [3, 8].

Generally, scleritis requires systemic therapy. Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or immunomodulatory drugs can be indicated. Topical therapy is routinely insufficient. The treatment must be individualized according to the severity of scleritis, response to treatment, adverse effects, and presence of associated diseases [3, 13–15]. Oral corticosteroids (1 mg/weight kg) supplemented with periorbital or subconjunctival steroid injections were the first therapeutic regimen introduced [13, 14]. In cases of therapeutic failure of corticosteroids, immunosuppressive drugs were added. Methotrexate (MTX) [16] was the first choice, but azathioprine, cyclophosphamide [17], and cyclosporine [18] were also helpful. In other cases, other immunomodulatory drugs were effective, such as biologics, which were ordered by rheumatologists [14]. More recently, tumor necrosis factor (TNF) alpha inhibitors such as adalimumab and infliximab have shown promise in the treatment of non-infectious scleritis refractory to other treatments. This consists of regularly repeated infusions since the treatment effect is short-lived. All patients on immunomodulatory therapy must be strictly monitored by rheumatologists to avoid systemic complications with the medication [14].



Figure 1. Slit lamp picture of diffuse scleritis of the temporal part of the left eye. We can see involvement of the deep scleral vessels.

5.2. Uveitis

Uveitis is a common, sight-threatening group of disorders, all of which are characterised by inflammation of the uveal tract (iris, ciliary body, and choroid). According to the International Uveitis Study Group (IUSG) formed in 1978, uveitis is defined as a group of vision threatening disorders causing intra-ocular inflammation in the uvea and its adjacent tissues, such as optic nerve and vitreous humor.

Depending on which area of the uvea is mostly inflamed, uveitis can be divided into four types according to its anatomical locations: anterior, intermediate, posterior, and panuveitis. Diagnosis of anterior uveitis is made by the presence of anterior chamber (AC) cells and flare, which can be seen in iritis and iridocyclitis [19]. In cases of intermediate uveitis, the inflammation is in the vitreous and peripheral retina. Posterior uveitis refers to an inflammation of the retina and choroid, including choroiditis, retinitis, chorioretinitis, retinal vasculitis, and neuroretinitis. Panuveitis is when there is no predilectional places of the uveitis.

According to the underlying etiology of the condition, uveitis could be also clinically categorized as idiopathic, infectious (caused by herpes simplex virus, Toxoplasmosis, Toxocariasis, varicella- zoster virus, syphilis, Lyme disease, Bartonellosis, cytomegalovirus, tuberculosis), non-infectious (endogenous uveitis: like JIA associated uveitis, HLA-B27 associated uveitis, spondyloarthritis- associated uveitis, caused by systemic disorders like sclerosis multiplex and idiopathic uveitis) and masquerade uveitis (trauma, tumors) [20].

In pediatric uveitis the most common cause of the inflammation is JIA, in adult patient it is idiopathic uveitis.

Uveitis can be further sub-classified based on its duration and onset. A limited uveitis is defined as inflammation that lasts for less than three months. If inflammation persists for more than three months, it is considered as persistent uveitis. According to the onset of uveitis, it can be classified into acute, chronic or recurrent uveitis. Acute uveitis has sudden onset and limited duration of inflammation. Recurrent uveitis is when there are more than three month gaps between the preceding and relapsed uveitis. When the inflammation is persistent and uveitis recurs less than three months after treatment is discontinued, it is defined as chronic uveitis [21].

Uveitis constitutes a major cause of ocular morbidity, and it leads to 5-10% of visual impairment worldwide [22].

Treatments of uveitis are based on the degree of inflammation and the presence of risk factors and complications. It depends on the background (infectious or non-infectious uveitis) and the laterity (unilateral or bilateral) of the inflammation. It should be started as soon as diagnosis is made, and may follow a stepladder approach, which starts by using from the least aggressive to the more aggressive treatments and continues to induce remission of inflammation.

First-line treatment for non-infectious uveitis is represented by corticosteroid monotherapy. Corticosteroids can be administered topically as drops (preferably prednisolone 1% or dexamethasone 0.1%), especially in anterior uveitis as they are able to penetrate well into the anterior segment or subconjunctival or peribulbar injections: prednisone or prednisolon [23-25]. Also in posterior cases intravitreal triamcinolon- acetamide injection or biodegradable dexamethasone could be injected. [26]. Local corticosteroids have side effects like elevation of intraocular pressure and can induce posterior cataract formation. Sometimes secondary infections may appear and it can reactivate latent herpes simplex virus infection.

Oral prednisone is the most commonly used drug, at an initial dose of 1–2 mg/kg, to be tapered based on clinical response. When the inflammation is severe with involvement of all of

the uveal layers and eventually the optic nerve, intravenous corticosteroids are needed to achieve ocular remission. Usually, methylprednisolone is the drug of choice, at 30 mg/kg (maximum dosage 1 gram) intravenously for three consecutive days or every other day three times a week, followed by oral corticosteroids [27]. The most common adverse effects of systemic corticosteroids are osteoporosis, acne, high blood pressure, depression, stomach ulcers, diabetes, increased appetite, weight gain and muscle weakness.

Immunosuppressive agents represent the therapeutic option when quiescence is not obtained with corticosteroids, or in cases of reactivation or new complications, and are used as corticosteroid-sparing drugs to reduce inflammation and control the disease [28]. There are four types of immunomodulator therapy: 1. antimetabolites, 2. T-cell inhibitors, 3. alkylating agents with cytotoxic effect, and 4. biological therapies. The gold standard is methotrexate (antimetabolite), a folate analogue, which can inhibit DNA replication and RNA transcription. In cases of therapeutic failure or complications there are azathioprine (purin analogue) and mycophenolate mofetil (inosine monophosphate dehydrogenase inhibitor). T cell inhibitors like cyclosporin is effective in combination. Alkylating agents have cytotoxic effects and because of this a lot of severe side effects, so we use them when there are no other choices [28].

When treating uveitis with the above mentioned immunosuppressive agents and the uveitis persists for more than three months, or the uveitis reoccurs, or there are new complications, we have to change therapy to systemic biologic agents.

The most widely used biologic compounds for treating uveitis are represented in adults by the tumor necrosis factor alpha inhibitors (anti-TNF- α) in intermedier, posterior, and panuveitis. Anti-TNF- α is also recommended for children in cases of anterior uveitis [29]. The utilisation of TNF- α antagonist adalimumab is approved for uveitis by the EMA and could be used in Hungary since 2016 [30].

5.2.1. Pediatric uveitis

Uveitis in children accounts for 5 - 10% of total uveitis cases [31]. The estimated prevalence of uveitis is 100/100,000 and the incidence is 17 to 52 cases per 100,000 population [31]. Even though uveitis is less common in children than in adults, juvenile uveitis causes a higher rate of vision loss and secondary complications than in adults because uveitis is diagnosed late in these cases. Usually the kids are diagnosed when they already have

complications. [32]. Both adult and juvenile uveitis show a slight female predominance [33]. Of all diagnosed children, anterior uveitis cases are 40%, posterior cases are 40%, intermediate cases are 15%, and panuveitis is 5%. [34]. The visual complications can be more severe in the pediatric group due to a higher prevalence of posterior uveitis [31].

Uveitis may manifest as an independent specific eye disorder, or in association with systemic or autoimmune diseases [35].

Uveitis is mostly idiopathic, even though it may vary in different age groups of children. Other possible causes of uveitis are inflammation from infection (herpes simplex, varicella zoster, cytomegalovirus, toxoplasmosis, toxocariasis), trauma drug induced and systemic or autoimmune conditions [36].

Among the non-infectious causes of uveitis, juvenile idiopathic arthritis (JIA) is the most common systemic disease [37].

JIA is the most prevalent rheumatic disease in children and is a heterogeneous group of chronic arthropathies with an onset before the age of 16 along with at least six weeks of duration. [38]. JIA-associated uveitis is the most common extra-articular manifestation [39], that represents a risk for serious complications, including permanent loss of vision. [40]. The risk factors for developing uveitis in JIA patients include female gender, antinuclear antibody (ANA) positivity, oligoarticular arthritis, and early age of arthritis onset [41]. In patients with JIA, the intraocular inflammation is characterized by an insidious onset and chronic course of bilateral anterior uveitis. During slit lamp inspection, inflammatorical cells in the anterior chamber (AC) can be detected [42].

Children who are too young to communicate cannot complain about eye symptoms that indicate the existence of intraocular inflammation, which leads to a delay in prompt diagnosis and treatment [43]. There were 47% of JIA patients with legal blindness at least one eye on the first visit to the ophthalmological department. [44].

5.2.2. Uveitis in adults

The term “endogenous uveitis” describes ocular inflammatory disorders associated with no known infections or other exogenous causes.

The estimated prevalence of non-infectious uveitis in adults is 121/100,000. The incidence and prevalence varies worldwide, in Hungary it is about 14-17/100,000 [45].

In the developed world, the most common known cause of noninfectious uveitis is HLA-B27-associated uveitis [46]. The prevalence of HLA-B27 varies widely, It is estimated that 30-80% of patients with seronegative spondyloarthropathy are HLA-B27 positive.

Uveitis can occur as a manifestation of many systemic inflammatory conditions, including the spondyloarthritis family of disorders, sarcoidosis, Behçet's disease other systemic rheumatic and systemic disorders like multiple sclerosis, psoriatic arthritis, Crohn disease, SLE. Drug or hypersensitivity reactions are rare causes of uveitis.

Pseudo-uveitis or masquerade-syndrome can be caused by trauma, intraocular bodies or tumors like oculocerebral lymphoma, melanoma, retinoblastoma or metastases.

There are special ophthalmologic entities causing endogenous uveitis like birdshot retinopathy, multifocal choroiditis, pars planitis, Fuchs heterochromic cyclitis, phacoantigenic uveitis, Posner-Schlossman syndrome, white dot syndromes and sympathetic ophthalmia.

Uveitis of unexplained origin, also known as idiopathic uveitis, represents 23–44% of cases according to recent studies. [47].

The working age group (20–50 years) appears to be the most affected. There is a higher frequency of uveitis in female adult patients than in male ones. [48].

The most common non-infectious uveitis in the developed world is HLA-B27 associated uveitis. The most common location of non-infectious uveitis is anterior, representing 47.5 to 93% of all cases [48].

The incidence of panuveitis and posterior uveitis is similar: about 20% of all uveitis cases, and intermediate uveitis is the least frequent form of uveitis, about 10–15% of all cases [48].

5.3. Rare bilateral uveitis in SARS CoV2 pandemic

The SARS-CoV-2 virus is known as the severe acute respiratory syndrome coronavirus. In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak as pandemic. The virus would spread to the respiratory system of the same individual with the ocular system acting as a passage [50-52]. The SARS-CoV-2 may also constitute the risk factor for reactivation of the herpes family viruses [53]. Herpesviridae family uses latency as an escape or evasion mechanism for the host's immune system. The most common gate for human herpes viruses is the pharynx. After getting inside the human body, they use various mechanisms to spread. After the initial infection, herpes viruses remain in a latent state in different cells. They can be later reactivated in cases of immunodeficiency. This can occur because of many

reasons, like stress, malnutrition, immunosuppressive drugs, and infections by other pathological agents like viruses [50-52].

White dot syndromes are a group of inflammatorical chorioretinopathies in which the common defining clinical feature is the presence of multiple discrete white lesions located at deeper levels of the retina and choroid. Different white dot syndromes have different etiology, epidemiology, relevant history, test findings, assessment options, and the role of the ophthalmologists differs in managing patients with different white dot syndromes [54, 55]. Multiple evanescent white dot syndrome (MEWDS) is a rare posterior uveitis where numerous white dots can be seen in the posterior pole and midperiphery [56]. Symptoms of MEWDS include unilateral/bilateral blurred vision, visual field loss, photopsias, and floaters.

5.4.: Modern ophthalmic imaging - Imaging procedures used in patients with inflammatory diseases

5.4.1. Optical coherence tomography (OCT)

OCT has become the most important non-invasive diagnostic technique to evaluate ophthalmic pathologies including the macula with cross-sectional tissue imaging [57, 58]. Since the introduction of OCT in 1991, it has become an essential tool in ophthalmology [59]. It is a non-contact, painless method for detailing ocular structures with high resolution in vivo.

OCT uses light in the near-infrared spectral range (in the 800–840 nm wavelength range) and penetrates at a depth of several hundred microns in the tissue.

OCT provides real-time, non-invasive imaging of the retina. It can follow and reproduce quantitative and qualitative retinal thickness [60,61].

These images correlate well with retinal histology [62]. With OCT datasets-exact information can be given about the dynamics of disease progression and also about the response to treatment based on analyzing the retinal anatomy [63].

OCT is also suitable for detecting and monitoring uveitic ME and the changes in the fluid distribution in eyes with ME, as well as detecting the morphology of the vitreoretinal interface [64].

OCT is based on the principle of Michelson interferometry, where a low-coherence light beam is directed at the target tissue, and the scattered back-reflected light is combined with a second beam (reference beam). The resulting interference patterns are used to reconstruct an axial A-scan, which represents the beam's path. From all of the A-scans (time amplitude scan), a two-dimensional cross-sectional image of the target tissue can be reconstructed, called B-scan (brightness amplitude scan). These B-scans are repeated at multiple adjacent positions using a raster scan pattern, then a three-dimensional volume of structural and flow information can be structured [60,61]. The scanning beam allows acquisition of cross-sectional images of the tissue structure. The axial resolution and imaging range of the OCT are determined by the light source and the characteristics of detector rather than the focusing optics. [60,61].

OCT measures retinal thickness automatically. The distance between the vitreoretinal interface and the anterior surface of the retinal pigment epithelium is generally 200–275 μm , and the foveal depression has a range from 170 to 190 μm . The axial resolution is 3.9 $\mu\text{m}/\text{pixel}$, and the lateral resolution is 5.7 $\mu\text{m}/\text{pixel}$. Using several algorithms, cube scans also allow measurement of the volume of the macula [64, 65]. The image acquisition time is limited by the patient's ability to avoid eye movements and by the availability of tracking software that adjusts for eye movements.

Second-generation OCT is the spectral domain OCT (SD-OCT), based on the Fourier transformation principle. By eliminating the moving reference mirror, the number of A-scans increases significantly, which results in faster imaging and higher resolution. SD-OCTs axial resolution is 4-6 μm , while that of the first generation time-domain (TD-OCT) was 10 μm . The scanning speed of SD-OCT can exceed 100,000 A-scans per second. These systems operate at scanning rates of approximately 27,000–70,000 A-scans per second. As the A-scan density increases, resolution becomes higher, and SD-OCT produces better quality B-scans. Higher scanning speed reduces the effect of artifacts made by eye motion and produces images that provide a true picture of the retina [66]. The large, dense raster scans make it possible to obtain detailed surfaces of individual retina layers over large areas, resulting in segmentation maps [67, 68].

OCT imaging also has limitations. Since OCT utilizes light beams, media opacities can interfere with optimal imaging opposite to ultrasound's sound waves. Patient cooperation is necessary as eye and patient movement can diminish the image's quality.

Originally, OCT technology was used to image the posterior segment of the eye. This technique with its further development, became suitable for the examination of the ocular

surface and the anterior segment, too; such as the cornea, anterior chamber and iris. The lens, as well as measurement of the axial length of the eye can be examined by OCT, too. [69].

Currently, the most modern OCT devices are also based on Fourier domain OCT system, these are swept-source OCTs (SS-OCT). The light source used in SS-OCT is more complex compared to SD-OCT, but the detector is simpler. Deeper tissue is achieved by SS-OCT than SD-OCT due to the longer wavelength range penetration resulting in the detection of the vitreoretinal boundary surface and the chorioidea [70].

5.4.2. Ultra widefield fundus imaging (UWFI)

UWFI is becoming increasingly popular in ophthalmology [71] because it can produce up to 200-degree images [72]. More than 80% of the surface of the retina can be imaged, the peripheral retina can be photographed through small pupils [73] in cases where examination of the peripheral fundus may be limited due to pupil size. In addition to imaging, UWFI also provides valuable information about the peripheral vasculature and other changes in the retina that would be overlooked by traditional imaging systems [74]. The use of appropriate light filters allows fundus autofluorescence and angiographic imaging. UWFI can be used in the assessment of posterior uveitis, retinal vascular diseases with significant peripheral non-perfusion, and in patients with peripheral chorioretinal tumors. [75]. Color photographs of the anterior or posterior segment could describe lesion size, color, location, and morphologic characteristics. They are also utilized to evaluate the clinical progression or regression of the disease. In addition, the images have important role in establishing a baseline when a relapsing and remitting inflammatory process should be assessed (like the presence of new posterior synechiae in anterior uveitis) or capturing the inflammation of the transitory posterior segment that is characteristic of different types of uveitis. [74].

5.4.3. Ultra widefield fundus autofluorescence (FAF)

FAF imaging is another noninvasive imaging technique for analyzing the posterior segment of the eye. This method maps the fluorescent property of lipofuscin, a breakdown product of retinal proteins within the retinal pigment epithelium (RPE) [76, 77]. Hyperautofluorescence shows the increased metabolic activity of the RPE due to the loss of

photoreceptors, and hypoautofluorescence occurs with loss or blockage of RPE cells [76, 77]. This method is also useful in posterior uveitis that involves the outer retina, RPE, and inner choroid [76,77]. In many cases, hyperautofluorescence occurs with increased disease activity in posterior uveitis and fades and darkens as the inflammation subsides. [76].

5.4.4. Ultra widefield fundus fluorescein angiography (FLAG)

FLAG is an essential imaging modality for evaluating eyes with chorioretinal disease and structural complications caused by posterior uveitis. After injecting fluorescein dye intravenously, a series of filtered posterior segment images provides a functional and structural view of retinal (and choroidal) vasculature and anatomy.

Macular edema, retinal vasculitis, secondary choroidal or retinal neovascularization, edema and inflammation of the optic nerve, as well as retinal and choroidal inflammation can be detected by FLAG. Several retinochoroidopathies and white dot syndromes have characteristic appearances on FLAG. Wide and ultra-wide-field FLAG can identify retinal vascular pathology that can not be noted by clinical examination. [78].

6. Patients and methods

6.1 Patients

6.1.1. Scleritis patients

We analyzed retrospectively the data of patients with scleritis at the University of Szeged in the Department of Ophthalmology between January 1, 2017 and December 31, 2021. Twenty-seven eyes of 24 patients (7 males and 17 females) were included in this study, who were diagnosed with non-infectious scleritis. The mean age of the patients was 57.75 years (range: from 30 to 77 years).

Scleritis was diagnosed by the presence of the following parameters: (1) acute or subacute symptom onset; (2) eye pain with or without decreased visual acuity; (3) posterior sclerochoroidal wall thickening. Scleritis was classified as diffuse, nodular, or necrotizing. The location of inflammation was also recorded.

6.1.2. Juvenile uveitic patients

We analyzed retrospectively the data of children with uveitis at the University of Szeged in the Department of Ophthalmology between January 1, 2017 and May 31, 2021. Childhood uveitis of non-infectious origin was also analyzed in those cases when adalimumab therapy was immediately started with the indication of the uveitis. We did not select those patients for the study whose indication for treatment was their underlying systemic disease.

In this period, we treated 46 children in our uveitis center. Their average age at the diagnosis of uveitis was 11 (3–18) years. Their gender distribution was the same (23 girls, 23 boys).

We initiated for 11 of the 46 children (23.9%) adalimumab therapy for uveitis. The average age of patients at the start of adalimumab treatment was 10 (4–13) years. Three boys (27%) and eight girls (73%) were treated with adalimumab.

6.1.3. Adult uveitic patients

In our study, we examined retrospectively the data of adult non-infectious uveitic patients treated with adalimumab at our Department between January 2017 and December 2021. Those patients were included who received adalimumab, that was given with the indication of non-infectious uveitis, and the patients received the medication at least for 3 months.

The average age was 51 years, the youngest patient was 20 years old and the oldest one was 80 years old at the beginning of therapy.

6.1.4. MEWDS patient

A 47-year-old female patient was examined in our department because of bilateral photophobia and blurred vision in both eyes and decreased vision in her left eye. She visited our department in November 2020, that was the peak year of Covid.

6.2 Methods

6.2.1 Ophthalmologic examinations

Patients with scleritis, as well as adult and pediatric uveitic patients underwent standard ophthalmic examinations including visual acuity test (using Kettesy's decimal visual chart or early treatment of diabetic retinopathy study (ETDRS) visual chart), intraocular pressure with applanation tonometer or non-contact tonometer (iCare), slit-lamp biomicroscopic examination of the anterior segment of the eye using Haag-Streit (Liebefeld-Bern, Switzerland) slit-lamp, and fundus ophthalmoscopic examination with 90 or 78 D ocular lenses (060123, Bellevue,

WA,USA). Examination before the authorization of biological therapy was carried out as specified in the prescription [79].

6.2.2 OCT

OCT examinations were taken by SD-OCT Spectralis OCT system (Heidelberg Engineering, Heidelberg, Germany, Software version: Heidelberg Eye Explorer 1.9.13.0). OCT scan parameters were as follows: infrared scan; pattern size: $20^{\circ} \times 20^{\circ}$; 25 sections; 240 μm between B-scans; 512 A-scans. OCT examination was performed in all of the cases at the time of their check-in at our uveitis outpatient clinic. For standardization, all examinations were performed by the same technician. The thickness of the retina was measured between the inner limiting membrane and Bruch's membrane in the central macular region.

6.2.3 UWFI

UWF images (colour and FAF) were taken by Optos, California (Optos, Marlborough, MA, USA Software version: Window Server 2008 (R 3.1-4.1) or Windows 7 SP 64-bit) by the same technician.

The Optomap obtained with the patients' eyes in the primary position, were acquired at the same visit. The instrument is able to obtain wide-field images of approximately 180–200 degrees.

6.3 Ethics

Our studies were conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Human Investigation Review Board at the University of Szeged, Albert Szent-Györgyi Clinical Center (protocol code 4693 and date of approval 20/Jan/2020).

7. Results

7.1 Scleritis patients

The mean age of the patients was 57.75 years (range: from 30 to 77 years) The demographic and clinical data of the 24 patients are shown in Table 1. Bilateral disease was found at three patients. Thirteen patients (54%) had associated systemic disease: rheumatoid arthritis (n = 5); granulomatosis with polyangiitis, formerly known as Wegener granulomatosis (n = 1); ulcerative colitis (n = 1); collagenosis (n = 1); dermatopolymyositis (n = 1); pemphigoid (n = 1); non-differentiated collagenosis (NDC) syndrome (n = 1); ankylosing spondylitis (n = 1); and Cogan syndrome (n = 1). Twenty-four anterior and three posterior scleritis was diagnosed at the patients in our Department. Among the twenty-four eyes diagnosed with anterior scleritis, there were 16 with diffuse scleritis and 8 with nodular anterior scleritis. One patient had peripheral ulcerative keratitis, one had retinal detachment, and one had hydro-keratopathy.

Age (years)	30-77	
Mean age (years)	57.75	
Gender	7 male: 17 female	
Laterity	21 unilateral: 3 bilateral	
Background of scleritis		
	rheumatoid arthritis	5
	Wegener granulomatosis	1
	ulcerative colitis	1
	collagenosis	1
	dermatopolymyositis	1
	pemphigoid	1
	non-differentiated collagenosis	1
	ankylosing spondylitis	1
	Cogan-syndrome	1
	unknown etiology	11

Table 1.: Demographic and clinical data of our scleritis patients

Figure 2 shows the picture of cystoid macular edema (CME) in one of the scleritic patients. Fluid-filled cyst-like spaces can be seen between outer plexiform and inner nuclear layer of the retina.

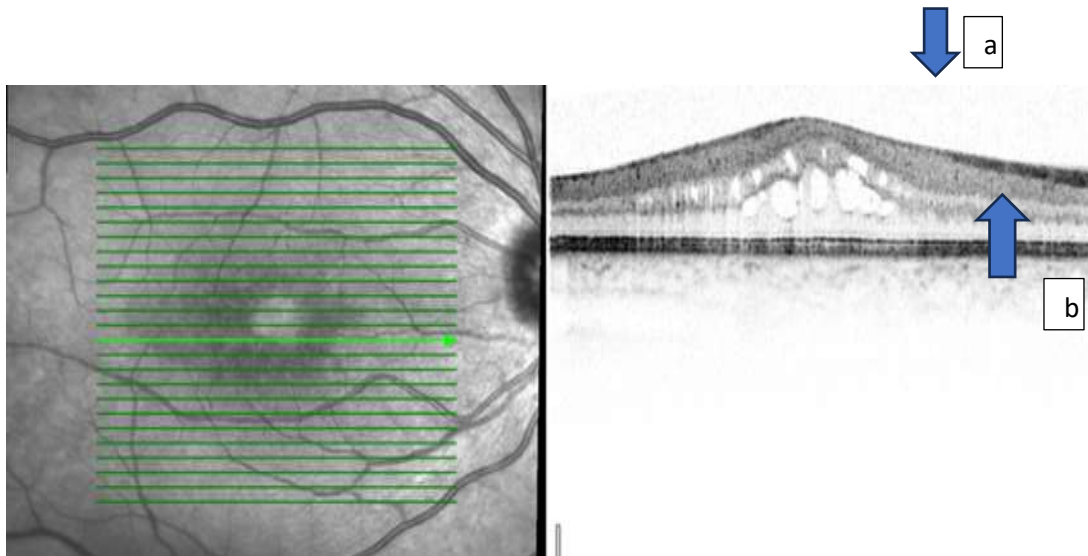


Figure 2. OCT image of the right eye of a 30-year-old woman showing CME a) loss of the foveal depression and b) intra-retinal cysts in the outer and inner nuclear layer of the retina. OCT scale: 512*496, high speed mode, 20°

Figure 3 demonstrates diffuse macular edema (DME) where we can see disturbance of the retinal structure and low reflective areas looking similar to sponge.

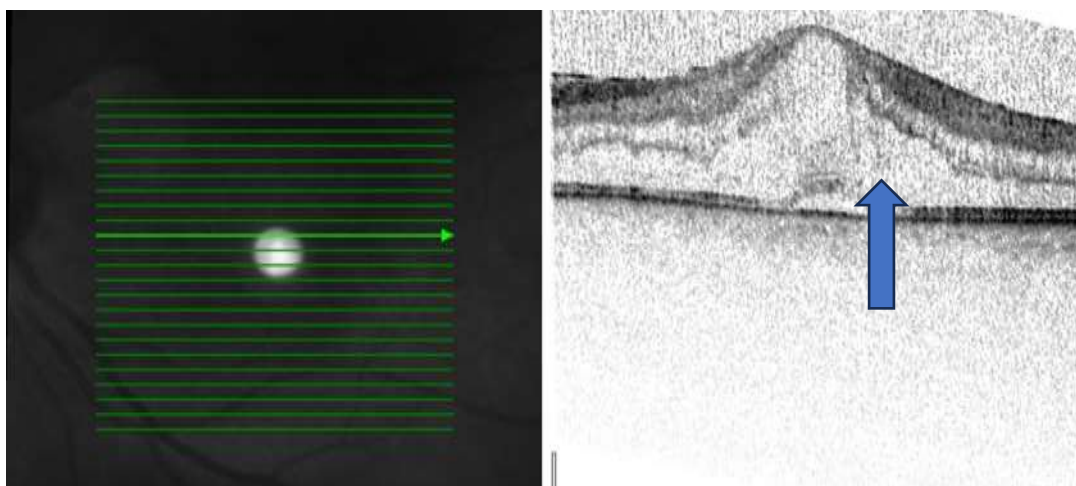


Figure 3. OCT image of a 57 year-old female patient DME (by the arrow) is characterized by the disturbance of the layered retinal structure or low reflective areas looking like a sponge. The complication of corticosteroid therapy is the cataract formation- that can explain the quality of the image. OCT scale: 512*496, high speed mode 20°

Figure 4 demonstrates a picture of a scleritic patient with serous detachment (SRD). where we can see fluid accumulation in the subretinal space between the sensory retina and the retinal pigment epithelium.

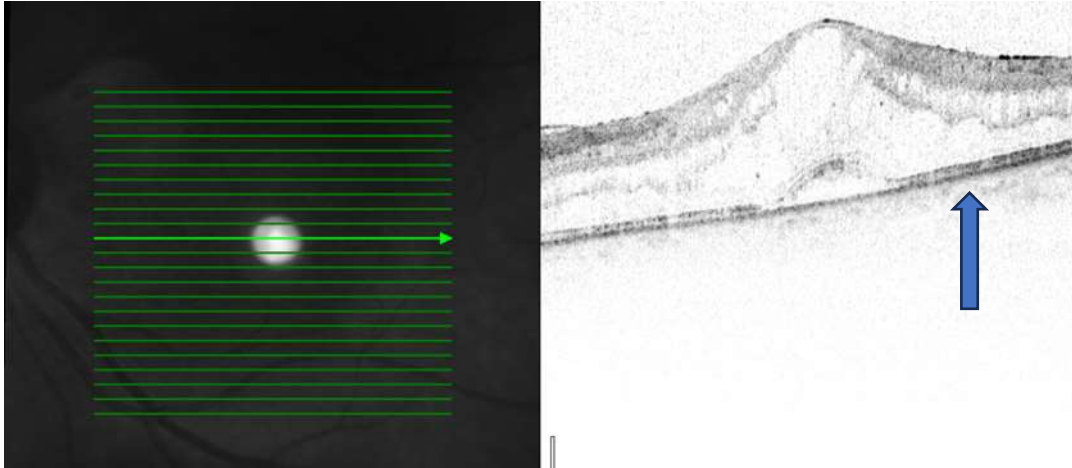


Figure 4. OCT image of SRD of a scleritic 54 year-old female patient fluid accumulates in the subretinal space between the sensory retina and the retinal pigment epithelium. OCT scale:512*496, high speed mode,20°

Figure 5. presents an OCT image of ERM showing as a hyperreflective line adhering to the retina. This complication is commonly seen in recurrent uveitis or in other ocular inflammation.

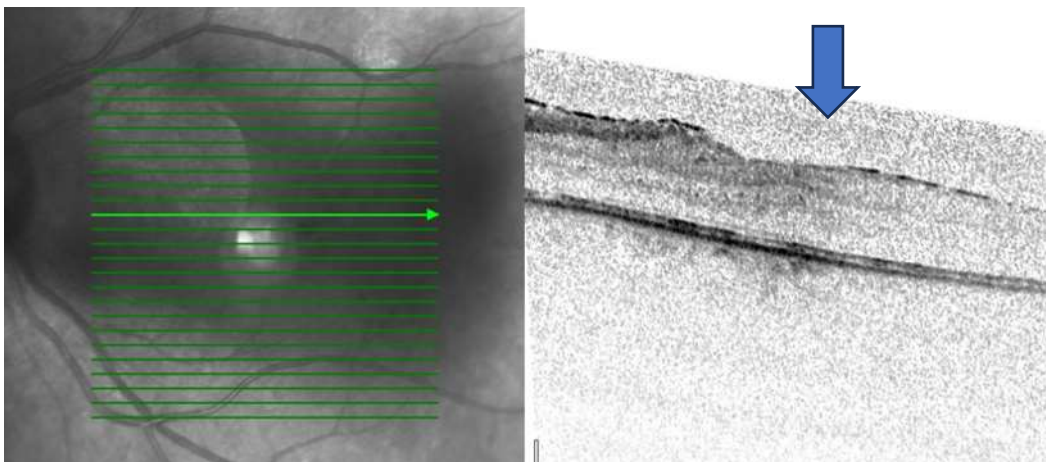


Figure 5. OCT image of a 42-year-old male patient, a reflective layer on the top of the internal limiting membrane, the ERM is attached to the retinal surface on the left eye. OCT scale:512*496, high speed mode,20°

OCT findings	Number of Patients (% of total no = 24)	CRT (um)	VA (ETDRS)
cystoid macular edema	3 (12%)	558	22 + 30
diffuse macular edema	1 (4%)	328	19 + 30
serous retinal detachment	1 (4%)	288	33 + 30
epiretinal membrane	3 (12%)	402	45 + 30

Table 2. OCT findings in scleritis patients treated at our Department

Table 2. shows the OCT findings of the scleritis patients. The overall mean VA of all of our scleritic patients was 28 + 30 letters with correction, and the mean CRT at the central fovea was 291.7 μ m.

The mean VA was 22 + 30 letters, 19 + 30 letters, and 33 + 30 letters in patients with CME, DME, and SRD, respectively.

The mean CRT was 558 μ m, 328 μ m, and 288 μ m in our patients with CME, DME, and SD, respectively. CRT was the thickest in cases of CME and thinnest in the case of SRD. The macular thickness, as seen on OCT, is objective and correlates with BCVA.

The patients with CME were treated with triamcinolone (TA) injection sub-tenonally when topical non-steroid eye drops were ineffective.

OCT examinations showed ERM in three patients (12%). None of our patients with ERM needed vitrectomy surgery so far due to the close OCT follow-up.

7.2 Pediatric uveitic patients

The average age of the children with uveitis at the beginning of adalimumab therapy was 10 (4–13) years. In this period, we treated 46 children in our uveitis center. Table 3 demonstrates the clinical data of the uveitic children that received adalimumab.

	Gender	Etiology	Localization	Age	Treatment before adalimumab	RE before Th	LE before Th	RE after Th	LE after Th
1.	girl	pJIA	AU	10	Maxidex,Ciclo,NSAID,MTX	1.0	1.0	1.0	1.0
2.	girl	JIA	AU	4	Medrol,MTX	1.0	1.0	1.0	1.0
3.	girl	pJIA	AU	6	Maxidex,MTX	1.0	1.0	1.0	1.0
4.	girl	JIA	AU	9	Maxidex,Ciclo,Medrol,Sc Dexam,MTX	0.6	0.8	1.0	1.0
5.	girl	JIA	Panuveitis	11	Maxidex,Ciclo,Medrol,Sc Dexam,MTX	0.7	0.6	1.0	1.0
6.	boy	JIA	Panuveitis	7	Maxidex,MTX	0.6	0.06	1.0	1.0
7.	boy	JIA	AU	12	Maxidex,Ciclo,Medrol,Sc Dexam,MTX	1.0	1.0	1.0	1.0
8.	girl	JIA	Panuveitis	13	Medrol, MTX,ST Kenalog	0.01	1.0	1.0	1.0
9.	boy	JIA	Panuveitis	12	Maxidex,Medrol,MTX,Sandimmun	0.3	0.7	0.6	0.6
10.	girl	idiopathic	Panuveitis	10	Medrol,MTX,ST Kenalog	0.6	1.0	1.0	1.0
11.	girl	JIA	AU	9	Maxidex,Medrol,MTX	1.0	1.0	1.0	1.0

Table 3. The gender, etiology, localisation, age, treatment and visual acuity of uveitic children before and after the adalimumab therapy

Based on the localization of the inflammation, the anterior uveitis was the most common (36.9%, 17/46), followed by the posterior uveitis (26%, 12/46), panuveitis (21%, 10/46), and finally the intermediate form (15%, 7/46) of uveitis. Most of our patients (45.6%, 21/46) had JIA background; 1 child (2%, 1/46) suffered from acute myeloid leukemia; uveitis was associated with systemic scleroderma in 1 child (2%, 1/46); and HLA-B27-associated arthritis was found also in 1 child (2%, 1/46). In 14 patients (30%, 14/46). The triggering factor was infection in 14 patients (30 %, 14/46). There were no autoimmune disease or infection proven in 30% (17/46) of our patients. The treatment of children with adalimumab was proved by the Ministry of Human Resources (EMMI) [79]. Therapy is performed according to the protocols. On the basis of the protocol, we initiated for 11 of the 46 children (23.9%) adalimumab therapy to treat their uveitis. Before starting the treatment with adalimumab (according to the protocol), all patients received systemic steroid treatment. It was followed by disease-modifying antirheumatic drugs (DMARD), since various complications resulting from uveitis had already appeared at couple of children in this group: in 2 children (18%) "band" keratopathy, in 2 patients (18%) secondary glaucoma that was controlled with eye drops, in 2 cases (18%) cataract, and in 2 children (18%) cystoid macular edema (CME) (Figure 6). Unfortunately one

child was diagnosed with Hodgkin's lymphoma during his treatment, hence his adalimumab therapy was immediately stopped. The 10 patients who are currently being treated with adalimumab, also receive methotrexate therapy as stated in the protocol. [79].

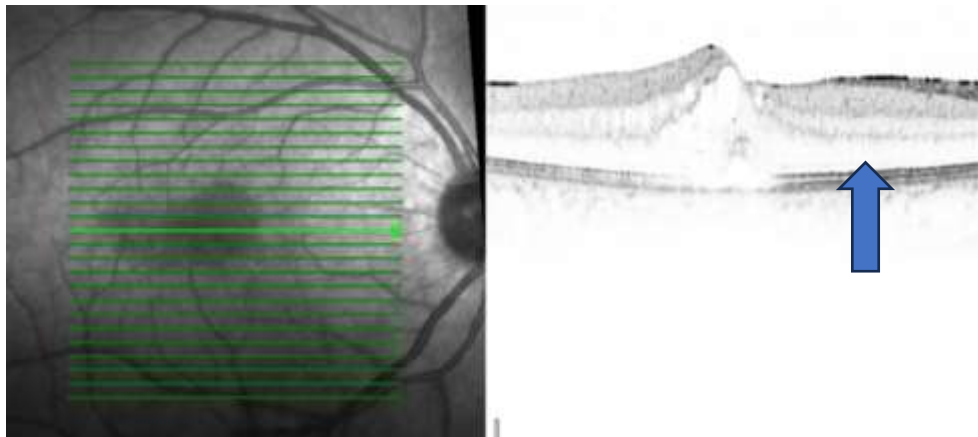


Figure 6. OCT picture of CME of an 11-year-old girl's right eye at the start of the treatment. OCT scale: 512*496, high speed mode, 20°

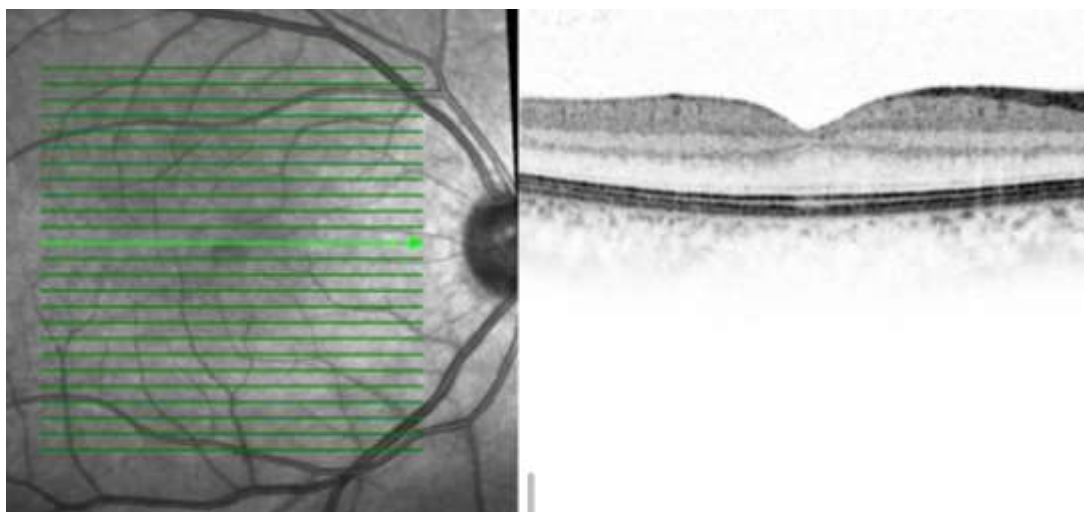


Figure 6. b. OCT picture of of an 11-year-old girl's right eye after a month of adalimumab treatment. It can be seen that the edema disappeared. OCT scale: 512*496, high speed mode, 20°the edema disappeared

The uveitis activity showed significant improvement while the patients were continuously treated with adalimumab, or the inflammation completely disappeared. Another advantage of the adalimumab therapy was that no additional local therapy was necessary against the vision-threatening macular complications.

The average change in visual acuity (VA) of the 11 children is presented on Figure 7. The average of the best corrected VA at the start of the adalimumab treatment on the right eye was 0.71, and on the left eye it was 0.83. This value improved to 0.96 in both eyes by the end of the follow-up period.

Within a month after starting treatment, we found complete remission in all 10 patients. No transient, local skin reaction occurred. Since a pediatric oncologist diagnosed classical Hodgkin's lymphoma in one child after 14 months of the start of adalimumab therapy, his treatment was immediately stopped.

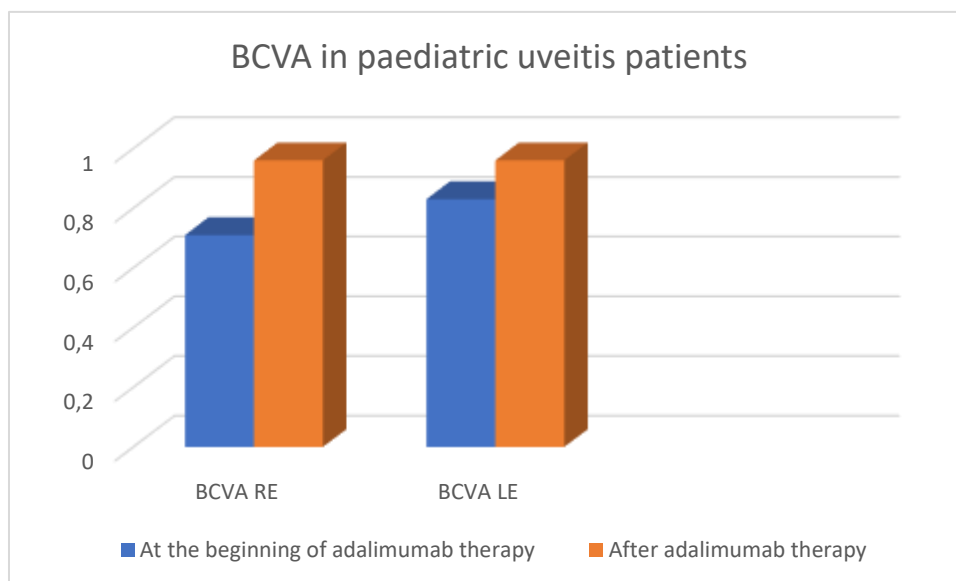


Figure 7. The average change in visual acuity applying adalimumab therapy

7.3 Adult uveitic patients

We examined the data of those patients who received adalimumab, which was given with the indication of non-infectious uveitis, and those patients got the adalimumab at least for 3 months. Eighteen people (12 women, 6 men) met our criteria. The data of these patients are summerized in Table 4.

Age (years)	20- 80	
Mean age (years)	51	
Gender	6 male:12 female	
Laterity	6 unilateral:12 bilateral	
Anatomical localization	intermediate	7
	posterior	3
	panuveitis	8
Background of uveitis	rheumatoid arthritis	1
	seronegative spondylarthritis	1
	juvenile idiopathic arthritis	1
	ANA positive discoid lupus erythematosus	1
	serpiginous chorioretinopathy	1
	idiopathic	13

Table 4. Demographic and clinical data of our adult non-infectious uveitic patients treated with adalimumab

The average age was 51 years, the youngest patient was 20 years old, and the oldest one was 80 years old at the beginning of the therapy.

In terms of anatomical localization, the uveitis was intermediate in 7 (39%) patients, and in 3 (17%) and 8 (44%) cases posterior uveitis and panuveitis was detected, respectively.

Unilateral uveitis was found in 6 of 18 patients (33%), (right sided in 2 cases; left sided in 4 cases), and the uveitis was bilateral in 12 (67%) cases.

After the anamnesis, laboratory tests and imaging procedures, inflammatory origin of the uveitis was determined in 5 (28%) patients. Rheumatoid arthritis, seronegative spondyloarthritis, juvenile idiopathic arthritis (JIA), ANA positive discoid lupus erythematosus, and serpiginous chorioretinopathy was confirmed in 1-1 case. The etiology of the disease remained unknown in the remaining 13 (72%) patients, these uveitic cases were idiopathic.

The first-line treatment for non-infectious uveitis is corticosteroid, most of the patients received parabolbar and/or subtenon corticosteroid injections. Fourteen (77%) patients received corticosteroid systemically. The oral steroid therapy caused side effects in 6 out of the 14 patients blood pressure fluctuation and blood sugar imbalance developed in 4 people, and 2 patients had increased intraocular pressure.

Immunomodulant therapy is the second step in the uveitic patients' treatment when the first corticosteroid therapy failed or there was no respond to that treatment at all. Six (33%) patients received systemic immunosuppressive treatment prior to adalimumab therapy, this was most often cyclosporin and/or methotrexate. In one person, the immunosuppressive drugs caused side effects: azathioprine caused fever and limb pain, and cyclosporin led to deterioration of kidney function.

The last step in the treatment of uveitis is the biological therapy. Side effects occurred in 5 (28%) patients during adalimumab therapy in the follow-up period:

- a) Paradoxical psoriasis developed in 2 cases. The treatment with adalimumab was suspended for this reason in one of them. As soon as her skin symptoms were resolved and uveitis recurred, the therapy was restarted. The adalimumab could not started at the other person who had psoriasis until the end of the follow-up period since her skin problems remained.
- b) In one person, fever occurred several times during the adalimumab therapy, so the treatment was abolished.
- c) Red, non-itchy spots appeared all over the body of one patient, especially her upper body was associated with a burning sensation. The exact etiology of this skin symptom remained unknown. The symptoms were resolved with dermatological treatment without the need to stop adalimumab therapy.
- d) Another patient reported local erythema at the subcutaneous injection site. The redness and swelling disappeared within 4-5 days after administration with persistant adalimumab therapy.

The proportion of active uveitis decreased significantly using adalimumab.

We examined the proportion of the 18 patients who received local and/or systemic treatment for uveitis when starting and stopping adalimumab.

We compared the incidence one of the most common complications of uveitis, the cystoid macular edema (CME) at the beginning and the end of the follow-up period.

At the start of our study, we detected CME in a total of 16 (8 right, 8 left) eyes. At the end of the follow-up period, 4 eyes (1 right, 3 left) were affected by CME.

Figure 8 shows the changes of the best corrected visual acuity values at the start and at the end of the follow up of adalimumab therapy

At the beginning of our study, the average best corrected visual acuity (BCVA) of the right eye was 0.63, and the left eye was 0.67. Average VA measured at the end of the follow-up period became less in both eyes, 0.55 in the right eye and 0.63 in the left eye. Despite the adalimumab therapy, the VA decreased in 3 eyes because of band keratopathy, in 4 cases because of cataract, and in 2 eyes irreversible damage of the macula was responsible for the decrease.

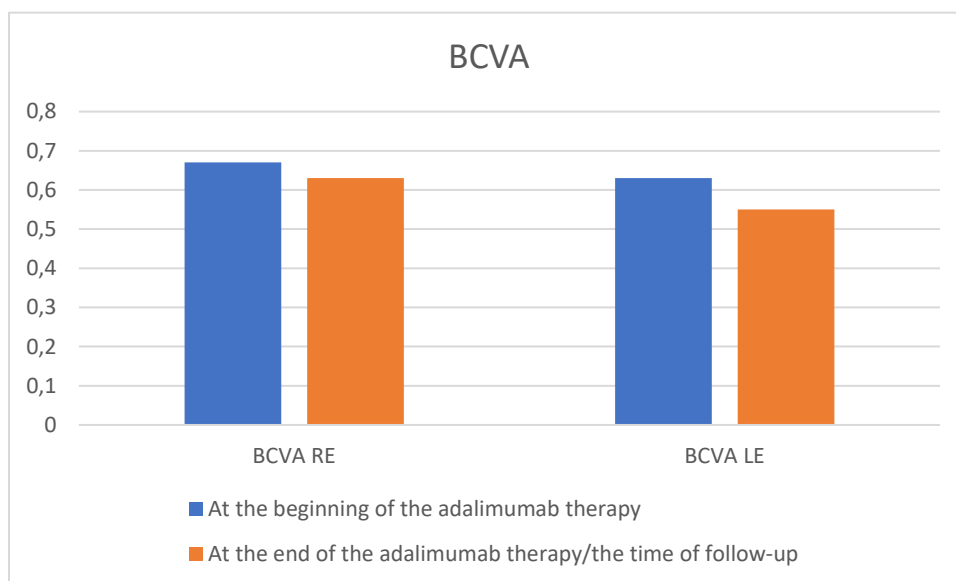


Figure 8. Illustration of the average change in visual acuity. with adalimumab therapy

7.4. MEWDS patient

One patient was diagnosed with MEWDS during SARS-CoV-2 at our Department.

We examined a 47-years-old female patient with bilateral photophobia and blurred vision in both eyes in November 2020. She had negative test for the SARS-Co-V-2 infection a week before admission to our department, but she was positive 21 days before her ocular signs appeared. At that time she presented chills and fever with a temperature of 40.0°C, associated with complete loss of taste.

The ocular anamnesis excluded previous episodes of uveitis, ophthalmic, and systemic infections, or autoimmune diseases. Her ophthalmological history proved that she has had annual check-ups for hypermetropy of +3.5 dioptries (D) in her right and +4.5 D in her left eye without any remarkable ocular pathology. At her appearance after SARS CoV illness, the vision was decreased in her left eye.

According to the patient, her vision got worse gradually and progressively. BCVA of the right eye was 1.0 with +3.5 D and blurred vision; BCVA of the left eye was 0.2 with +4.5 D correction. Intraocular pressure was in normal range, slit lamp examination did not show any alterations of the anterior segments of both sides, and no cells were seen in the anterior chamber. Fundusoscopic examinations with dilated pupils showed mild vitritis on both sides probably because of the “spilled over” cells from the anterior chamber. The optic disc was normal on both sides, and no swelling was detected. Multifocal, flat, and grayish-white placoid lesions in the retinal pigment epithelium (RPE) level of the retina on both sides were revealed. In addition, the macular region was also involved on the left side.

Figure 9. shows inflammatory lesions in the level of the outer retina. The disruption of the ellipsoid zone could be seen and that could make the foveal area granular. Furthermore, OCT image showed swelling of the outer retinal layers and granules at the level of RPE. Discontinuities in inner segment - outer segment junction and mild attenuation of external limiting membrane have been reported in acute phase. Recurrent episodes may result in the thinning of the outer nuclear layer.

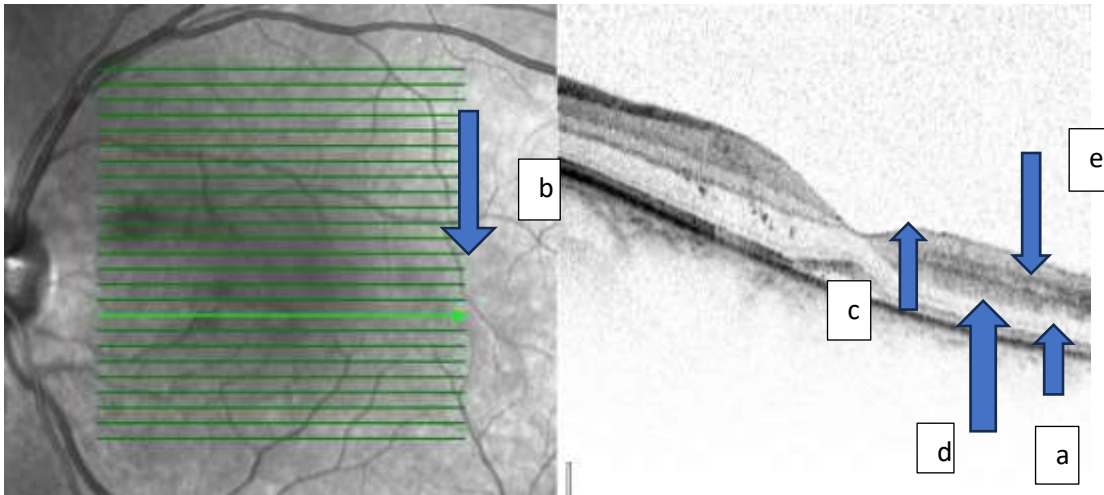


Figure 9. OCT picture of our 47 year-old female patient's left eye: a) the disruption of the ellipsoid zone b) the granular foveal area, c) the swelling of the outer retinal layers d) granules at the level of RPE and e) subretinal serosity

On the FLAG picture early and late hyperfluorescence of the white spots could be seen. In addition, diffuse and patchy late stainings were detected at the level of RPE and retina. The wreath-like hyperfluorescence corresponded to the dots and could be seen clinically. After resolutions of the acute lesions, window defects could be noted, corresponding to the clinical granularity seen there. No vasculitis could be detected. We performed Optos FLAG in order to get more information about the periphery of the eyes. The initial autofluorescence images showed hyperautofluorescence corresponding to the white dots (Figure 10).



Figure 10. UWFI, FAF picture of the right eye of our 47 year old female patient: the white dots appear as hyperautofluorescent dots.

In the recovery phase, the areas of hyperautofluorescence became less and smaller as seen on Figure 11.

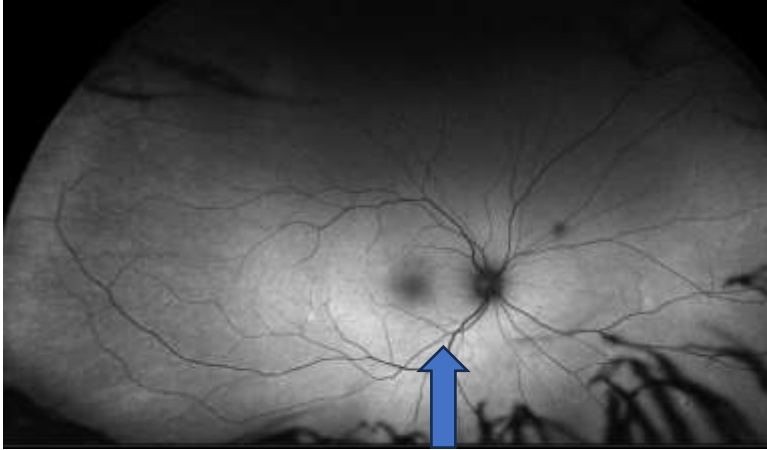


Figure 11. UWFI, FAF picture of the right eye: the white dots disappeared

We suspected infectious (viral) and immune-related origin complicated by macular involvement. Hence, the patient underwent haematological and serological examinations for uveitis.

The local therapy started according to the European Reference Network's recommendations for patients with uveitis during the COVID-19 pandemic. The European Reference Networks are virtual networks connecting healthcare professionals around Europe with expertise in rare diseases, which allows them to discuss patient's diagnosis and care. Our patient received corticosteroid injection (1 mg, dexamethasone, ratiopharm) into the orbital floor of both sides every other day, and corticosteroid drops five times a day. In order to prevent severe ciliary spasm and synechiae formation, dilatation of the pupil was initiated (cycloplegic eye drops 5 times a day). In addition, we gave her acyclovir orally (5×800 mg/day) as her test was positive for acute herpes simplex infection.

The clinical symptoms regressed completely in 4 weeks and at the 1-month follow-up visit, the whitish inflammatory dots regressed but did not disappear totally. The macular involvement on the left eye resolved. The VA of the patient returned to 1.0 with hyperopic spherical correction. The laboratory data excluded antinuclear antigen-associated uveitis, HLA-

B27 positivity, lupus anti-coagulant (LAC), toxoplasma, cytomegalovirus, Borellia, Toxocara, and Epstein-Barr antibodies-associated uveitis. We examined the patient after COVID infection, the lab values were taken at her first visit at the Department of Ophthalmology. The herpes simplex IgM and IgG levels were elevated.

The patient had elevated IgG for SARS-CoV-2 from the nasopharyngeal swab using reverse transcription polymerase chain reaction (RT-PCR) and the past infection of the SARS-CoV-2 virus was confirmed.

8. Discussion

8.1. Examination of scleritic patients

Although scleritis is a rare disease characterized by inflammation of the sclera and adjacent ocular structures, its complications are vision-threatening. Studies have led to significant progress in understanding the epidemiology, immunopathogenesis, severity assessment, treatment, and prognosis of this potentially sight-threatening disease [3]. The reason why the sclera is susceptible to inflammatory reaction is that the vasculature around the sclera consist of end arteries both on the superficial, both on the deeper part of the arteries. [14].

OCT is suitable for detecting and monitoring inflammatory macular edema, the changes in fluid distribution in these cases, and the morphology of the vitreoretinal interface [57].

Using OCT, we could find the adequate diagnosis leading to the best, complex treatment and follow-up of the disease. OCT can give more information about the depth of the inflammation and the prediction of visual outcomes than previous examinations such as ultrasound, for example.

The thickness of the retina and macula measured by OCT is a potential indicator of retinal inflammation. Four studies used OCT to measure retinal/macular thickness and compared it with the presence of retinal vasculitis. Their results suggest that increased retinal/macular thickness correlates with retinal vasculitis [80]. There is no report in the literature about using OCT to detect any macular entity in cases of scleritic patients.

The most common and vision-decreasing complication of inflammation is ME, which can persist or recur despite improvement or resolution of the ocular inflammation. ME always appears as retinal thickening with intraretinal cavities of reduced reflectivity on OCT [81]. CME represents a common pathologic change in the retina and occurs in a variety of pathological conditions, such as intraocular inflammation. In pars planitis, there is an accumulation of T-cell inflammatory mediators associated with CME. ME may appear in central or branch retinal vein occlusion, diabetic retinopathy, and most commonly following cataract extraction (Irvin–Gass syndrome) [57, 58]. Diffuse macular edema is the main pattern in diabetic macular edema.

SRD, with the elevation of the retina, occur in a variety of disorders, including central serous chorioretinopathy (CSC), age-related macular degeneration (AMD), systemic lupus erythematosus (SLE), and choroidal ischemic disorders, such as accelerated hypertension, pre-eclampsia, eclampsia, systemic corticosteroid usage, or in some choroidal tumors and inflammatory disorders, for example, in Vogt–Koyanagi–Harada’s disease [57].

On OCT images, ERM appears as a hyperreflective line adhering to the retina. In recent studies, secondary ERMs were associated with worse VA in comparison to idiopathic ERM. This complication is commonly seen in recurrent uveitis or other ocular inflammation [82]. Its therapy is epiretinal membrane peeling with a pars plana vitrectomy procedure [83].

Kempen and coworkers described the use of OCT in patients with uveitis and tried to detect early ME [64]. Markomichelakis et al. defined uveitic ME and noted three different patterns of fluid accumulation that were the same as in diabetic ME: diffuse macular edema (DME), cystoid macular edema (CME), and serous retinal detachment (SRD) [84, 85].

Iannetti et al. also reported OCT findings in patients with ME from uveitis—58% had CME, and 42% had DME. SRD was noted in 28% of all cases [82].

Comparing the OCT data of our scleritis series with Kempen et al. and with Iannetti et al., we diagnosed three patients with CME (12%), one patient (4%) with DME, and one patient (4%) with SRD among all scleritic patients. CME and DME lead to reduced VA, which can affect patients’ quality of life. The vision was 22 + 30 in the case of CME and 19 + 31 in DME. The central retina thickness was the thickest in cases of CME and the least thick in cases of SRD.

The visual impact of ERM in eyes with inflammation is not clear. The presence of ERM in the macular area suggests the hypothesis of tractional mechanism as an origin or cofactor of appearing macular edema during inflammatory diseases. ERM can be independent of the type of macular edema and the type of inflammation [83, 86]. It is known that in most eyes with inflammatory ERM, VA remains stable if intraocular inflammation and co-morbidities are treated appropriately [82]. ERM occurs in approximately 6% of patients over the age of 60 [82]. Although none of the patients was older than 60 years in our study, OCT examinations showed ERM in three patients (12%), and their vision remained stable at 45 + 30. ERMs can be classified as idiopathic or secondary in an already-existing ocular pathology. Most idiopathic ERMs are thought to result from fibroglial proliferation on the inner surface of the retina secondary to a break in ILM during posterior vitreous detachment. Glial cells, retinal pigment

epithelium (RPE) cells, and myofibroblasts are shown to be mostly involved in ERM formation [82].

Inflammatorical conditions that involve the sclera could damage the outer BRB, and despite the healthy retinal capillary endothelium, macular edema might occur. Other causes may also increase the macular thickness, such as inflammatorical ERM formation with associated vitreomacular traction [81].

We can state that OCT findings help ophthalmologists determine visual outcomes. ME and ERM can cause worsening of vision, but visual improvement can be achieved by systemic and additional ophthalmologic therapy.

CME, SRD, DME, and ERM negatively affect VA. Especially in chronic scleritis cases, ME and ERM could work as biomarkers since they provide an objective, measurable method of evaluating the disease process. Some biomarkers can help researchers to identify the risk factors of the disease. In long-standing (chronic or persistent) or frequently recurrent pathologies, VA will not improve despite the best therapy because of the injury of the photoreceptors. The limitation of our study is the low number of patients, as the prevalence of scleritis is six cases per 10,000 people.

To the best of our knowledge, this is the first report that investigates macula in anterior scleritic patients. We detected OCT examinations of all of our patients since we thought that OCT would be a suitable, non-invasive method to detect macular pathology, and our results proved that it was.

As a result of our study we can say that the reduced VA in cases of scleritis patients could be the consequence of macular involvement. Besides treating scleritis patients, the examination of their macula by OCT is also very important in order to detect any macular complications caused by inflammation since CME is the leading cause of decreased vision. OCT maybe performed routinely in scleritis patients to detect and monitor structural changes in the macula. ERM is also associated with poor vision. Macular pathologies seen on OCT could modify the management of scleritis. OCT plays an important role in measuring inflammatorical activity, determining the severity of inflammation, choosing the best treatment, the response to treatment, and avoiding legal blindness. Biomarkers on OCT pictures in scleritic patients, such as CME, DME, SRD, and ERM, are also very useful in order to find the right diagnosis and treatment on time.

There is no report in the literature about using OCT to detect any macular entity in cases of scleritic patients.

8.2 Examination of uveitic patients

Uveitis can develop in all age groups and it is one of the leading causes of preventable blindness in the world [45]. It frequently takes a chronic course and presents bilaterally with recurrent inflammation. Its etiology is mostly idiopathic, in children, it is commonly associated with systemic disease entities such as JIA [38]. Both diagnosis and therapy of uveitis can be significantly challenging for the ophthalmologists, since children often do not or cannot formulate their complaints precisely. For this reason, severe ophthalmic complications are often detected at patients' first ophthalmological examination [87].

Treatment for uveitis is based on a stepladder approach, which include topical and systemic corticosteroids, immunosuppressants, and newly emerging biologic agents. Biologic therapies such as adalimumab particularly have revolutionized the treatment of severe or sight-threatening uveitis

Within a month after starting the adalimumab treatment, we found complete remission in all 10 pediatric patients. In adults, 4 patient (22%) still had posterior uveitis, and 14 patients (78%) were in remission during the follow-up period.

The significance of the TNF inhibitor adalimumab therapy is that it reduces the need for additional local or systemic corticosteroids during treatment. This is particularly important in children. In our pediatric patients, no additional corticosteroid therapy was needed. However, TNF-alpha inhibitors may also result in a drug-induced lupus-like syndrome (that can also generate ophthalmic disorders). In our Department one child was diagnosed with Hodgkin's lymphoma. His adalimumab therapy was immediately stopped. No transient, local skin or other reaction occurred.

Side effects occurred in 5 (28%) patients during adalimumab therapy in the follow-up period in adults. In case of 2 patients, paradoxical psoriasis developed. Fever occurred several times during the use of the therapy in one patient, hence the therapy was stopped. In another patient red, non-itchy spots appeared all over her body, but mainly on the upper body that was

associated with a burning sensation. The spots disappeared in a few days without therapy. One patient reported local erythema at the subcutaneous injection site, but redness and swelling disappeared.

The use of biologics has greatly improved the outcome of non-infectious uveitis.

The ultimate goals of treatment of uveitis were to preserve vision, prevent secondary complications and avoid side effects of local and systemic therapies. However, despite the most modern therapeutic options, childhood uveitis is often accompanied by serious ophthalmological complications and residual symptoms. This is partly caused by the inflammation itself, and partly by the side effects of various local and systemic drugs. The optimal time to start the therapy and the exact duration of the treatment have not yet been fully clarified, hence further investigations are necessary.[88].

Suhler and coworkers reported a clinical response to adalimumab in 68% of treated patients (21 of 31) after 10 weeks of treatment and a durable response in 39% at 50 weeks [89]. That is the time when we have to follow-up closely the patients to avoid deterioration.

In our Department, we discovered an improvement in BCVA and total remission of uveitis. In children: the average of the best corrected VA at the start of the adalimumab treatment in the right eye was 0.71, and in the left eye was 0.83. This value improved to 0.96 in both eyes by the end of the follow-up period. In adults at the beginning of our study, the averaged best corrected visual acuity (BCVA) in the right eye was 0.63, and in the left eye was 0.67. Average VA measured at the end of the follow-up period became less in both eyes, 0.55 in the right eye and 0.63 in the left eye. The cause of the deterioration of VA was the irreversible damage of anterior and posterior segment of their eyes.

With the continued development of newer medications and methods, the future for uveitis can be promising. Our results demonstrate that adalimumab combined with methotrexate in children and adalimumab monotherapy in adults was a safe and successful treatment for uveitis.

In our study, we made follow-ups by basic ophthalmic examinations and OCT as a modern ophthalmic imaging procedure to follow the third-line therapy in both paediatric and adult uveitic patients. At the beginning of the therapy we diagnosed CME in 2 children (18%). After initiating the adalimumab, CME disappeared in both cases. In adult uveitic patients, at the start of our study, we detected CME in a total of 16 (8 right, 8 left) eyes. At the end of the

follow-up period, only 4 eyes (1 right, 3 left) were affected by CME thanks to the adalimumab therapy.

8.3. Examination of MEWDS patient

SARS-CoVs can produce many types of ocular manifestations from anterior segment pathologies like conjunctivitis and anterior uveitis to sight-threatening conditions like retinitis and optic neuritis [52, 53].

The lesions found at our patient support the hypothesis that a herpes infection can manifest after SARS CoV-2 infection. MEWDS is an acute, multifocal, and rarely bilateral retinopathy. The multiple white infiltrations or foci could be seen at the level of the outer retina. There is a strong female predominance. In our case, SARS-CoV-2 could trigger the inactive herpes simplex infection that caused MEWDS. Recovery of vision in a few weeks was coincident with the return of the serum IgM values to normal [56, 90]. We could make the prompt diagnosis and follow-ups by using OCT as a non-contact diagnostic tool- that was very important during SARS-2 Covid pandemic [91].

OCT showed inflammatory lesions in the level of the outer retina. The disruption of the ellipsoid zone could produce granular foveal area. OCT images showed swelling of the outer retinal layers and granules at the level of RPE. We detected discontinuities in inner segment - outer segment junction and mild attenuation of external limiting membrane in acute phase that disappeared a few weeks later.

Early and late hyperfluorescence of the white spots could be seen on the UWFI FLAG picture. We also performed Optos FLAG in order to get more information about the periphery of the eyes. No vasculitis could be detected. The UWFI FAF images showed hyperautofluorescence corresponding to the white dots in the acute phase.

Despite that the natural course of MEWDS is excellent, and no intervention is required, in the time of SARS-CoV-2 pandemic, local steroid therapy was recommended to keep the best visual acuity [92, 93].

Making non-contact examinations, follow-ups in time of the pandemic was essential.

As retinal imaging technic continues to improve, the understanding of eye disease processes continues getting better and better. Newer technologies helps ophthalmologists to achieve appropriate diagnosis and treatment of disease entities. They contributed to improve patient care and management in current ophthalmic practice.

9. Summary

1. To the best of our knowledge, we reported first the investigation of macula with OCT in anterior scleritic patients. The changes seen on OCT pictures correlated well with the severity of the ophthalmic disease.

2. We classified the ME into three subgroups: cystoid macular edema (CME), diffuse macular edema (DME) and serous retinal detachment (SRD).

ME and ERM could work as biomarkers in chronic scleritis cases, since their presence helps evaluating the course of the disease. These changes affect the treatment of scleritis.

3. As a result of our research work, we were the first to publish in the Hungarian literature the ophthalmic examinations of paediatric uveitic patients treated with adalimumab in Hungary. The most common cause of uveitis in children is JIA. In 73% of these cases, uveitis occurred within the first year of the onset of arthritis and could be the first sign of JIA.

The data of adult uveitic patients treated at our Department were also analyzed. We provided real-world clinical data supporting the treatment efficacy and safety of adalimumab for the patients with vision-threatening uveitis in Hungary. We found improved or stable vision and decreased need to use additional therapy like prednisolone, immunosuppressive drugs, or local dexamethason therapy.

4. We found that macular complications affect the prognosis and the treatment in uveitis independently on the etiology of the uveitis.

5. SARS-CoV-2 would trigger the inactive herpes simplex infection to cause MEWDS. We were the first who presented a bilateral MEDWS case caused by SARS CoV2. We showed the usefulness of modern non-contact imaging procedures (like OCT, OCTA and Optos) in time of SARS-CoV-2 pandemic.

10. Acknowledgment

I would like to express my sincere gratitude to Dr. Nicolette Sohar whose guidance, enthusiasm, and inspiration make this work possible. She always guided me with her valuable advices and instructions. I would like to express my thanks for her friendship.

I would like to thank Professor Edit Tóth Molnár, Head of the Department of Ophthalmology for providing me the opportunity to work in the department and to complete my work.

I acknowledge to Professor Andrea Facskó providing me the possibility to work at the Department of Ophthalmology under her leadership.

I am indebted to Ms Enikő Szabó for her help in editing the formal requirements.

I owe my thanks to all members of the Department of Ophthalmology for their help.

Finally, I thank my family, especially my husband and my sons for their love, encouragement, support, understanding and for giving me a peaceful and happy background.

11. Bibliography

- [1] Cunningham, E.T.; McCluskey, P.; Pavesio, C.; et al. Scleritis. *Ocul Immunol Inflamm* 2016, 24, 2–5.
- [2] Ahn, S.J.; Oh, J.Y.; Kim, M.K.; et al. Clinical Features, Predisposing Factors, and Treatment Outcomes of Scleritis in the Korean Population. *Korean J Ophthalmol* 2010, 24, 331–335.
- [3] Sims, J. Scleritis: Presentations, disease associations and management. *Postgrad MedJ* 2012, 88, 713–718.
- [4] Diogo, M.; Jager, M.; Ferreira, T. CT and MR Imaging in the Diagnosis of Scleritis. *Am J Neuroradiol* 2016, 37, 2334–2339.
- [5] Sen, H.N.; Sangave, A.A.; Goldstein, D.A.; et al. A Standardized Grading System for Scleritis. *Ophthalmology* 2011, 118, 768–771.
- [6] Bin Ismail, M.A.; Lim, R.H.F.; Fang H.M.; et al. Ocular Autoimmune Systemic Inflammatory Infectious Study (OASIS) - report 4: analysis and outcome of scleritis in an East Asian population. *J Ophthalmic Inflamm Infect* 2017, 7, 6.
- [7] Chung, Y.-R.; Kim, Y.H.; Seung Yeop Lee, S.Y.; et al. Insights into the pathogenesis of cystoid macular edema: leukostasis and related cytokines. *Int J Ophthalmol* 2019, 18, 1202–1208.
- [8] Vermeirsch, S.; Testi, I.; Pavesio, C. Choroidal involvement in non-infectious posterior scleritis. *J Ophthalmic Inflamm Infect* 2021, 11, 41.
- [9] Watson, P.; Romano, A. The impact of new methods of investigation and treatment on the understanding of the pathology of scleral inflammation. *Eye* 2014, 28, 915–930.
- [10] Wieringa, W.G.; Wieringa, J.E.; ten Dam-von Loon, N.H.; Los, L.I. Visual Outcome, Treatment Results, and Prognostic Factors in Patients with Scleritis. *Ophthalmology* 2013, 120, 379–386.
- [11] Vergouwen, D.; Rothova, A.; Berge, J.T.; et al. Current insights in the pathogenesis of scleritis. *Exp Eye Res* 2020, 197, 108078.
- [12] Majumder, P.D.; Agrawal, R.; McCluskey, P.; Biswas, J. Current Approach for the Diagnosis and Management of Noninfective Scleritis. *Asia-Pac J Ophthalmol* 2020, 10, 212–223.
- [13] Dong, Z.-Z.; Gan, Y.-F.; Zhang, Y.-N.; et al. The clinical features of posterior scleritis with serous retinal detachment: A retrospective clinical analysis. *Int J Ophthalmol* 2019, 12, 1151–1157.
- [14] Agrawal, R.; Lee, C.S.; Gonzalez-Lopez, J.J.; et al. Flurbiprofen: A Nonselective Cyclooxygenase (COX) Inhibitor for Treatment of Noninfectious, Non-necrotizing Anterior Scleritis. *Ocul Immunol Inflamm* 2016, 24, 35–42.
- [15] Rossi, D.C.; Ribi, C.; Guex-Crosier, Y. Treatment of chronic non-infectious uveitis and scleritis. *Swiss Med Wkly* 2019, 149, w20025.

- [16] Sands, D.S.; Chan, S.C.; Gottlieb, C.C. Methotrexate for the treatment of noninfectious scleritis. *Can J Ophthalmol* 2018, 53, 349–353.
- [17] Suelves, A.M.; Arcinue, C.A.; González-Martín, J.M.; et al. Analysis of a Novel Protocol of Pulsed Intravenous Cyclophosphamide for Recalcitrant or Severe Ocular Inflammatory Disease. *Ophthalmology* 2013, 120, 1201–1209.
- [18] Kaçmaz, R.O.; Kempen, J.H.; Newcomb, C.; et al. Cyclosporine for ocular inflammatory diseases. *Ophthalmology* 2010, 117, 576–584.
- [19] Clarke, L.N.; Sen, E.S.; Ramanan, A.V. Juvenile idiopathic arthritis associated uveitis. *Ped Rheumatol Online J* 2016, 14(1), 27.
- [20] Rosenbaum, J.; Bodaghi, B.; Couto C.; et al. New observations and emerging ideas in diagnosis and management of non-infectious uveitis: A review. *Semin Arthritis Rheum* 2019, 49(3), 438-445.
- [21] Jacquot, R.; Sève, P.; Jackson, T.L.; et al. Diagnosis, Classification, and Assessment of the Underlying Etiology of Uveitis by Artificial Intelligence: A Systematic Review. *J Clin Med* 2023, 12, 3746.
- [22] Tsirouki, T.; Dastiridou, A.; Symeonidis, C.; et al. A Focus on the Epidemiology of Uveitis. *Ocul Immunol Inflamm* 2018, 26(1), 2-16.
- [23]. Jung, J.L.; Harasawa, M.; Patnaik, J.L.; et al. Subtenon Triamcinolone Acetonide Injection with Topical Anesthesia in Pediatric Non-Infectious Uveitis. *Ophthalmol Ther* 2022, 11, 811-820.
- [24]. McHarg, M.; Young, L.; Kesav, N.; et al. Practice patterns regarding regional corticosteroid treatment in noninfectious uveitis: a survey study. *J Ophthalmic Inflamm Infect* 2022, 12, 3.
- [25] Gamalero, L.; Simonini, G.; Ferrara, G.; et al. Evidence-Based Treatment for Uveitis. *Isr Med Assoc J* 2019, 7, 475-479.
- [26]. Thorne, J.E.; Sugar, E.A.; Holbrook, J.T.; et al. Periocular triamcinolone vs, intravitreal triamcinolon vs. intravitreal dexamethasone implant for the treatment of uveitis macular edema. *Ophthalmol* 2019, 126, 283-295.
- [27] Ferrara, G.; Petrillo, M.G.; Giani, T.; et al. Clinical Use and Molecular Action of Corticosteroids in the Pediatric Age. *Int J Mol Sci* 2019, 20, 444.
- [28] Wu, X.; Tao, M.; Zhu, L.; et al. Pathogenesis and current therapies for non-infectious uveitis. *Clin Exp Med* 2023, 23(4), 1089-1106.
- [29] Skrabl-Baumgartner, A.; Seidel, G.; Langner-Wegscheider, B.; et al. Drug monitoring in long-term treatment with adalimumab for juvenile idiopathic arthritis-associated uveitis. *Arch Dis Child* 2019, 104(3), 246-250.
- [30] Smeller, L.; Sümegi, V.; Tóth-Molnár, E.; Sohár, N. Biological therapy of uveitis in children. *Orv Hetil* 2022, 163(35), 1402–1408.
- [31] Maleki, A.; Anesi, S.D.; Look-Why, S; et al. Pediatric uveitis: A comprehensive review *Surv Ophthalmol.* 2022, 67(2), 510-529.

- [32] Chang, M.H.; Shantha, J.G.; Fondriest, J.J.; et al. Uveitis in Children and Adolescents. *Rheum Dis Clin North Am* 2021, 47(4), 619-641.
- [33] Sen, H.N.; Davis, J.; Ucar, D.; et al. Gender Disparities in Ocular Inflammatory Disorders. *Curr Eye Res* 2015, 40(2), 146–161.
- [34] Al-Haddad, C.; BouGhannam, A.; Fattah, M.A.; et al. Patterns of uveitis in children according to age: comparison of visual outcomes and complications in a tertiary center. *BMC Ophthalmol* 2019, 19, 137.
- [35] Leibowitz, J.A.; Woods, A.T.; Kesselman, M.M.; Mayi, B.S. Uveitis as a Predictor of Predisposition to Autoimmunity. *Cureus* 2020, 12(3), e7451.
- [36] Rahman, N.; Petrushkin, H.; Solebo, A.L. Paediatric autoimmune and autoinflammatory conditions associated with uveitis. *Ther Adv Ophthalmol* 2020, 12, 2515841420966451.
- [37] Yildirim, D.G.; Hasanreisoglu, M.; Bakkaloglu, S.A. Comparison of pediatric patients with idiopathic uveitis, and uveitis due to juvenile idiopathic arthritis and Behçet's disease. *Postgrad Med* 2023, 135(1), 79-85.
- [38] Yang, P.; Zhong, Z.; Su, G.; et al. Retinal vasculitis, a common manifestation of idiopathic pediatric uveitis. *Retina* 2021, 41, 610–619.
- [39] Clarke, S.L.; Sen, E.S.; Ramanan, A.V. Juvenile idiopathic arthritis-associated uveitis. *Pediatr Rheumatol Online J* 2016, 27, 14(1), 27.
- [40] Carlsson, E.; Beresford, M.W.; Ramanan, A.V.; et al. Juvenile Idiopathic Arthritis Associated Uveitis. *Children (Basel)* 2021, 27, 8(8), 646.
- [41] Kostik, M.M.; Gaidar, E.V.; Sorokina, L.S.; et al. Uveitis Is a Risk Factor for Juvenile Idiopathic Arthritis' Significant Flare in Patients Treated With Biologics. *Front Pediatr* 2022, 10, 849940.
- [42] Paroli, M.P.; Del Giudice, E.; Francesca Giovannetti, F.; et al. Management Strategies of Juvenile Idiopathic Arthritis-Associated Chronic Anterior Uveitis: Current Perspectives. *Clin Ophthalmol* 2022, 16, 1665–1673.
- [43] Loh, A.R.; Chiang, M.F. Pediatric Vision Screening. *Pediatr Rev* 2018, 39(5), 225–234.
- [44] Foeldvari, I.; Maccora, I.; Petrushkin, H.; et al. New and Updated Recommendations for the Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis and Idiopathic Chronic Anterior Uveitis. *Arthritis Care Res (Hoboken)* 2023, 75(5), 975-982.
- [45] Géhl, Zs.; Szepessy, Zs.; Nagy, Z.Zs. Ophthalmic use of TNF α inhibitor: adalimumab treatment in uveitis. *Orv Hetil* 2021, 162(34), 1370–1375.
- [46] Joltikov, K.A.; Lobo-Chan, A-M. Epidemiology and Risk Factors in Non-infectious Uveitis: A Systematic Review. *Front Med (Lausanne)* 2021, 8, 695904.
- [47] Thorne, J.E.; Suhler, E.; Skup, M.; et al. Prevalence of noninfectious uveitis in the united states: a claims-based analysis. *JAMA Ophthalmol* 2016, 134, 1237–1245.
- [48] Kalogeropoulos, D.; Asproudis, I.; Stefaniotou, M.; et al. The large Hellenic Study of Uveitis: epidemiology, etiologic factors and classification. *Int Ophthalmol*. 2023, 43(10), 3633-3650.

- [49] El Jammal, T.; Loria, O.; Jamilloux, Y.; et al. Uveitis as an Open Window to Systemic Inflammatory Diseases. *J Clin Med* 2021, 10, 281.
- [50] Emrani, J.; Ahmed, M.; Jeffers-Francis, L.; et al. SARS-COV-2, infection, transmission, transcription, translation, proteins, and treatment: a review. *IntJ Biol Macromol* 2021, 93(Pt B), 1249–1273.
- [51] Ocansey, S.; Abu, E.K.; Abraham, C.H.; et al. Ocular symptoms of SARSCoV-2: indication of possible ocular transmission or viral shedding. *Ocul Immunol Inflamm* 2020, 16, 28(8), 1269–1279.
- [52] Sen, M.; Honavar, S.G.; Sharma, N.; Sachdev, M.S. COVID-19 and eye: a review of ophthalmic manifestations of COVID-19. *Indian J Ophthalmol* 2021, 69(3), 488–509.
- [53] Le Balc'h, P.; Pinceaux, K.; Pronier, C.; et al. Herpes simplex virus and cytomegalovirus reactivations among severe COVID-19 patients. *Crit Care* 2020, 24, 530.
- [54] Papasavvas, I.; Mantovani, A.; Tugal-Tutkun, I.; et al. Multiple evanescent white dot syndrome (MEWDS): update on practical appraisal, diagnosis and clinicopathology; a review and an alternative comprehensive perspective. *J Ophthalmic Inflamm Infect* 2021, 11, 45.
- [55] Mount G.R.; Evan J.; Kaufman E.J. White Dot Syndromes. *StatPearls* [Internet], 2023, <https://www.ncbi.nlm.nih.gov/books/NBK557854/>
- [56] Maldonado, M.D.; Romero-Aibar, J.; Pérez-San-Gregorio M.A. COVID-19 pandemic as a risk factor for the reactivation of herpes viruses. *Epidemiol Infect* 2021, 149, e145.
- [57] Farci, R.; Sellam, A.; Coscas, F.; et al. Multimodal OCT Reflectivity Analysis of the Cystoid Spaces in Cystoid Macular Edema. *Biomed Res Int* 2019, 2019, 7835372.
- [58] Leitgeb, R. En face optical coherence tomography: A technology review. *Biomed Opt Express* 2019, 10, 2177–2201.
- [59] Trichonas, G.; Kaiser, P.K. Optical coherence tomography imaging of macular oedema. *Br J Ophthalmol* 2014, 98 (Suppl. S2), ii24–ii29.
- [60] Bhende, M.; Shetty, S.; Parthasarathy, M.K.; Ramya, S. Optical coherence tomography: A guide to interpretation of common macular diseases. *Indian J Ophthalmol* 2018, 66, 20–35.
- [61] Bouma, B.E.; de Boer, J.F.; Huang, D.; et al. Optical coherence tomography. *Nat Rev Methods Prim* 2022, 2, 79.
- [62] Hee, M.R.; Izatt, J.A.; Swanson, E.A.; et al. Optical Coherence Tomography of the Human Retina. *Arch Ophthalmol* 1995, 113, 325–332.
- [63] Smeller, L.; Toth-Molnar, E.; Sohar, N. Optical Coherence Tomography: Focus on the Pathology of Macula in Scleritis Patients. *J Clin Med* 2023, 12(14), 4825.
- [64] Kempen, J.H.; Sugar, E.A.; Jaffe, G.J.; et al. Fluorescein Angiography versus Optical Coherence Tomography for Diagnosis of Uveitic Macular Edema. *Ophthalmology* 2013, 120, 1852–1859.
- [65] Han, I.C.; Jaffe, G.J. Evaluation of Artifacts Associated with Macular Spectral-Domain Optical Coherence Tomography. *Ophthalmology* 2010, 117, 1177–1189.e4.

- [66] Spaide, R.F.; Curcio, C.A. Anatomical correlates to the bands seen in the outer retina by optical coherence tomography: Literature review and model. *Retina* 2011, 31, 1609–1619.
- [67] Staurenghi, G.; Sadda, S.; Chakravarthy, U.; Spaide, R.F. Proposed lexicon for anatomic landmarks in normal posterior segment spectral-domain optical coherence tomography: The IN*OCT consensus. International Nomenclature for Optical Coherence Tomography (IN*OCT) Panel. *Ophthalmology* 2014, 121, 1572–1578.
- [68] Krebs, I.; Smretschnik, E.; Moussa, S.; et al. Quality and Reproducibility of Retinal Thickness Measurements in Two Spectral-Domain Optical Coherence Tomography Machines. *Investig. Ophthalmol. Vis Sci* 2011, 52, 6925–6933.
- [69] Ang, M.; Baskaran, M.; Werkmeister, R.M.; et al. Anterior segment optical coherence tomography. *Prog Retin Eye Res* 2018, 66, 132–156.
- [70] Lavinsky, F.; Lavinsky, D. Novel perspectives on swept-source optical coherence tomography. *Int J Retin Vitr* 2016, 2, 25.
- [71] Midena, E.; Marchione, G.; S. Di Giorgio, S.; et al. Ultra-wide-field fundus photography compared to ophthalmoscopy in diagnosing and classifying major retinal diseases. *Sci Rep* 2022, 12, 19287.
- [72] Tripathy, K.; Chawla, R.; Venkatesh, P.; et al. Ultrawide Field Imaging in Uveitic Non-dilating Pupils. *J Ophthalmic Vis Res* 2017, 12(2), 232–233.
- [73] Tripathy, K.; Chawla, R.; Vohra, R. Evaluation of the fundus in poorly dilating diabetic pupils using ultrawide field imaging. *Clin Exp Optom* 2017, 100(6), 735–736.
- [74] Patel, S.N.; Shi, A.; Wibbelsman, T.D.; Klufas, M.A.; Ultra-widefield retinal imaging: an update on recent advances. *Ther Adv Ophthalmol* 2020, 12, 2515841419899495.
- [75] Sorkhabi, M.A.; Potapenko, I.O.; et al. Assessment of anterior uveitis through anterior-segment optical coherence tomography and artificial intelligence-based image analyses. *Transl Vis Sci Technol* 2022, 11(4), 7.
- [76] Pole, C.; Ameri, H. Fundus Autofluorescence and Clinical Applications. *J Ophthalmic Vis Res* 2021, 16(3), 432–461.
- [77] Yung, M.; Klufas, M.A.; Sarraf, D. Clinical applications of fundus autofluorescence in retinal disease. *Int J Retin Vitr* 2016, 2, 12.
- [78] Laovirojjanakul, W.; Acharya, N.; Gonzales, J.A. Ultra-widefield fluorescein angiography in intermediate uveitis. *Ocul Immunol Inflam* 2017, 17, 1–6.
- [79] European Medicines Agency. Humira (adalimumab). EU summary of product characteristics, 2016. Available from: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf [accessed: January 25, 2021]
- [80] Dhirachaikulpanich, D.; Chanthongdee, K.; Zheng, Y.; Beare, N.A.V. A systematic review of OCT and OCT angiography in retinal vasculitis. *J Ophthalmic Inflamm Infect* 2023, 13, 1.
- [81] Massa, H.; Pipis, S.Y.; Adewoyin, T.; et al. Macular edema associated with non-infectious uveitis: Pathophysiology, etiology, prevalence, impact and management challenges. *Clin Ophthalmol* 2019, 13, 1761–1777.

- [82] Iannetti, L.; Tortorella, P.; D'ambrosio, E.; et al. Epiretinal Membranes in Patients with Uveitis: Morphological and Functional Analysis with Spectral Domain Optical Coherence Tomography. *Biomed Res Int* 2013, 2013, 284821.
- [83] Iuliano, L.; Fogliato, G.; Gorgoni, F.; et al. Idiopathic epiretinal membrane surgery: Safety, efficacy and patient related outcomes. *Clin Ophthalmol* 2019, 13, 1253–1265.
- [84] Markomichelakis, N.N.; Halkiadakis, I.; Pantelia, E.; et al. Patterns of macular edema in patients with uveitis: Qualitative and quantitative assessment using optical coherence tomography. *Ophthalmology* 2004, 111, 946–953.
- [85] Gupta, S.; Shah, D.N.; Joshi, S.N.; et al. Patterns of Macular Edema in Uveitis as Diagnosed by Optical Coherence Tomography in Tertiary Eye Center. *Nepal J Ophthalmol* 2018, 10(19), 39-46.
- [86] Kumar, D.A.; Maitra, P.; Agarwal, A. Epiretinal membrane profile on spectral domain optical coherence tomography in patients with uveitis. *Indian J Ophthalmol* 2019, 67, 376–381.
- [87] Žuber Z. Oligoarticular onset juvenile idiopathic arthritis as the most common cause of disability of children and young adults. *Reumatologia* 2019, 57(4), 189-191.
- [88] Pilly, B.; Heath, G.; Tschuor, P.; et al. Overview and recent developments in the medical management of pediatric uveitis. *Expert Pharmacother* 2013, 14, 1787-1795.
- [89] Suhler, E.B.; Jaffe, G.J.; Fortin, E.; et al. Long-Term Safety and Efficacy of Adalimumab in Patients with Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis. *Ophthalmology* 2021, 128(6), 899-909.
- [90] Tartari, F.; Spadotto, A.; Zengarini, C.; et al. Herpes zoster in COVID-19-positive patients. *Int J Dermatol* 2020, 59(8), 1028–1029.
- [91] Smeller, L.; Toth-Molnar, E.; Sohar, N. White Dot Syndrome Report in a SARS-CoV-2 Patient Case Rep *Ophthalmol* 2022, 13, 744–750.
- [92] Smith, J.R.; Lai, T.Y.Y. Managing uveitis during the COVID-19 pandemic. *Ophthalmology* 2020, 127(9), e65–67.
- [93] Beltrán-García, J.; Osca-Verdegal, R.; Pallardó, F.V.; et al. Sepsis and coronavirus disease 2019: common features and anti-inflammatory therapeutic approaches. *Crit Care Med* 2020, 48(12), 1841–1844.



Article

Optical Coherence Tomography: Focus on the Pathology of Macula in Scleritis Patients

Lilla Smeller *, Edit Toth-Molnar and Nicolette Sohar

Department of Ophthalmology, University of Szeged, 6720 Szeged, Hungary;
toth-molnar.edit@med.u-szeged.hu (E.T.-M.); sohar.nicolette@med.u-szeged.hu (N.S.)
* Correspondence: lsmeller@gmail.com; Tel.: +36-62-545488

Abstract: Optical coherence tomography (OCT) is a non-invasive imaging technique for high-resolution, cross-sectional tissue imaging of the eye. During the past two and a half decades, OCT has become an essential tool in ophthalmology. It is a painless method for examining details of ocular structures in vivo with high resolution that has revolutionized patient care following and treating scleritis patients. **Methods:** Twenty-four patients diagnosed with scleritis were selected for this study. All of the patients went through basic ophthalmological examinations, such as visual acuity testing (VA), intraocular pressure measurement (IOP), slit lamp examination, ophthalmoscopic examination, and OCT. OCT examinations were taken by SD-OCT Spectralis OCT system (Heidelberg Engineering, Heidelberg, Germany). **Results:** Twenty-seven eyes of 24 patients (7 males and 17 females) were included in this study, who were diagnosed with scleritis. OCT examinations showed epiretinal membrane (ERM) in three patients (12%), cystoid macular edema (CME) (three cases, 12%), diffuse macular edema (DME) (one case, 4%), and serous retinal detachment (SRD) (one case, 4%). **Conclusions:** OCT proved to be a valuable, non-invasive method for detecting macular pathology in patients with scleritis. Despite the best treatment regimen applied, macular involvement resulting in reduced visual acuity (VA) can develop, which we could detect with OCT since macular edema (ME) is the leading cause of decreased vision due to the damaged outer blood–retina barrier (BRB) in inflammation. OCT investigation is a highly important method for early detection of ocular complications in scleritis in order to prevent blindness.

Keywords: scleritis; optical coherence tomography; macular edema; epiretinal membrane



Citation: Smeller, L.; Toth-Molnar, E.; Sohar, N. Optical Coherence Tomography: Focus on the Pathology of Macula in Scleritis Patients. *J. Clin. Med.* **2023**, *12*, 4825. <https://doi.org/10.3390/jcm12144825>

Academic Editor: Enrico Borrelli

Received: 6 June 2023

Revised: 16 July 2023

Accepted: 19 July 2023

Published: 21 July 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Scleritis is a chronic and painful, vision-threatening inflammatory disease that is characterized by edema and cellular infiltration of the scleral and episcleral tissues. The most common etiology is inflammatory (noninfectious in 90% of all scleritis patients), either idiopathic or in the context of systemic disease. Scleritis is commonly associated with systemic autoimmune disorders [1], including rheumatoid arthritis, systemic lupus erythematosus, relapsing polychondritis, spondylarthropathies, granulomatosis with polyangiitis, formerly known as Wegener granulomatosis, polyarteritis nodosa, and giant cell arteritis [1–3].

Scleritis may be classified as anterior and posterior ones based on the anatomical location of the inflammation. The most common clinical forms are diffuse scleritis and nodular scleritis [3] (Figure 1). Necrotizing scleritis is much less frequent and associated with systemic autoimmune disorders. Posterior scleritis is characterized by flattening of the posterior aspect of the globe, thickening of the posterior coats of the eye, and retrobulbar edema [4,5].



Figure 1. Anterior segment picture of diffuse scleritis of the temporal part of the left eye.

Scleritis is a rare disease. Although well-defined incidence rates are hard to find, the prevalence is estimated to be six cases per 10,000 people. Anterior scleritis is demonstrated in 94% of the cases, and posterior scleritis is diagnosed only in 6% of the patients [3,5–7]. In differential diagnosis, episcleritis is of utmost importance as it refers to the inflammation of the superficial episcleral tissue. Episcleritis is usually idiopathic, poses no serious threat to vision, and does not affect the adjacent tissues in the eye. Vessels have a reddish hue compared to the deeper-bluish hue in scleritis [3,5–7].

Ocular complications of scleritis, which cause vision loss and eye destruction, appear as a result of the extending scleral inflammation [3,8]. Scleritis is usually painful and can lead to vision loss due to progressive inflammation of the ocular tissues or even morbidity and mortality due to an underlying collagen vascular disease [1–3].

The etiology of scleritis remains unclear. Scleritis is commonly associated with systemic autoimmune disorders and systemic vasculitis. Immunohistochemistry studies reveal that there is a localized scleral vasculitis, most likely secondary to the deposition of circulating immune complexes, in patients with necrotizing scleritis [9,10].

Scleritis may often pose a diagnostic challenge since the clinical features are subtle and diagnostic modalities are limited [1,2]. The diagnosis of scleritis is usually based on clinical assessment and ultrasonography. B-scan ultrasound is the most useful confirmatory analysis for posterior scleritis diagnosis [11]. It can show the diffuse thickness of the choroid because of the increased amount of fluid in subtenon space and around the optic nerve, the so-called T sign [3].

The variability in clinical presentations and also in ultrasonography findings, as well as unfamiliarity with the diagnosis, account for the fact that scleritis is one of the most underdiagnosed conditions in ophthalmology [3,7].

Generally, scleritis requires systemic therapy. Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or immunomodulatory drugs can be indicated. Topical therapy is routinely insufficient. The treatment must be individualized according to the severity of scleritis, response to treatment, adverse effects, and presence of associated diseases [3,12–14]. Oral corticosteroids (1 mg/weight kg) supplemented with periorbital and subconjunctival steroid injections were the first therapeutic regimen introduced [12,13]. In case of therapeutic failure of corticosteroids, immunosuppressive drugs were added. Methotrexate (MTX) [15] was the first choice, but azathioprine, cyclophosphamide [16], and cyclosporine [17] were also helpful. In other cases, other immunomodulatory drugs were effective, such as biologics, which were ordered by rheumatologists [13]. Scleritis may pose a diagnostic challenge since the clinical features are subtle and diagnostic modalities are limited.

More recently, tumor necrosis factor (TNF) alpha inhibitors such as infliximab have shown promise in the treatment of non-infectious scleritis refractory to other treatments. This consists of regularly repeated infusions since the treatment effect is short-lived. However, TNF-alpha inhibitors may also result in a drug-induced lupus-like syndrome (that can also generate ophthalmic disorders) as well as an increased risk of lymphoproliferative disease. All patients on immunomodulatory therapy must be strictly monitored by rheumatologists to avoid systemic complications with the medication [13].

Optical coherence tomography (OCT) has become the most important non-invasive diagnostic technique to evaluate ophthalmic pathologies, also involving the macula with cross-sectional tissue imaging [18,19]. Since the introduction of OCT in 1991, it has become an essential tool in ophthalmology [20].

It is a non-contact, painless method for detailing ocular structures in vivo with high resolution. OCT uses light in the near-infrared spectral range (in the 800–840 nm wavelength range) and penetrates at a depth of several hundred microns in the tissue. It provides real-time, non-invasive imaging of the retina. OCT can be used to follow and reproduce quantitative and qualitative retinal thickness [21,22]. OCT images correlate well with retinal histology [23].

With OCT datasets, we can give exact information about the dynamics of disease progression and response to treatment based on analyzing the retinal anatomy. OCT is also suitable for detecting and monitoring uveitic macular edema and the changes in the fluid distribution in eyes with macular edema, as well as detecting the morphology of the vitreoretinal interface [21–24].

OCT is based on the principle of Michelson interferometry, where a low-coherence light beam is directed at the target tissue, and the scattered back-reflected light is combined with a second beam (reference beam). The resulting interference patterns are used to reconstruct an axial A-scan, which represents the beam's path. From all of the A-scans (time amplitude scan), a two-dimensional cross-sectional image of the target tissue can be reconstructed, called B-scan (brightness amplitude scan). These B-scans are repeated at multiple adjacent positions using a raster scan pattern, then a three-dimensional volume of structural and flow information can be structured [21,22]. The scanning beam allows for the acquisition of cross-sectional images of the tissue structure. Light source and detector characteristics determine the axial resolution and imaging range of an OCT, not the focusing optics. [21,22].

Normal retinal tissue has different reflectivity patterns on OCT. The nerve fibers and the retinal pigment epithelium display high, the plexiform and the nuclear layers display medium, and the photoreceptors display low reflectivity [25].

The OCT measures retinal thickness automatically. The distance between the vitreoretinal interface and the anterior surface of the retinal pigment epithelium is generally 200–275 μm , and the foveal depression has a range from 170 to 190 μm . The axial resolution is 3.9 $\mu\text{m}/\text{pixel}$, and the lateral resolution is 5.7 $\mu\text{m}/\text{pixel}$. Using several algorithms, cube scans also allow measurement of the volume of the macula [26].

The image acquisition time is limited by the patient's ability to avoid eye movements and the availability of tracking software that adjusts for eye movements. We use spectral domain OCT (SD-OCT); its scanning speed can exceed 100,000 A-scans per second. SD-OCT systems operate at scanning rates of approximately 27,000–70,000 A-scans per second. As the A-scan density increases, resolution becomes higher, and SD-OCT produces better-quality B-scans. Higher scanning speed reduces the effect of artifacts made by eye motion and produces images that provide a true picture of the retina [27]. The large, dense raster scans make it possible to obtain detailed surfaces of individual retina layers over large areas, resulting in segmentation maps [28,29].

With OCT datasets, we can give exact information about the dynamics of disease progression and response to treatment based on analyzing the retinal anatomy [21,22].

OCT imaging also has limitations; as OCT utilizes light beams, media opacities can interfere with optimal imaging in spite of ultrasound's sound waves. Patient cooperation is necessary as eye and patient movement can diminish the image's quality.

In posterior scleritis, different manifestations of choroidal involvement are known on OCT: increased choroidal thickness, choroidal vasculitis, presentation as a choroidal or subretinal mass in nodular posterior scleritis, and choroidal folds, choroidal effusion and exudative retinal detachment [6,11].

Macular edema (ME) is defined as a thickening of the macular region caused by the breakdown of the outer and/or inner blood–retina barrier leading to increased permeability of the retinal pigment epithelium and the retinal vasculature. The leakage from perifoveal capillaries results in the accumulation of intracellular and extracellular fluid [18]. ME can persist or recur despite improvement or resolution of the ocular inflammation [18,24,30]. Visual acuity could be decreased because of ME due to impaired cell function relationships in the retina [31].

Three patterns of macular edema can be revealed: Cystoid macular edema (CME) is the formation of fluid-filled cyst-like spaces between the outer plexiform and inner nuclear layer of the retina. Diffuse macular edema (DME) is characterized by the disturbance of the layered retinal structure or low reflective areas looking similar to a sponge. In serous retinal detachment (SRD), fluid accumulates in the subretinal space between the sensory retina and the retinal pigment epithelium [32] (Figures 2–4).

Symptoms of macular edema include metamorphopsia, micropsia, blurred vision, a central scotoma, and reduction in contrast or color sensitivity. The clinical diagnosis of macular edema can be challenging in mild cases or when visualization of the fundus is impaired by poor pupillary dilation, corneal disorders, cataract, vitreous hemorrhage, and other ocular media opacities [30].

Causes of fluid accumulation include inflammatory, infectious, and neoplastic diseases of the choroid or retina. Retinal dystrophies and other retinal vascular abnormalities, including retinal arterial macroaneurysms and retinal telangiectasia, can also cause different types of edema in the macula.

Cystoid macular edema (CME) represents a common pathologic change in the retina and occurs in a variety of pathological conditions, such as intraocular inflammation. In pars planitis, there is an accumulation of T-cell inflammatory mediators associated with CME. ME may appear in central or branch retinal vein occlusion, diabetic retinopathy, and most commonly following cataract extraction (Irvin–Gass syndrome). E2-prostaglandins can also cause disruption of the tight junctions of the retinal capillaries causing CME. Niacin or nicotine acid intoxication can also be a rare cause of CME [18,21].

Diffuse retinal thickening is the main pattern in diabetic macular edema.

Serous detachments, with the elevation of the retina, occur in a variety of disorders, including central serous chorioretinopathy (CSC), age-related macular degeneration (AMD), systemic lupus erythematosus (SLE), and choroidal ischemic disorders, such as accelerated hypertension, pre-eclampsia, eclampsia, systemic corticosteroid usage, or in some choroidal tumors and inflammatory disorders, for example, in Vogt–Koyanagi–Harada's disease [18].

When ME is found on OCT images, the therapy has to be extended or changed to save vision. In persistent ME and decreased best corrected visual acuity (BCVA), local therapy is needed, such as non-steroid drops. If this treatment is ineffective, corticosteroid injection is needed, either intravitreally or sub-tenonly, or an intravitreal steroid implant should be applied in order to treat this complication.

On OCT images, ERM appears as a hyperreflective line adhering to the retina. In recent studies, secondary ERMs were associated with worse visual acuity in comparison to idiopathic ERM. This complication is commonly seen in recurrent uveitis or other ocular inflammation [33] (Figure 5). Its therapy is epiretinal membrane peeling with a pars plana vitrectomy procedure [34].

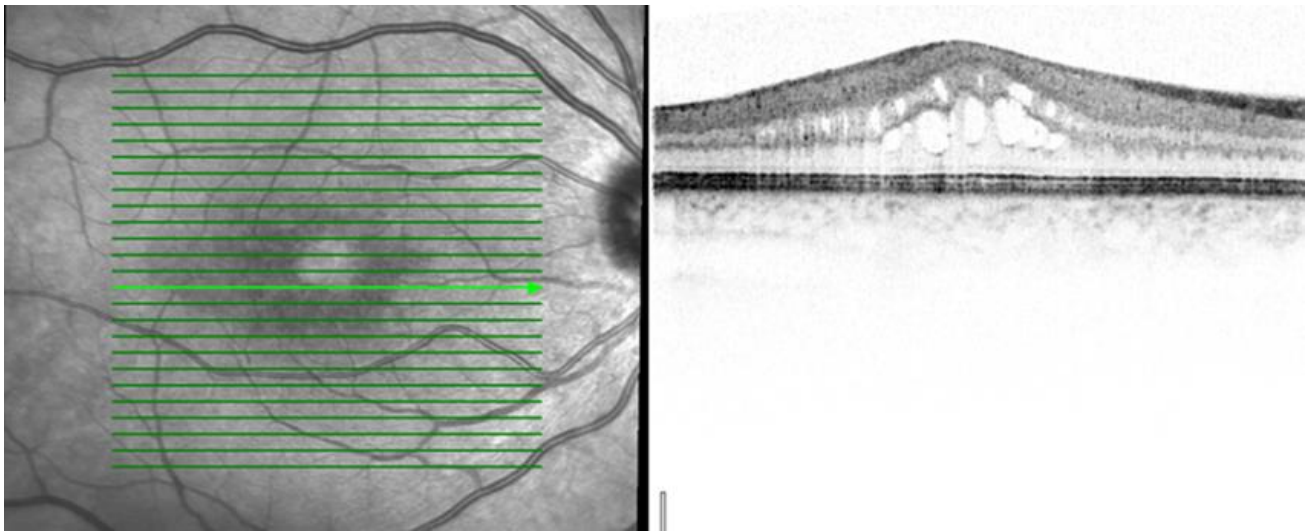


Figure 2. OCT of the right eye of a 28-year-old woman showing CME with loss of the foveal depression and intra-retinal cysts in the outer and inner nuclear layer of the retina. OCT scale: 512×496 , high-speed mode, 20° .

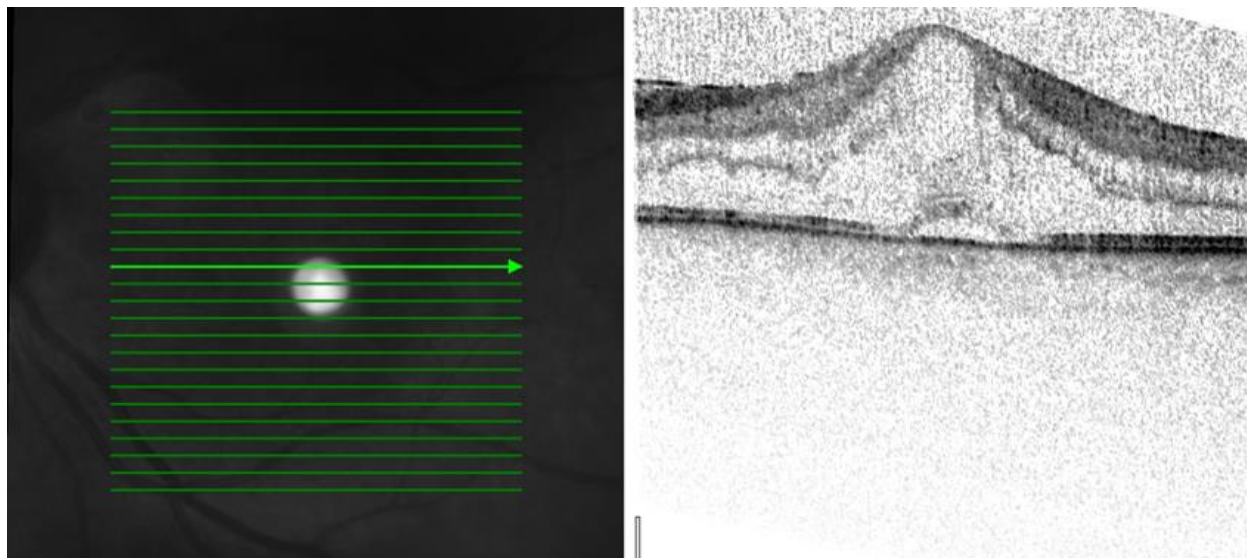


Figure 3. On this OCT image: DME is characterized by the disturbance of the layered retinal structure or low reflective areas looking similar to a sponge. The complication of corticosteroid therapy is cataract formation which can explain the quality of the image. OCT scale: 512×496 , high-speed mode, 20° .

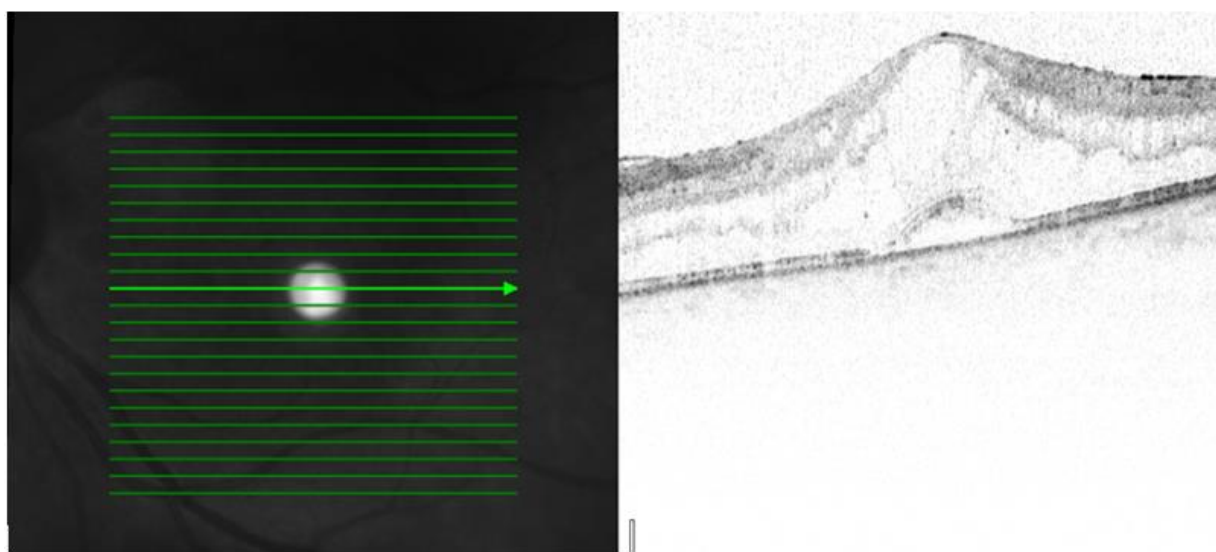


Figure 4. OCT image from left eye: In SRD, fluid accumulates in the subretinal space between the sensory retina and the retinal pigment epithelium. OCT scale: 512×496 , high-speed mode, 20° .

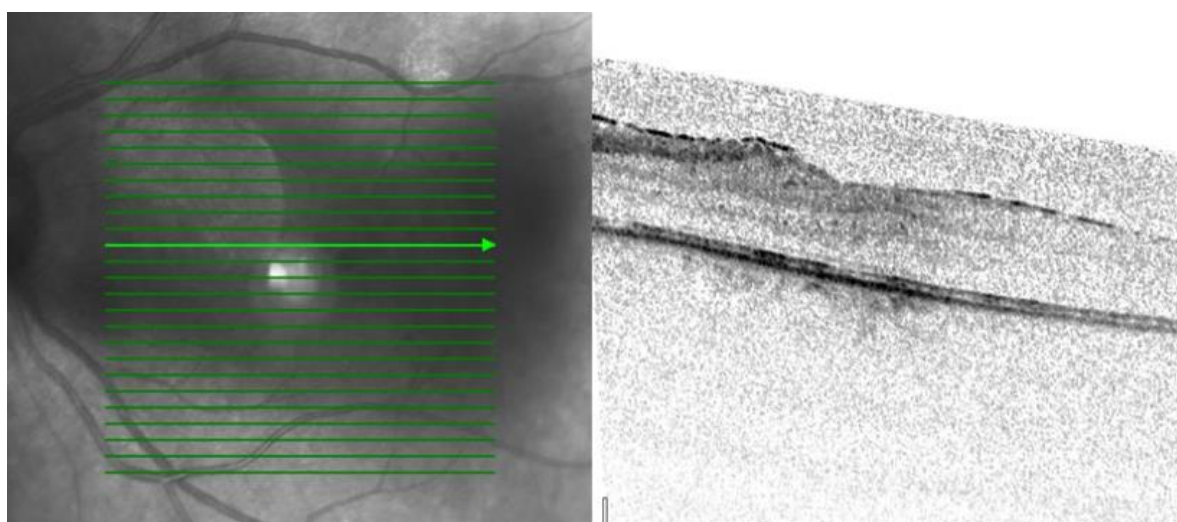


Figure 5. OCT image of the epiretinal membrane (ERM): a reflective layer on the top of the internal limiting membrane (ILM) of a 28-year-old patient. The ERM is attached to the retinal surface of the left eye. OCT scale: 512×496 , high-speed mode, 20° .

Biomarker's definition by the United States National Institutes of Health (NIH) is “a characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention, including therapeutic interventions” [35].

The aims of this study were to investigate scleritic patients with basic ophthalmological examination methods and with OCT in order to find any macular complications and also to determine whether the macular complications could affect the prognosis and the treatment and become biomarkers since previously, macula was not examined in scleritis patients.

2. Materials and Methods

Twenty-seven eyes of 24 patients (7 males and 17 females) were included in this study, who were diagnosed with non-infectious scleritis. The mean age was 57.75 years (range: from 30 to 77 years).

Scleritis was diagnosed by the presence of the following parameters: (1) acute or sub-acute symptom onset; (2) eye pain with or without decreased visual acuity; (3) posterior sclerochoroidal wall thickening. Scleritis was classified as diffuse, nodular, or necrotizing. The location of inflammation was also recorded.

First, all of the patients went through basic ophthalmological examinations such as visual acuity (VA) testing. Visual acuity was tested by the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, intraocular pressure measurement (Goldman tonometry), slit lamp examination, indirect ophthalmoscopic examination, and OCT.

OCT examinations were taken by SD-OCT Spectralis OCT system (Heidelberg Engineering, Heidelberg, Germany, Software version: Heidelberg Eye Explorer 1.9.13.0).

OCT scan parameters were as follows: infrared scan; pattern size: $20^{\circ} \times 20^{\circ}$; 25 sections; 240 μm between B-scans; 512 A-scans.

OCT examination was performed in all of the cases at the time of their presentation at our uveitis outpatient clinic. For standardization, all examinations were performed by the same technician. The thickness of the retina was measured between the inner limiting membrane and Bruch's membrane in the central macular region. In addition to these investigations, all participants were subjected to laboratory tests and rheumatological examinations to find out if there were any associated systemic diseases.

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. In this manuscript, we, the authors, state that subjects have given their written informed consent to publish their case (including publication of images). Information revealing the subject's identity is avoided. All patients can be identified by numbers or aliases and not by their real names.

Human subject research has been performed with the approval of the Regional and Institutional Review Board of Human Investigations at the University of Szeged and with appropriate participants' informed consent in compliance with the Helsinki Declaration.

This study's protocol was reviewed and approved by the Regional and Institutional Review Board of Human Investigations at the University of Szeged, approval number 5053. Date of approval 20 January 2020.

We state that written and signed informed consent was obtained from all participants for publication of the details of their medical cases and any accompanying images.

3. Results

The demographic and clinical data of the 24 patients are shown in Table 1. Three patients had bilateral disease. Thirteen patients (54%) had associated systemic disease: rheumatoid arthritis ($n = 5$); granulomatosis with polyangiitis, formerly known as Wegener granulomatosis ($n = 1$); ulcerative colitis ($n = 1$); collagenosis ($n = 1$); dermatopolymyositis ($n = 1$); pemphigoid ($n = 1$); non-differentiated collagenosis (NDC) syndrome ($n = 1$); ankylosing spondylitis ($n = 1$); and Cogan syndrome ($n = 1$). There were twenty-four anterior and three posterior scleritis.

Table 1. Demographic and clinical data of our scleritis patients.

Age (years)	30–77	
Mean age (years)	57.75	
Gender	7 male: 17 female	
Laterity	21 unilateral: 3 bilateral	
Background of scleritis		
	rheumatoid arthritis	5
	Wegener granulomatosis	1
	ulcerative colitis	1
	collagenosis	1
	dermatopolymyositis	1
	pemphigoid	1
	non-differentiated collagenosis	1
	ankylosing spondylitis	1
	Cogan-syndrome	1
	unknown etiology	11

Among the twenty-four eyes diagnosed with anterior scleritis, there were 16 with diffuse scleritis and 8 with nodular anterior scleritis. One patient had peripheral ulcerative keratitis; one had retinal detachment, and one had hydro-keratopathy.

Table 2 presents the data dealing with the macula. After investigating the patients, five of them (18.5%) had macular disorders. Their visual acuities were below 37 + 30 letters on the early treatment of diabetic retinopathy study (ETDRS) chart. OCT demonstrated three patterns of macular edema in the examined patients CME three cases (12%), DME one case (4%), and SRD one case (4%).

Table 2. OCT findings in our patients.

OCT Findings	Number of Patients (% of Total no = 24)	CRT (μm)	VA (ETDRS)
cystoid macular edema	3 (12%)	558	22 + 30
diffuse macular edema	1 (4%)	328	19 + 30
serous retinal detachment	1 (4%)	288	33 + 30
epiretinal membrane	3 (12%)	402	45 + 30

The overall mean VA of all the scleritic patients was 28 + 30 letters with correction, and the mean retinal thickness at the central fovea was 291.7 μm in our patients.

The mean VA was 22 + 30 letters in patients with CME, 19 + 30 letters in patients with DME, and 33 + 30 letters in our patients with SRD. The mean CRT was 558 μm in patients with CME, 328 μm in patients with DME, and 288 μm in our patients with SD. The central retina thickness (CRT) was the thickest in cases of CME and thinnest in cases of SRD.

The macular thickness, as seen on OCT, is objective and correlates with BCVA.

The patients with CME were treated with triamcinolone (TA) injection sub-tenonally when topical non-steroid eye drops were ineffective.

OCT examinations showed ERM in three patients (12%).

None of our patients with ERM have gone through vitrectomy surgery so far due to the close OCT follow-up.

4. Discussion

Although scleritis is a rare disease characterized by inflammation of the sclera and adjacent ocular structures, its complications are vision-threatening. Studies have led to significant progress in understanding the epidemiology, immunopathogenesis, severity assessment, treatment, and prognosis of this potentially sight-threatening disease [3,12].

OCT has the advantage of being a fast and noninvasive imaging technique that provides a quantitative assessment of the macular thickness to monitor the clinical course and helps make therapeutic decisions. We can follow the activity of the disease and the response to therapy. It is suitable for detecting and monitoring inflammatory macular edema, the changes in fluid distribution in these cases, and the morphology of the vitreoretinal interface [18,36].

Using OCT, we could find the adequate diagnosis leading to the best, complex treatment and follow-up of the disease. OCT can give more information about the depth of the inflammation and the prediction of visual outcomes than previous examinations such as ultrasound, for example. The thickness of the retina and macula measured by OCT is a potential indicator of retinal inflammation. Four studies used OCT to measure retinal/macular thickness and compared it with the presence of retinal vasculitis. The results suggest that increased retinal/macular thickness correlates with retinal vasculitis. [37].

There is no report in the literature about using OCT to detect any macular entity in cases of scleritic patients.

The most common and vision-decreasing complication of inflammation is ME, which can persist or recur despite improvement or resolution of the ocular inflammation. ME is an important cause of reduced visual acuity in many retinal diseases, for example, diabetic retinopathy, retinal vein occlusion, age-related macular degeneration, uveitis, and following intraocular surgery. ME always appears as retinal thickening with intraretinal cavities of reduced reflectivity on OCT [30].

Kempen et al. described the use of OCT in patients with uveitis and tried to detect early ME [24]. Markomichelakis et al. defined uveitic ME and noted three different patterns of fluid accumulation that were the same as in diabetic ME: diffuse macular edema (DME), cystoid macular edema (CME), and serous retinal detachment (SRD) [32].

Iannetti et al. also reported OCT findings in patients with ME from uveitis—58% had CME, and 42% had DME. SRD was noted in 28% of all cases [38]. Comparing the OCT data of our series, we diagnosed three patients with CME (12%), one patient (4%) with DME, and one patient (4%) with SRD among all scleritic patients.

CME and DME lead to reduced VA, which can affect patients' quality of life. The vision was 22 + 30 in the case of CME and 19 + 31 in DME. The central retina thickness was the thickest in cases of CME and the least thick in cases of SRD.

The visual impact of ERM in eyes with inflammation is not clear. The presence of ERM in the macular area suggests the hypothesis of tractional mechanism as an origin or cofactor of appearing macular edema during inflammatory diseases. ERM can be independent of the type of macular edema and the type of inflammation [34,36,39].

It is known that in most eyes with inflammatory ERM, visual acuity remains stable if intraocular inflammation and co-morbidities are treated appropriately [33,40]. ERM occurs in approximately 6% of patients over the age of 60 [33,40]. Although none of the patients was older than 60 years in our study, OCT examinations showed ERM in three patients (12%), and their vision remained stable at 45 + 30.

ERMs can be classified as idiopathic or secondary in an already-existing ocular pathology. Most idiopathic ERMs are thought to result from fibroglial proliferation on the inner surface of the retina secondary to a break in ILM during posterior vitreous detachment. Glial cells, retinal pigment epithelium (RPE) cells, and myofibroblasts are shown to be mostly involved in ERM formation [33].

On OCT, ERMs are seen as a highly reflective layer on the inner retinal surface. The membrane is adherent to the retina, but sometimes, it can be separated from the inner aspect of the retina, which enhances its visibility by OCT. Secondary effects of the membrane can be the loss of the normal foveal contour, increased retinal thickness, and the presence of cystoid changes [40].

The effectiveness of subconjunctival steroid therapy and the introduction of highly effective systemic immunosuppressive drugs and biologicals have had a significant impact on controlling this potentially blinding and painful inflammatory eye disease [41]. The macular complications influenced the visual prognosis and the treatment as well.

The main cause leading to macular edema is the breakdown of either the inner or outer, or both blood–retina barriers (BRB) and is a consequence of chronic inflammation. Extracellular fluid is accumulated either in the intraretinal or the subretinal space. The macular edema can be found in the outer nuclear layer or extend more superficially or deeply before affecting all retinal layers. This results from the sum-up of cytotoxic and vasogenic effects due to immunological aggression [30].

The outer (BRB) is important for maintaining the adhesion between the retinal pigment epithelium (RPE) and photoreceptors. Inflammatorical conditions that involve the sclera could damage the outer BRB, and despite the healthy retinal capillary endothelium, macular edema might occur. Other causes may also increase the macular thickness, such as inflammatorical ERM formation with associated vitreomacular traction [30].

TNF can also have a significant part in the pathogenesis of ME. Infliximab is currently licensed to be used as a third-line agent in scleritis therapy following the development of tolerance or failure to respond to first-line corticosteroid and to second-line corticosteroid-sparing agents. Until now, it is not proven that the earlier introduction of anti-TNF agents would give additional benefits to the management of ME and the preservation of visual function [10]. It is proven that inhibiting the level of TNF- α decreases the incidence of ME [10,14].

We can state that OCT findings help ophthalmologists determine visual outcomes. ME and ERM can cause worsening of vision, but visual improvement can be achieved by systemic and additional ophthalmologic therapy. CME, SRD, DME, and ERM negatively affect VA. Especially in chronic scleritis cases, ME and ERM could work as biomarkers since biomarkers provide an objective, measurable method of evaluating the disease process. Some biomarkers can help researchers to identify the risk factors of the disease [35]. The photoreceptor layer is concerned with the fact that, because of the long-standing (chronic or persistent) or frequently recurrent pathologies, visual acuity will not be better in spite of the best therapy.

The limitation of our study is the low number of patients, as the prevalence of scleritis is six cases per 10,000 people.

5. Conclusions

OCT has revolutionized patient care because it allows early, accurate diagnosis and better follow-up of patients. To the best of our knowledge, this is the first report that investigates macula in anterior scleritic patients. We detected OCT examinations of all of our patients since we thought that OCT would be a suitable, non-invasive method to detect macular pathology, and our results proved that it was. We found that the reduced VA in cases of scleritis patients could be the consequence of macular involvement.

In conclusion, besides treating scleritis patients, the examination of their macula by OCT is also very important in order to detect any macular complications caused by inflammation since CME is the leading cause of decreased vision. ERM is also associated with poor vision. Macular pathologies seen on OCT can modify the management of scleritis.

OCT plays an important role in measuring inflammatorical activity, determining the severity of inflammation, choosing the best treatment, the response to treatment, and avoiding legal blindness. Biomarkers on OCT in scleritic patients, such as CME, DME, SRD, and ERM, are also very useful in order to find the right diagnosis and treatment in time.

Author Contributions: Investigation, N.S. and L.S.; writing—original draft preparation, N.S. and L.S.; writing—review and editing, N.S. and L.S.; supervision, E.T.-M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Human Investigation Review Board University of Szeged Albert Szent-Györgyi Clinical Centre (protocol code 4693 and date of approval 20 January 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AMD	age-related macular degeneration
BCVA	best corrected visual acuity
BRB	blood–retina barrier
CME	cystoid macular edema
CRT	central retina thickness
DME	diffuse macular edema
ERM	epiretinal membrane
ETDRS	early treatment of diabetic retinopathy study
ME	macular edema
MTX	methotrexate
NIH	National Institution of Health
OCT	optical coherence tomography
RPE	retinal pigment epithelium
SLE	Systemic Lupus Erythematosus
SRD	serous retinal detachment
TA	triamcinolone-acetate
VA	visual acuity

References

1. Cunningham, E.T.; McCluskey, P.; Pavesio, C.; Wakefield, D.; Zierhut, M. Scleritis. *Ocul. Immunol. Inflamm.* **2016**, *24*, 2–5. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Ahn, S.J.; Oh, J.Y.; Kim, M.K.; Lee, J.H.; Wee, W.R. Clinical Features, Predisposing Factors, and Treatment Outcomes of Scleritis in the Korean Population. *Korean J. Ophthalmol.* **2010**, *24*, 331–335. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Sims, J. Scleritis: Presentations, disease associations and management. *Postgrad. Med. J.* **2012**, *88*, 713–718. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Diogo, M.; Jager, M.; Ferreira, T. CT and MR Imaging in the Diagnosis of Scleritis. *Am. J. Neuroradiol.* **2016**, *37*, 2334–2339. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Sen, H.N.; Sangave, A.A.; Goldstein, D.A.; Suhler, E.B.; Cunningham, D.; Vitale, S.; Nussenblatt, R.B. A Standardized Grading System for Scleritis. *Ophthalmology* **2011**, *118*, 768–771. [\[CrossRef\]](#)
6. Vermeirsch, S.; Testi, I.; Pavesio, C. Choroidal involvement in non-infectious posterior scleritis. *J. Ophthalmic Inflamm. Infect.* **2021**, *11*, 41. [\[CrossRef\]](#)
7. Watson, P.; Romano, A. The impact of new methods of investigation and treatment on the understanding of the pathology of scleral inflammation. *Eye* **2014**, *28*, 915–930. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Wieringa, W.G.; Wieringa, J.E.; Loon, N.H.T.D.-V.; Los, L.I. Visual Outcome, Treatment Results, and Prognostic Factors in Patients with Scleritis. *Ophthalmology* **2013**, *120*, 379–386. [\[CrossRef\]](#)
9. Vergouwen, D.; Rothova, A.; Berge, J.T.; Verdijk, R.; van Laar, J.; Vingerling, J.; Schreurs, M. Current insights in the pathogenesis of scleritis. *Exp. Eye Res.* **2020**, *197*, 108078. [\[CrossRef\]](#)
10. Majumder, P.D.; Agrawal, R.; McCluskey, P.; Biswas, J. Current Approach for the Diagnosis and Management of Noninfective Scleritis. *Asia-Pac. J. Ophthalmol.* **2020**, *10*, 212–223. [\[CrossRef\]](#)
11. Dong, Z.-Z.; Gan, Y.-F.; Zhang, Y.-N.; Zhang, Y.; Li, J.; Zheng, H.-H. The clinical features of posterior scleritis with serous retinal detachment: A retrospective clinical analysis. *Int. J. Ophthalmol.* **2019**, *12*, 1151–1157. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Agrawal, R.; Lee, C.S.; Gonzalez-Lopez, J.J.; Khan, S.; Rodrigues, V.; Pavesio, C. Flurbiprofen: A Nonselective Cyclooxygenase (COX) Inhibitor for Treatment of Noninfectious, Non-necrotizing Anterior Scleritis. *Ocul. Immunol. Inflamm.* **2016**, *24*, 35–42. [\[CrossRef\]](#)
13. Rossi, D.C.; Ribi, C.; Guex-Crosier, Y. Treatment of chronic non-infectious uveitis and scleritis. *Swiss Med. Wkly.* **2019**, *149*, w20025. [\[CrossRef\]](#)
14. Wakefield, D.; Di Girolamo, N.; Thurau, S.; Wildner, G.; McCluskey, P. Scleritis: Challenges in immunopathogenesis and treatment. *Discov. Med.* **2013**, *16*, 153–157. [\[PubMed\]](#)
15. Sands, D.S.; Chan, S.C.; Gottlieb, C.C. Methotrexate for the treatment of noninfectious scleritis. *Can. J. Ophthalmol.* **2018**, *53*, 349–353. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Selves, A.M.; Arcinue, C.A.; González-Martín, J.M.; Kruh, J.N.; Foster, C.S. Analysis of a Novel Protocol of Pulsed Intravenous Cyclophosphamide for Recalcitrant or Severe Ocular Inflammatory Disease. *Ophthalmology* **2013**, *120*, 1201–1209. [\[CrossRef\]](#)
17. Kaçmaz, R.O.; Kempen, J.H.; Newcomb, C.; Daniel, E.; Gangaputra, S.; Nussenblatt, R.B.; Rosenbaum, J.T.; Suhler, E.B.; Thorne, J.E.; Jabs, D.A.; et al. Cyclosporine for ocular inflammatory diseases. *Ophthalmology* **2010**, *117*, 576–584. [\[CrossRef\]](#)
18. Farci, R.; Sellam, A.; Coscas, F.; Coscas, G.J.; Diaz, G.; Napoli, P.E.; Souied, E.; Galantuomo, M.S.; Fossarello, M. Multimodal OCT Reflectivity Analysis of the Cystoid Spaces in Cystoid Macular Edema. *Biomed. Res. Int.* **2019**, *2019*, 7835372. [\[CrossRef\]](#)
19. Leitgeb, R. En face optical coherence tomography: A technology review. *Biomed. Opt. Express* **2019**, *10*, 2177–2201. [\[CrossRef\]](#)
20. Trichonas, G.; Kaiser, P.K. Optical coherence tomography imaging of macular oedema. *Br. J. Ophthalmol.* **2014**, *98* (Suppl. S2), ii24–ii29. [\[CrossRef\]](#)

21. Bhende, M.; Shetty, S.; Parthasarathy, M.K.; Ramya, S. Optical coherence tomography: A guide to interpretation of common macular diseases. *Indian J. Ophthalmol.* **2018**, *66*, 20–35. [[CrossRef](#)] [[PubMed](#)]
22. Bouma, B.E.; de Boer, J.F.; Huang, D.; Jang, I.-K.; Yonetsu, T.; Leggett, C.L.; Leitgeb, R.; Sampson, D.D.; Suter, M.; Vakoc, B.J.; et al. Optical coherence tomography. *Nat. Rev. Methods Prim.* **2022**, *2*, 79. [[CrossRef](#)]
23. Hee, M.R.; Izatt, J.A.; Swanson, E.A.; Huang, D.; Schuman, J.S.; Lin, C.P.; Puliafito, C.A.; Fujimoto, J.G. Optical Coherence Tomography of the Human Retina. *Arch. Ophthalmol.* **1995**, *113*, 325–332. [[CrossRef](#)] [[PubMed](#)]
24. Kempen, J.H.; Sugar, E.A.; Jaffe, G.J.; Acharya, N.R.; Dunn, J.P.; Elner, S.G.; Lightman, S.L.; Thorne, J.E.; Vitale, A.T.; Altaweel, M.M. Fluorescein Angiography versus Optical Coherence Tomography for Diagnosis of Uveitic Macular Edema. *Ophthalmology* **2013**, *120*, 1852–1859. [[CrossRef](#)] [[PubMed](#)]
25. Huang, D.; Swanson, E.A.; Lin, C.P.; Schuman, J.S.; Stinson, W.G.; Chang, W.; Hee, M.R.; Flotte, T.; Gregory, K.; Puliafito, C.A.; et al. Optical Coherence Tomography. *Science* **1991**, *254*, 1178–1181. [[CrossRef](#)] [[PubMed](#)]
26. Spaide, R.F.; Curcio, C.A. Anatomical correlates to the bands seen in the outer retina by optical coherence tomography: Literature review and model. *Retina* **2011**, *31*, 1609–1619. [[CrossRef](#)]
27. Han, I.C.; Jaffe, G.J. Evaluation of Artifacts Associated with Macular Spectral-Domain Optical Coherence Tomography. *Ophthalmology* **2010**, *117*, 1177–1189.e4. [[CrossRef](#)]
28. Staurenghi, G.; Sadda, S.; Chakravarthy, U.; Spaide, R.F. Proposed lexicon for anatomic landmarks in normal posterior segment spectral-domain optical coherence tomography: The IN*OCT consensus. International Nomenclature for Optical Coherence Tomography (IN*OCT) Panel. *Ophthalmology* **2014**, *121*, 1572–1578. [[CrossRef](#)]
29. Krebs, I.; Smretschnik, E.; Moussa, S.; Brannath, W.; Womastek, I.; Binder, S. Quality and Reproducibility of Retinal Thickness Measurements in Two Spectral-Domain Optical Coherence Tomography Machines. *Investig. Ophthalmol. Vis. Sci.* **2011**, *52*, 6925–6933. [[CrossRef](#)]
30. Massa, H.; Pipis, S.Y.; Adewoyin, T.; Vergados, A.; Patra, S.; Panos, G.D. Macular edema associated with non-infectious uveitis: Pathophysiology, etiology, prevalence, impact and management challenges. *Clin. Ophthalmol.* **2019**, *13*, 1761–1777. [[CrossRef](#)]
31. Pichi, F.; Invernizzi, A.; Tucker, W.R.; Munk, M.R. Optical coherence tomography diagnostic signs in posterior uveitis. *Prog. Retin. Eye Res.* **2019**, *75*, 100797. [[CrossRef](#)] [[PubMed](#)]
32. Markomichelakis, N.N.; Halkiadakis, I.; Pantelia, E.; Peponis, V.; Patelis, A.; Theodossiadi, P.; Theodossiadi, G. Patterns of macular edema in patients with uveitis: Qualitative and quantitative assessment using optical coherence tomography. *Ophthalmology* **2004**, *111*, 946–953. [[CrossRef](#)] [[PubMed](#)]
33. Iannetti, L.; Tortorella, P.; D’ambrosio, E.; Spena, R.; Zito, R.; Gharbiya, M. Epiretinal Membranes in Patients with Uveitis: Morphological and Functional Analysis with Spectral Domain Optical Coherence Tomography. *Biomed. Res. Int.* **2013**, *2013*, 284821. [[CrossRef](#)] [[PubMed](#)]
34. Iuliano, L.; Fogliato, G.; Gorgoni, F.; Corbelli, E.; Bandello, F.; Codenotti, M. Idiopathic epiretinal membrane surgery: Safety, efficacy and patient related outcomes. *Clin. Ophthalmol.* **2019**, *13*, 1253–1265. [[CrossRef](#)] [[PubMed](#)]
35. Califf, R.M. Biomarker definitions and their applications. *Expl. Biol. Med.* **2018**, *243*, 213–221. [[CrossRef](#)]
36. Do, D.V.; Cho, M.; Nguyen, Q.D.M.; Shah, S.M.; Handa, J.T.; Campochiaro, P.A.; Zimmer-Galler, I.; Sung, J.U.; Haller, J.A. Impact of optical coherence tomography on surgical decision making for epiretinal membranes and vitreomacular traction. *Retina* **2007**, *27*, 552–556. [[CrossRef](#)]
37. Dhirachaikulpanich, D.; Chanthongdee, K.; Zheng, Y.; Beare, N.A.V. A systematic review of OCT and OCT angiography in retinal vasculitis. *J. Ophthalmic Inflamm. Infect.* **2023**, *13*, 1. [[CrossRef](#)]
38. Iannetti, L.; Accorinti, M.; Liverani, M.; Caggiano, C.; Abdulaziz, R.; Pivetti-Pezzi, P. Optical Coherence Tomography for Classification and Clinical Evaluation of Macular Edema in Patients with Uveitis. *Ocul. Immunol. Inflamm.* **2008**, *16*, 155–160. [[CrossRef](#)]
39. Kumar, D.A.; Maitra, P.; Agarwal, A. Epiretinal membrane profile on spectral domain optical coherence tomography in patients with uveitis. *Indian J. Ophthalmol.* **2019**, *67*, 376–381. [[CrossRef](#)] [[PubMed](#)]
40. Vinos, S.A.; Campochiaro, P.A.; Conway, B.P. Ultrastructural and electron-immunocytochemical characterization of cells in epiretinal membranes. *Investig. Ophthalmol. Vis. Sci.* **1990**, *31*, 14–28.
41. Ingaralingam, S.; Rauz, S.; Murray, P.I.; Barry, R.J. Effectiveness of pharmacological agents for the treatment of non-infectious scleritis: A systematic review protocol. *Syst. Rev.* **2020**, *9*, 54–57. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

A biológiai terápia helye a gyermekkori uveitis ellátásában

Smeller Lilla dr.¹ ■ Sümegi Viktória dr.²
Tóth-Molnár Edit dr.¹ ■ Sohár Nicolette dr.¹

¹Szegedi Tudományegyetem, Általános Orvostudományi Kar, Szemészeti Klinika, Szeged

²Szegedi Tudományegyetem, Általános Orvostudományi Kar, Reumatológiai és Immunológiai Klinika, Szeged

Bevezetés: A gyermekkori uveitisek kezelésében 2016 óta van lehetőség biológiai terápia alkalmazására. Szemészeti indikáció esetén adalimumabbal indítható terápia, mely egy tumor nekrozisfaktor-ellenes monoklonális antitest.

Célkitűzés: Klinikánk uveitisambulanciáján a gyermekkori uveitis miatt kezelt betegek adatainak retrospektív feldolgozása alapján a nem fertőzőes eredetű uveitis esetén alkalmazott adalimumabkezelésről szerzett tapasztalataink összefoglalása.

Betegek és módszerek: Restrospektív módon elemeztük a Szegedi Tudományegyetem Szemészeti Klinikáján 2017. 01. 01. és 2021. 05. 31. között uveitis miatt gondozott gyermekek adatait.

Eredmények: 2017 és 2021 között 46 uveitises gyermeket vizsgáltunk klinikánkon. A 23 lány és 23 fiúgyermek átlag-életkora 11 év volt. Közülük 21 gyermek szenvedett juvenilis idiopathiás arthritisben, 14 gyermeknél igazolódott infekció, 3 gyermeknél hematológiai betegség okozta az elváltozást, 8 gyermeknél idiopathiás eredetű volt a gyulladás. Krónikus, súlyos uveitis miatt 11 gyermeknél indítottunk biológiai terápiát az Európai Gyógyszerügynökség engedélye alapján. 3 fiúgyermek és 8 lánygyermek részesült adalimumabkezelésben, átlagéletkoruk 10 év volt. 6 gyermeknél anterior, 5 gyermeknél panuveitis indikálta a kezelést. Az adalimumab alkalmazási leirata szerint 2 évnél idősebb gyermekeknek a krónikus, nem fertőzőes eredetű szemgyulladás kezelésére alkalmazható, amikor a gyulladás a szem elülső részét érinti. Panuveitises betegeink esetén gyermekreumatológus segítségét kértük a biológiai terápia engedélyezéséhez.

Következtetés: A gyermekkori uveitisek és azok terápiájának jelentősége kiemelkedő. A szemészeti kezelés célja a gyermekek látásélességének megőrzése és a szemészeti szövődmények megelőzése mellett a betegek megfelelő életminőségének biztosítása. Kiemelkedő fontosságú a korai diagnózis, a megfelelő terápia, a rendszeres kontrollvizsgálat. Az adalimumab hatékonyságát mutatja, hogy a kezelt gyermekek jelentős százalékánál sikerült a teljes látásélességet elérni, valamint a kezelés mellett újabb szemészeti szövődmény nem alakult ki. Orv Hetil. 2022; 163(35): 1402–1408.

Kulcsszavak: gyermekkori uveitis, biológiai terápia, adalimumab

Biological therapy of uveitis in children

Introduction: Biological therapy can be used in uveitis in children since 2016. With ophthalmological indication only adalimumab therapy can be started. Adalimumab is a monoclonal antibody that inhibits tumor necrosis factor alpha.

Objective: To summarize our experience with patients receiving adalimumab for pediatric non-infectious uveitis.

Patients and methods: We investigated our juvenile patients of non-infectious uveitis treated with adalimumab between 2017 and 2021 in a retrospective case series at the Department of Ophthalmology, Szeged University.

Results: Between 01 January, 2017 and 31 May, 2021, we examined 46 children with uveitis. The mean age of these 23 girls and 23 boys was 11 years. 21 of them had juvenile idiopathic arthritis, 14 had infectious uveitis, 3 had haematological disorders, 8 had idiopathic uveitis. Adalimumab was given to 11 patients because of severe, chronic uveitis. There were 3 boys and 8 girls, their mean age was 10 years. Adalimumab was given according to the licence of the European Medicines Agency. Indication was anterior uveitis at 6 children, panuveitis at 5 children. Adalimumab can be given to children over 2 years, who have chronic, non-infectious, anterior uveitis. Children with panuveitis received the therapy by the help of a pediatric rheumatologist.

Conclusion: The significance of pediatric uveitis and its therapy is emergent. Our aim was to preserve vision and decrease the possibilities of side effects and to provide a better life for these uveitic children. Early diagnosis, adequate therapy and regular ophthalmological check-ups are important. Children treated with adalimumab have good visual acuity due to the effectiveness of the therapy. No new ocular side effect was detected at the children treated with adalimumab.

Keywords: pediatric uveitis, biological therapy, adalimumab

Smeller L, Sümegi V, Tóth-Molnár E, Sohár N. [Biological therapy of uveitis in children]. *Orv Hetil.* 2022; 163(35): 1402–1408.

(Beérkezett: 2022. május 11.; elfogadva: 2022. június 9.)

Rövidítések

ANA = antinukleáris antitest; CMO = cystoid maculaoedema; DMARD = (disease-modifying anti-rheumatic drug) a betegséglefolyást módosító reumaellenes szer; EMA = (European Medicines Agency) Európai Gyógyszerügynökség; EMMI = Emberi Erőforrások Minisztériuma; HLA-B27 = humán leukocitaantigén B27; JIA = juvenilis idiopathiás arthritis; NEAK = Nemzeti Egészségbiztosítási Alapkezelő; OGYÉI = Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet; RF = reumafaktor; TINU = tubulointerstitialis nephritis és uveitis; TNF = tumornekrozis-faktor; UMS = uveitis „masquerade” szindróma

A gyermekkori uveitisek az uveitises esetek 5–10%-át teszik ki. Mind a diagnózis felállítását, mind a terápiát tekintve kihívás a kórkép a gyakorló szemészek számára. A betegség incidenciája megközelítőleg 50/100 000 fő, prevalenciája 100/100 000 fő. A gyermekkori vakság 10%-áért felelős az uveitis. Gyermekeknél a krónikus anterior uveitis fordul elő a leggyakrabban, ezt követi a posterior, az intermedier, majd a panuveitis [1–4]. A gyermekkori uveitisek a leggyakrabban önálló kórképként, idiopathiás formában fordulnak elő, számos esetben azonban poliszisztémás gyulladásos, illetve autoimmun kórképhez, főként juvenilis idiopathiás arthritishez (JIA) társulva jelentkezik [5–7]. Az uveitises gyermekek 50%-ában jelentkezik szemészeti szövődmények, a legtöbbször synechiák, zöld hályog és szürke hályog fordul elő. 25–40%-ban látásromlással jár a betegség, 10–20%-ban pedig teljes vakságot okozhat a macula, illetve a látóideg érintettsége miatt.

A szemészeti terápia elsődleges célja a szövődmények megelőzése és a látásélesség megőrzése [8, 9]. A tumornekrozisfaktor-alfa (TNF α)-gátlók csoportjába tartozó adalimumab 2016 óta alkalmazható gyermekkori, nem fertőzőes eredetű anterior uveitis esetén [10]. Intermedier, posterior és panuveitis esetén egyedi méltányossági kérelem beadására van lehetőség, melyet az Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézethez (OGYÉI) kell eljuttatni. Az OGYÉI-engedély birtokában a kezeléshez szükséges kérvény a Nemzeti Egészségbiztosítási Alapkezelő (NEAK) részére is benyújtandó. Indokolt esetben társszakmák segítségével indítható a biológiai terápia. Az adalimumabterápia kiemelt jelentőségét mutatja, hogy ez az első és egyben napjainkig az egyetlen, uveitisindikáció esetén alkalmazható biológiai terápiás készítmény [11–14].

A Klinikánkon kezelt uveitises gyermekek esetén biológiai terápiaként Humira került indításra. Az adalimumab adagolása az EMA (European Medicines Agency) hivatalos leirata szerint a következő: 2 éves kor feletti, 30 kg-nál kisebb testtömegű gyermekek és serdülők 20 mg-ot kaphatnak minden második héten subcutan injekció formájában. A kezelőorvos egy 40 mg-os kezdő dózist is felírhat, melyet egy héttel a szokásos, kéthetente 20 mg-os adagolás megkezdése előtt kell beadni. 2 éves kor feletti, legalább 30 kg testtömegű gyermekek és serdülők 40 mg-ot kapnak minden második héten. A kezelőorvos egy 80 mg-os kezdő dózist is felírhat, melyet egy héttel a szokásos, kéthetente 40 mg-os adagolás megkezdése előtt kell beadni.

Az adalimumabot metotrexáttal kombinálva javasolt alkalmazni [14–16]. A metotrexát egy folsavantagonista, mely hosszú ideig hatásos lehet, és biztonságosan adható. Terápiás dózisa 10–15 mg/m²/hét vagy 0,5–1 mg/kg/hét. Használata mellett folsavat kell alkalmaznunk 1 mg/kg/nap dózisban, a mellékhatások (csontvelő-szuppresszió, hányinger, fekélyek kialakulása a szájban, hajhullás) kivédésére.

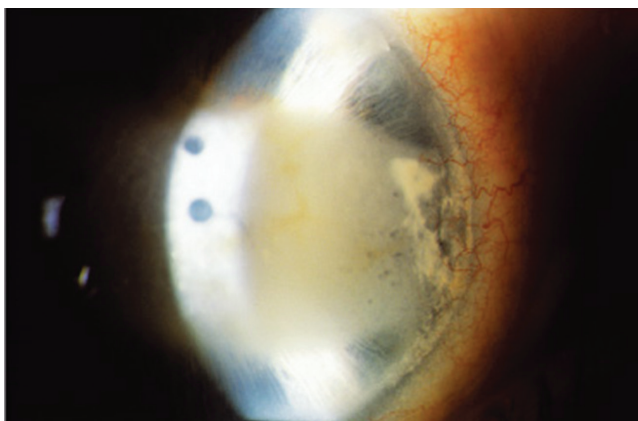
Célkitűzés

Közleményünkben a Klinikánk uveitiscentrumában uveitis miatt kezelt és adalimumabterápiában részesülő gyermekekkel kapcsolatos tapasztalatainkat foglaljuk össze. Kutatásunkhoz a Szegedi Tudományegyetem Etikai Bizottsága adott etikai engedélyt (engedélyszám: 5053).

Betegek és módszerek

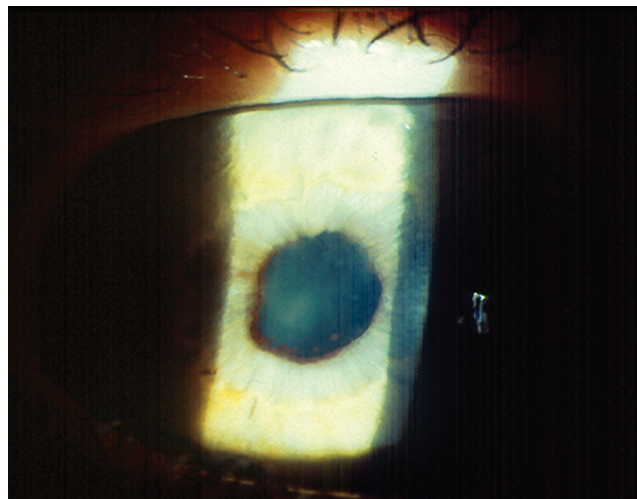
Retrospektív módon elemeztük a Szegedi Tudományegyetem Szemészeti Klinikáján 2017. január 1. és 2021. május 31. között uveitis miatt kezelt gyermekek adatait. Azokat az adalimumabbal kezelt gyermekkori, nem fertőzőes eredetű uveitises eseteket dolgoztuk fel, amelyeknél az adalimumabterápia uveitis indikációjával került indításra. A vizsgálatba nem válogattuk be azokat a betegeket, akiknél a kezelés indikációja a szisztémás alapbetegségük volt. A betegek átlagéletkora az adalimumabkezelés kezdetén 10 (4–13) év volt.

A biológiai terápia engedélyeztetése előtti kivizsgálást a gyógyszerleiratban meghatározottak szerint végeztük. A betegek vizsgálataiban, azok koordinálásában gyermekreumatológus kolléga volt segítségünkre [17–19].



1. ábra

„Band” keratopathia képe. A „band” keratopathia a krónikus elülső szegmentum gyulladására következtében felhalmozódó kalciumnak a Bowman-membránban való lerakódása következtében alakul ki, és a leggyakrabban az interpalpebralis cornea régiójában jelenik meg. A legmodernebb terápiás lehetőségek ellenére is súlyos szemészeti szövődeményekkel gyógyulhat.



2. ábra

Szürke hályog képe. Juvenilis idiopathiás arthritishez (JIA) társult uveitis esetén korai komplikációként, illetve a szteroidterápia mellékhatásaként szürke hályog jelentkezhethet

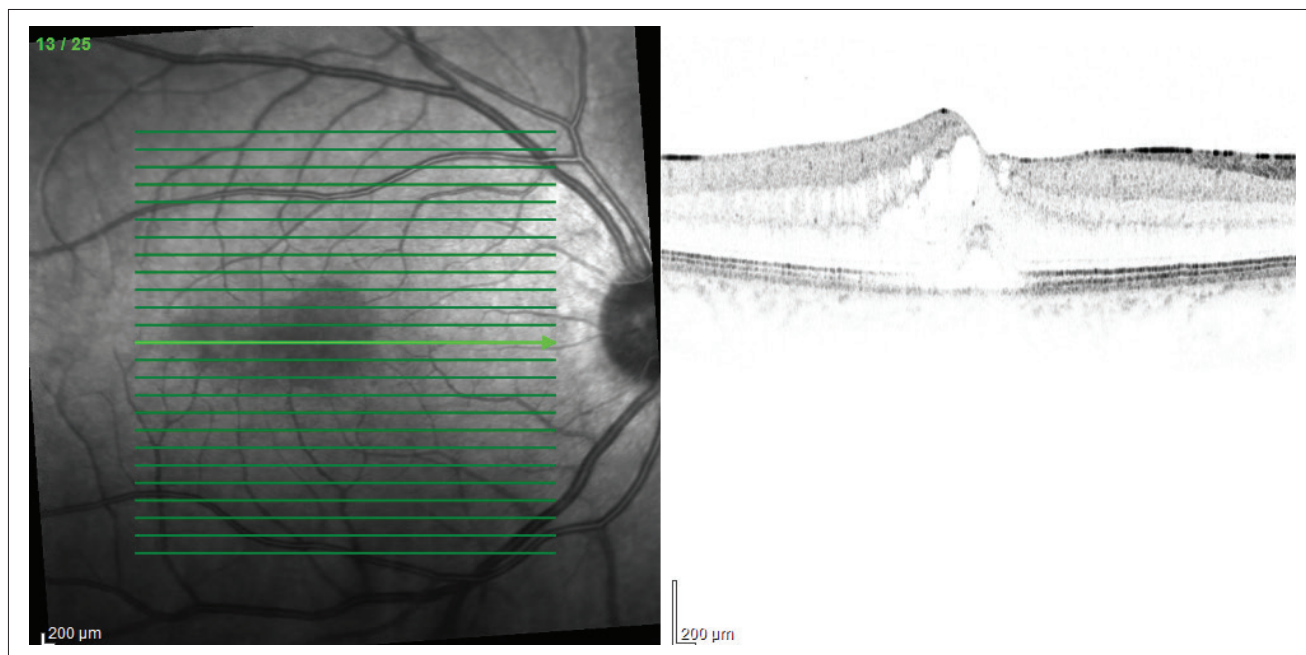
A diagnózis felállítása a fertőzések kizárását szolgáló szerológiai vizsgálatok (herpes simplex vírus 1–2, varicella zoster vírus, cytomegalovírus, Epstein–Barr-vírus, Toxocara, Toxoplasma, Borrelia burgdorferi, Treponema, hepatitis B, C), Quantiferon-teszt, szemészeti képalkotó eljárások, gyermekreumatológiai (ANA-, RF-, HLA-B27-mintavétel, szisztémás autoimmun betegségek vizsgálata), gyermekkardiológiai (szívechográfia), gyermekneurológiai (demyelinisációs kórkép kizárása), gyermekpulmonológiai (mellkasröntgen – sarcoidosis, tuberculosis kizárása), gyermeknefrológusi (TINU kizárása) konzíliumok segítségével történt [20–23].

Eredmények

A 2017. január 1. és 2021. május 31. közötti időszakban uveitiscentrumunkban 46 gyermeket kezeltünk, átlagos életkoruk az uveitis diagnózisakor 11 (3–18) év volt. Nemi megoszlásuk azonos volt (23 leány, 23 fiú).

A gyulladás lokalizációja alapján az anterior uveitis volt a leggyakoribb (36,9%, 17/46), ezt követte a posterior uveitis (26%, 12/46), a panuveitis (21%, 10/46) és végül az intermedier forma (15%, 7/46).

Betegeink nagy részénél (45,6%, 21/46) JIA állt a háttérben, 1 gyermeknél (2%, 1/46) akut myeloid leu-



3. ábra

Cystoid maculaoedema kezelés előtti OCT-képe

OCT = optikaikoherencia-tomográfia

1. táblázat | Az adalimumabkezelésben részesülő gyermekek adatai, az uveitis lokalizációja és a látásélesség változása

Nem	Kiváltó ok	Lokalizáció	Életkor kezdetkor	Terápia adalimumab előtt	Visus terápia előtt o. d.	Visus terápia előtt o. s.	Visus terápia után o. d.	Visus terápia után o. s.
1. Lány	pJIA	AU	10 év	Maxidex, ciclo, NSAID, MTX	1,0	1,0	1,0	1,0
2. Lány	JIA	AU	4 év	Medrol, MTX	1,0	1,0	1,0	1,0
3. Lány	pJIA	AU	6 év	Maxidex, Tobradex, MTX	1,0	1,0	1,0	1,0
4. Lány	JIA	AU	9 év	Maxidex, ciclo, sc. dexta, Medrol,	0,6	0,8	1,0	1,0
5. Lány	JIA	Panuveitis	11 év	Maxidex, ciclo, sc. dexta, Medrol, MTX	0,7	0,6	1,0	1,0
6. Fiú	JIA	Panuveitis	7 év	Maxidex, MTX	0,6	0,06	1,0	1,0
7. Fiú	JIA	AU	12 év	Maxidex, ciclo, sc. dexta, Medrol, MTX	1,0	1,0	1,0	1,0
8. Lány	JIA	Panuveitis	13 év	Pb. dexta, Medrol, MTX, Sub-Tenon Kenalog	0,01	1,0	1,0	1,0
9. Fiú	JIA	Panuveitis	12 év	Maxidex, Medrol, MTX, Sandimmun	0,3	0,7	0,6	0,6
10. Lány	Idiopathiás	Panuveitis	10 év	Maxidex, Medrol, MTX, Sub-Tenon Kenalog	0,6	1,0	1,0	1,0
11. Lány	JIA	AU	9 év	Maxidex, Medrol, MTX	1,0	1,0	1,0	1,0

AV = anterior weitis; ciclo = ciklopentolát; JIA = juvenilis idiopathiás arthritis; MTX = metotrexát; NSAID = nemszteroid gyulladáscsökkentő gyógyszer; o. d. = jobb szem; o. s. = bal szem; Pb. dexta = parabulbarisan alkalmazott dexametazoninjekció; pJIA = polyarticularis juvenilis idiopathiás arthritis; sc. dexta = subconjunctivalisan alkalmazott dexametazoninjekció

kaemiához, 1 gyermeknél (2%, 1/46) szisztémás sclerodermához és 1 gyermeknél (2%, 1/46) HLA-B27-asszociált arthritishoz társult az uveitis.

14 betegnél (30%, 14/46) infekció volt a kiváltó tényező: 7 esetben (15%, 7/46) *Toxocara canis*, 4 esetben (8,5%, 4/46) *Toxoplasma gondii*, 1 esetben (2%, 1/46) *Borrelia*-, 1 esetben *Bartonella*-, 1 esetben herpes simplex fertőzés igazolódott.

Betegeink 30%-ában (17/46) diagnosztikus vizsgálatainkkal nem volt kimutatható autoimmun kórkép vagy fertőzés.

A gyermekek kezelését az Emberi Erőforrások Minisztériuma (EMMI) által előírt, jelenleg érvényben lévő protokollok szerint végezzük, ezek alapján a 46 gyermekből 11-nél (23,9%) indítottunk a szakma szabályai szerint uveitis miatt adalimumabterápiát.

Az adalimumabbal kezelt betegcsoportban a kezelés megkezdése előtt már megjelentek az uveitis következtében kialakuló különböző szövődmények: 2 gyermeknél (25%) „band” keratopathia (1. ábra), 2 betegnél szemcseppekkel kontrollálható secundaer glaucoma, 2 esetben (18%) szürke hályog (2. ábra) és 2 gyermeknél (18%) cystoid maculaedema (CMO) (3. ábra) került diagnosztizálásra [12, 14, 16, 17]. A kezelés megkezdése előtt (a protokollnak megfelelően) minden beteg szisztémás szteroidkezelésben részesült. A jelenleg is kezelés alatt álló 10 beteg közül az adalimumabkezelési leiratnak megfelelően mindenki immunszuppresszív kezeléssel, metotrexáttal kombinált terápiát kap [20–23].

Az uveitis aktivitása a folyamatosan kezelés alatt álló betegeknek a megfigyelési időszak során jelentős javulást

mutatott, illetve teljes mértékben megszűnt [16]. A látóélesség változása is ezt tükrözi: a legjobb korrigált látóélesség átlaga az adalimumabkezelés kezdetén a jobb szemén 0,71, a bal szemén 0,83 volt. Ez az érték a követési időszak végén mindkét szemén 0,96-ra javult, mely azóta egyik beteg esetén sem mutatott ismételt romlást.

A kezelés megkezdését követően átlagosan 2,5 (1–7) hónapon belül mind a 10 betegnél teljes remissziót észleltünk. Átmeneti, lokális bőrreakció nem alakult ki. 1 gyermeknél a kezelés ideje alatt, a terápia indítása után 14 hónappal gyermekonkológus klasszikus Hodgkin-lymphomát diagnosztizált. Nála az adalimumabkezelést felfüggesztettük.

Az 1. táblázat mutatja a gyermekek nemét, a betegség kiváltó okát, a szemészeti tüneteket, az adalimumabkezelést megelőző terápiát, a terápia indításakor a gyermekek életkorát, a kezelés előtti és utáni látásélességet.

Megbeszélés

A gyermekkori uveitisek ritka kórképek. Mind a diagnózis, mind a terápia igazi kihívás a szemészorvos számára. A betegek megfelelő ellátásához multidiszciplináris szemléletre van szükségünk [8, 9, 20–22].

A gyermekek sokszor nem panaszkodnak, illetve nem tudják panaszukat pontosan megfogalmazni. Emiatt gyakran előfordul, hogy a betegek első szemészeti vizsgálatára akkor kerül sor, amikor már súlyos szemészeti szövődmények alakultak ki. A szemészeti vizsgálat ered-

ményességét nagyban befolyásolhatja a gyermek együttműködési képessége.

A diagnosztikus vizsgálatok rendszeres és pontos elvégzése segítheti a betegség és az alkalmazott terápia hatásosságának utánkövetését, ez azonban gyermekek esetén sokszor jelent kihívást a szemész számára.

A gyermekkori uveitisek gyakran kétoldali megjelenésűek, krónikus lefolyásúak, jellemző a gyulladás visszatérő jellege. A gyermekkori uveitisek differenciáldiagnosztikája eltér a felnőttek esetén ismert és alkalmazandó protokolltól, gyakran találkozhatunk „masquerade” megjelenéssel [8, 9]. Ezek klinikai megjelenésükben intraocularis gyulladást utánoznak. Jellemző az intraocularisan infiltráló sejtek jelenléte, aminek hátterében noninfekciózus és nonimmunmediált folyamatok állnak. Az uveitisszel diagnosztizált esetek közel 5%-ában „masquerade” szindróma áll a háttérben. Uveitis „masquerade” szindrómát (UMS-t) okozhatnak például hematológiai betegségek (lymphoma, leukaemia), intraocularis idegen test vagy a retina ischaemiás károsodása. Az UMS-t kiváltó kórképeket malignus (például lymphoma, leukaemia, medulloepithelioma, retinoblastoma) és nem malignus (például Coats-betegség, juvenilis xantogranuloma) csoportba sorolhatjuk.

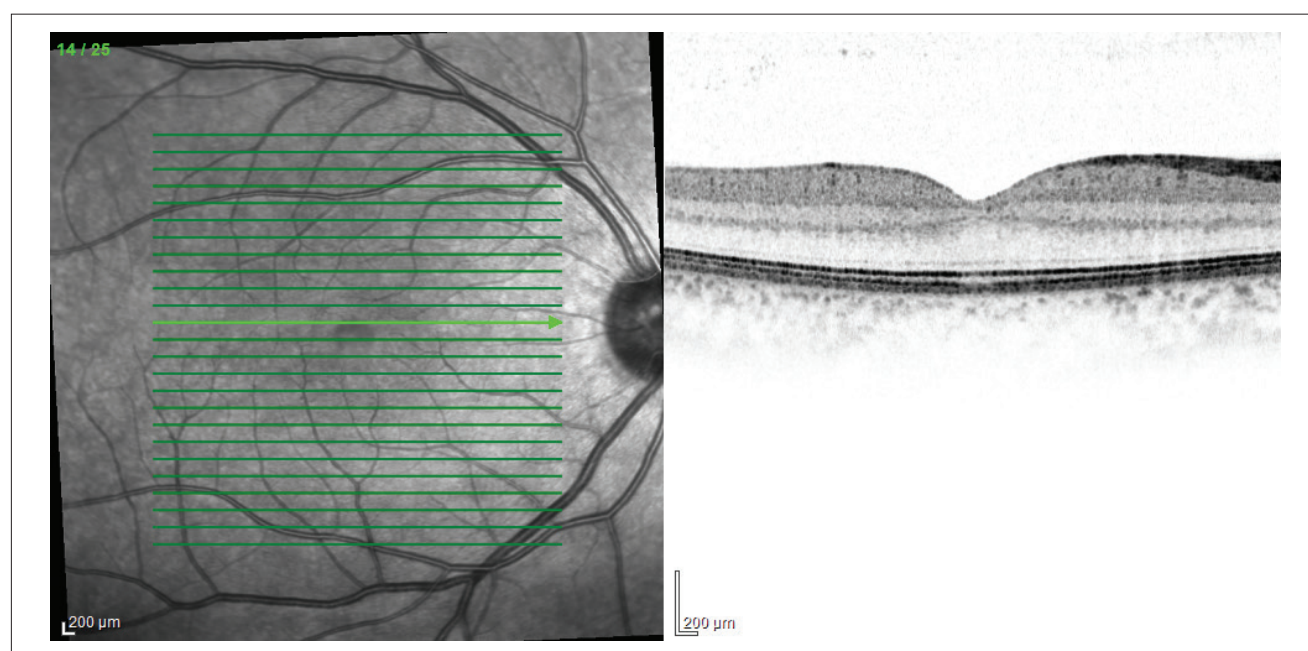
A gyermekkori uveitisek gyakran súlyos, krónikus, elhúzódó lefolyást mutató, terápiára nem vagy csak nehezen reagáló kórképek [16, 17]. Emiatt a megfelelő időben felállított pontos diagnózis és az időben megkezdett, „agresszív” terápia kiemelt jelentőséggel bír, hiszen a látásélesség elvesztése és a korán jelentkező szemészeti szövődmények ellen kell felvennünk a harcot. Kiemelkedő az a tényező is, hogy kisgyermekeknél az egyoldali

uveitis magában rejt az amblyopia kialakulásának veszélyét [8, 9].

Fontos megjegyezni, hogy a gyermekkori uveitis a legmodernebb terápiás lehetőségek ellenére is sokszor súlyos szemészeti szövődmény, maradványtünet mellett gyógyul. Ennek oka részben maga a gyulladás, másrészt egyes lokális és szisztémás szerek mellékhatásai. Szemészeti szövődményeként kialakulhat szürke hályog, intraocularis nyomásemelkedés, illetve glaucoma. A leggyakoribb szisztémás mellékhatások közé tartozik a pepticus fekélybetegség, a folyadékretenció, az elhízás, a cukorháztartás zavara és a fokozott thromboemboliás kockázat.

Az uveitisek terápiájában első vonalbeli szerként topikális kortikoszteroidot alkalmazunk. Amennyiben szükséges, ezt a kezelést a következő lépésben szisztémás szteroidterápiával egészítjük ki. Súlyos formában lökésterápiaként nagy dózisu parenteralis metilprednizolonkezelést indítunk, melyet alacsony dózisu, szájon keresztül adagolt szteroidkészítménnyel folytatunk.

Előfordul, hogy a gyulladás a fenti kezelés mellett 3 hónap alatt sem gyógyul, illetve szteroidreszponder lesz a beteg. Ebben az esetben szisztémás immunszuppresszív terápia, illetve betegségfolyást módosító reumaelenes szerek (DMARD-ok) bevezetése is szükséges. Napjainkban a metotrexát a leggyakrabban használt immunszuppresszív szer. Az irodalmi adatok alapján a gyermekek 73%-a jól reagál a kezelésre. Azoknál a gyermekeknél, akiknél nem érjük el a kívánt terápiás eredményt, a betegaktivitás magas volt, vagy súlyos gyulladást látunk metotrexáttérápia mellett is, harmadik vonalbeli terápiaként a biológiai terápia jön szóba [18, 19, 24–29].



4. ábra

Ugyanazon gyermek jobb szemének OCT-képe adalimumabterápia folyamán, 3 hónapos kezelés után

OCT = optikai koherencia-tomográfia

A betegségek patogenezisében szerepet játszó faktorkok ismeretének birtokában lehetőségünk van olyan terápiák kifejlesztésére és használatára, amelyek célzottan hatnak egyes sejtekre, citokinekre és gyulladásos faktorokra. A TNF α jelentőségének felfedezése óta próbálnak minél hatékonyabb TNF α -gátló kezelést kifejleszteni. Napjainkig öt TNF α -gátló készítményt hagytak jóvá autoimmun betegségek terápiájára. Felépítésüket tekintve az infliximab, az adalimumab, a certolizumab-pegol és a golimumab monoklonális antitestek, míg az etanercept fúziós fehérje [24, 29]. Hatásuk során gátolják a TNF α receptorhoz való kötődését és ezáltal a TNF α -szignalizációt. JIA-hoz kapcsolódó uveitis, spondylarthropathiához kapcsolódó uveitis, idiopathiás uveitis, sarcoidosis, Behcet-kór, számos noninfekciós uveitis, pars planitis esetén kerülhet sor az adalimumabterápia bevezetésére szemészeti indikációval. Az adalimumab rekombináns humán immunglobulin, monoklonális antitest, mely a TNF α p55 és p75 sejt felszíni receptorokhoz való kapcsolódását gátolja. Ezáltal módosítja a TNF indukálta biológiai válaszokat, illetve szabályozó funkciót is ellát. A fenti mechanizmus alapján csökkenti az elülső csarnok és az üvegtest gyulladását, valamint a retina vastagságát a macula területében [22–25, 28, 29] (4. ábra).

Az adalimumabterápia fontos hatása, hogy alkalmazása csökkenti a kortikoszteroid-igényt a kezelés során. Ennek gyermekkorban kiemelt jelentősége van, hiszen az általánosan alkalmazott kortikoszteroidok a csontrendszer fejlődésének gátlása által a növekedés elmaradását és a csontok gyakori törését okozhatják. Hirsutismus, striák, elhízás, hyperglykaemia, rossz sebgyógyulás lehet a terápia mellékhatása. Gyakran cushingoid megjelenés, peptikus fekély, myopathia, magas vérnyomás és pszichés zavar kísérheti a szteroidkezelést.

Az adalimumab mellékhatásprofilja alacsony, a jelenlegi tapasztalatok szerint nem provokál új, szemészeti mellékhatást.

A SYCAMORE-tanulmányban JIA-hoz kapcsolódó uveitises gyermekek adalimumabterápiában részesültek korábban beállított metotrexátkezelés mellett. Az adalimumabbal is kezelt gyermekeknél az uveitis jobban kontrollálható volt, az uveitis aktivitása lényegesen kisebb volt, továbbá csökkent a glükokortikoidszemcsepp-igényük is. A gyermekek jól tolerálták a kezelést, és a látásélesség tekintetében kitűnő eredményeket értek el. A terápia mellékhatásaként kisebb fertőzések, légzőszervi és emésztőrendszeri panaszok jelentkeztek. Hosszú távon kialakuló mellékhatások – mint például daganatos betegségek, demyelinisációs betegségek – nem jelentkeztek az öt éves utánkövetés alatt [19, 28–31].

Klinikánkon a gyermekkori uveitisek esetén végzett adalimumabterápia adatainak retrospektív elemzése alapján elmondhatjuk, hogy eredményeink megegyeznek az irodalmi adatokkal.

Következtetés

Az adalimumab szerepe kiemelkedő a gyermekkori uveitisek terápiájában. A terápia indításának optimális időpontja és a kezelés alkalmazásának pontos időtartama még nem teljesen tisztázott, további vizsgálatok vannak ezzel kapcsolatban folyamatban. Az uveitises, különösen a biológiai terápiával kezelt gyermekeknél a társszakkákkal való együttműködés a betegek kivizsgálásában, a kezelésben, az utánkövetésben elengedhetetlen. Cikkünk célja az volt, hogy Magyarországon először ismertessük a gyermekkori uveitis miatt adalimumabterápiában részesülő betegekkel kapcsolatos tapasztalatainkat.

Anyagi támogatás: A közlemény megírása, illetve a kapcsolódó kutatómunka anyagi támogatásban nem részesült.

Szerzői munkamegosztás: S. L.: Betegvizsgálat, betegkövetés, a fotóanyag készítése, a publikáció megírása. S. V.: Betegvizsgálat, betegkövetés. T.-M. E.: A publikáció megírásának követése. S. N.: Betegvizsgálat, betegkövetés, a fotóanyag készítése, a publikáció megírásának követése. A cikk végleges változatát valamennyi szerző elolvasta és jóváhagyta.

Érdekltségek: A szerzőknek nincsenek érdekltségeik.

Irodalom

- [1] Angeles-Han ST, Rabinovich CE. Uveitis in children. *Curr Opin Rheumatol.* 2016; 28: 544–549.
- [2] Couto C, Frick MM, LaMattina K, et al. Chronic anterior uveitis in children. *Ocul Immunol Inflamm.* 2016; 24: 392–396.
- [3] Majumder PD, Biswas J. Pediatric uveitis. An update. *Oman J Ophthalmol.* 2013; 6: 140–150.
- [4] Tugal-Tutkun I. Pediatric uveitis. *J Ophthalmic Vis Res.* 2011; 6: 259–69.
- [5] Ozdal PC, Sen E, Yazici A, et al. Patterns of childhood – onset uveitis in a referral center in Turkey. *J Ophthalmic Inflamm Infect.* 2012; 2: 13–19.
- [6] Nalcacioglu-Yüksekkaya P, Ozdal PC, Teke MY, et al. Presumed herpetic anterior uveitis: a study with retrospective analysis of 79 cases. *Eur J Ophthalmol.* 2014; 24: 14–20.
- [7] Pan J, Kapur M, McCallum R. Noninfectious immune-mediated uveitis and ocular inflammation. *Curr Allergy Asthma Rep.* 2014; 14: 409.
- [8] Sohár N, Skribek Á, Hammer H. Visual acuity in cases of juvenile uveitis. [A látásélesség alakulása gyermekkori uveitis esetében.] *Szemészet* 2011; 148: 73–76. [Hungarian]
- [9] Sohár N. Pediatric uveitis. [Gyermeekkori uveitisek.] *Szemészet* 2017; 154: 191–198. [Hungarian]
- [10] Pilly B, Heath G, Tschuor P, et al. Overview and recent developments in the medical management of paediatric uveitis. *Expert Opin Pharmacother.* 2013; 14: 1787–1795.
- [11] Biester S, Deuter C, Michels H, et al. Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol.* 2007; 91: 319–324.
- [12] Maccora I, Sen E, Ramanan AV. Update on noninfectious uveitis in children and its treatment. *Curr Op Rheumatol.* 2020; 32: 395–402.

- [13] Géhl Zs, Szepessy Zs, Nagy ZZs. Ophthalmic use of TNF α inhibitor: adalimumab treatment in uveitis. [A TNF α -gátló szemészeti alkalmazása: adalimumabkezelés uveitisben.] Orv Hetil. 2021; 162: 1370–1375. [Hungarian]
- [14] European Medicines Agency. Humira (adalimumab). EU summary of product characteristics, 2016. Available from: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf [accessed: January 25, 2021].
- [15] Ramanan AV, Dick AD, Jones AP, et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. N Engl J Med. 2017; 376: 1637–1646.
- [16] Saurenmann RK, Levin AV, Rose JB, et al. Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. Rheumatology 2006; 45: 982–989.
- [17] Kiss J, Gaál V, Nyúl Z, et al. Clinical features and therapy of uveitis in childhood. [A gyermekkori uveitis klinikai jellemzői és terápiája.] Orv Hetil. 2019; 160: 1335–1339. [Hungarian]
- [18] Dohán J. Uveitis and treatment in childhood. [Gyermekekori uveitisek és kezelésük.] Orvosképzés 2014; 89: 39–41. [Hungarian]
- [19] Saurenmann RK, Levin AV, Feldman BM, et al. Risk of new-onset uveitis in patients with juvenile idiopathic arthritis treated with anti-TNF α agents. J Pediatr. 2006; 149: 833–836.
- [20] Ramanan AV, Dick AD, Benton D, et al. A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE trial). Trials 2014; 15: 14.
- [21] Durrani OM, Tehrani NN, Marr JE, et al. Degree, duration, and causes of visual loss in uveitis. Br J Ophthalmol. 2004; 88: 1159–1162.
- [22] Thomas AS. Biologics for the treatment of noninfectious uveitis: current concepts and emerging therapeutics. Curr Opin Ophthalmol. 2019; 30: 138–150.
- [23] Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol. 2000; 130: 492–513.
- [24] Jaffe GJ, Dick AD, Brézín AP, et al. Adalimumab in patients with active noninfectious uveitis. N Engl J Med. 2016; 375: 932–943.
- [25] Cordero-Coma M, Sobrin L. Anti-tumor necrosis factor- α therapy in uveitis. Surv Ophthalmol. 2015; 60: 575–589.
- [26] Benyó F, Farkas A, Horváth H, et al. Systemic biological treatment in ophthalmology. [Biológiai terápia szisztémás alkalmazása a szemészetben.] Orv Hetil. 2019; 160: 1744–1750. [Hungarian]
- [27] Rosenbaum JT. Evolving “diagnostic” criteria for axial spondyloarthritis in the context of anterior uveitis. Ocul Immunol Inflamm. 2016; 24: 445–449.
- [28] Markomichelakis NN, Theodossiadis PG, Pantelia E, et al. Infliximab for chronic cystoid macular edema associated with uveitis. Am J Ophthalmol. 2004; 138: 648–650.
- [29] Fodor M, Polyák-Pásztor D, Pásztor O, et al. The impact of adalimumab in the treatment of non-infectious uveitis. [Az adalimumab jelentősége a nem fertőzőes eredetű uveitisek kezelésében.] Szemészet 2020; 157: 62–68. [Hungarian]
- [30] Al-Janabi A, El Nokrashy A, Sharief L, et al. Long-term outcomes of treatment with biological agents in eyes with refractory, active, noninfectious intermediate uveitis, posterior uveitis, or panuveitis. Ophthalmology 2020; 127: 410–416.
- [31] Horton S, Jones AP, Guly C, et al. Adalimumab in juvenile idiopathic arthritis-associated uveitis: 5-year follow-up of the Bristol participants of the SYCAMORE Trial. Am J Ophthalmol. 2019; 207: 170–174.

(Smeller Lilla dr.,
6722 Szeged, Korányi fasor 10–11., 6720
e-mail: lsmeller@gmail.com)

„Habet in adversis auxilia qui in secundis commodat.”
(Ha segítesz, míg jó sorod van, balsorsodban segítségre lelsz.)

Case Report

White Dot Syndrome Report in a SARS-CoV-2 Patient

Lilla Smeller Edit Toth-Molnar Nicolette Sohar

Department of Ophthalmology, University of Szeged, Szeged, Hungary

Keywords

SARS-CoV-2 uveitis · COVID-19 white dot · Herpes simplex · Multiple evanescent white dot syndrome · Viral prodrome

Abstract

Our purpose was to report clinical features in bilateral white dot syndrome in a 47-year-old female patient who was tested positive for the SARS-CoV-2. A 47-year-old female visited our department with complaints of bilateral photophobia and blurred vision in both her eyes. She visited our department during the pandemic period after her PCR-proven SARS-CoV-2 positivity. Her symptoms were chills and fever with a temperature of 40.0°C, associated with fatigue, sweat, and complete loss of taste. Besides basic ophthalmological examinations, ocular diagnostic testing were made to differentiate between specific white dot syndromes with suggestive features of fluorescein angiography, optical coherence tomography, and fundus autofluorescence. Laboratory tests were ordered, including immunoserological and haematological ones. Eye examination revealed mild bilateral vitritis and white dots in the fundus of both eyes, including the macula explaining the blurred vision. Herpes simplex virus reactivation was proved, after the SARS-CoV-2 infection. Local corticosteroids were given according to the European Reference Network's recommendations for patients with uveitis during the COVID-19 pandemic. Our report demonstrates that white dot syndrome with blurred vision could be associated with SARS-CoV-2 infection, being potentially sight-threatening because of macular involvement. Ophthalmological examinations found posterior uveitis white dot syndrome, and this should call attention to the risk of acute 2019-CoV infection or occurred 2019-CoV infection. Immunodeficiency favours the occurrence of other viral infections, such as herpes virus infections. Everybody should be aware of the risk of 2019-CoV infection, especially professionals, social workers, and those who work or live with elder people and people with immunodeficiency.

© 2022 The Author(s).

Published by S. Karger AG, Basel

Correspondence to:
Nicolette Sohar, nicolette.sohar@gmail.com

Introduction

The SARS-CoV-2 virus is known as the severe acute respiratory syndrome coronavirus. In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak as pandemic. The cause is the coronavirus disease 2019 (COVID-19) [1]. Comparing with other viral outbreaks, COVID-19 infection has a relatively high morbidity and mortality rate, and the treatment options for COVID-19 infection are currently limited.

The mean incubation time from COVID-19 infection until the appearance of symptoms ranges from 4 to 7 days, while some of the patients have no or just a few symptoms. The majority of the patients with severe disease develop acute respiratory distress syndrome [2]. Coronaviruses (CoVs) are in a family of single-stranded, positive RNA (ribonucleic acid) viruses, characterized by spike proteins projecting from their envelopes [1, 2]. Current guidelines based on the experience from previous epidemics recommend the protection of the nose, the mouth, and the eyes because they contain susceptible mucous membranes.

The COVID-19 is also known to affect visual system, causing ocular manifestation. The ocular system may play a role in viral transmission. The virus may shed from ocular surface secretions and tears which facilitates viral spreading. The initial viral infection may also occur on ocular surface tissues. Otherwise, the virus may spread to the respiratory system of the same individual with the ocular system acting as a conduit [1–3].

The SARS-CoV-2 may also constitute the risk factor for reactivation of the herpes family viruses. Herpesviridae family uses latency as an escape or evasion mechanism for the host's immune system. The most common gate for human herpes viruses is the pharynx. After getting inside the human body, they use various mechanisms to spread. After the initial infection, herpes viruses remain in a latent state in different cells. They can be later reactivated in cases of immunodeficiency. This can occur by many reasons, like stress, malnutrition, immunosuppressive drugs, and infections by other pathological agents like viruses [3–5].

Case Report

A 47-year-old female patient came to our department because of bilateral photophobia and blurred vision in her eyes and decreased vision in her left eye. She visited our department in November 2020. She tested negative for the SARS-CoV-2 infection a week before admission to our department. She was positive for SARS-CoV-2 21 days before the ocular signs appeared, and then she presented chills and fever with a temperature of 40.0°C, associated with complete loss of taste. The ocular symptoms are displayed in Table 1.

The ocular anamnesis excluded previous episodes of uveitis, ocular, and systemic infections or autoimmune diseases. Ophthalmological history proved that she has had annual check-ups for hypermetropia of +3.5 dioptres (D) in her right and +4.5 dioptres in her left eye, without any remarkable ocular pathology. At present, her vision decreased in her left eye.

Table 1. Ocular signs

Blurred vision-both sides
Decreased vision-left side
Photophobia-both sides
Mild vitritis-both sides
Multifocal, greyish-white placoid lesions at the level of RPE-both sides
Macular involvement-left side

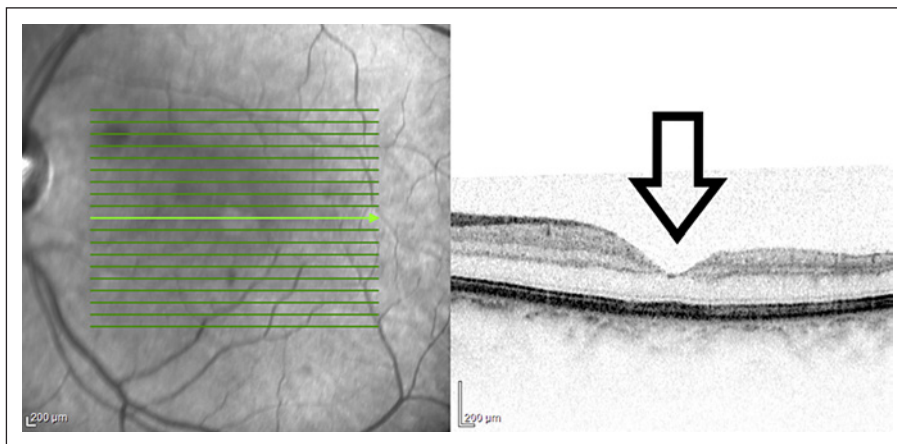


Fig. 1. OCT, Heidelberg. Left eye with macular involvement. Pigment epithelial detachment at first visit. OCT shows small projections in the outer retina corresponding to dots. Near infrared reflectance imaging highlight the granular fovea. OCT, optical coherence tomography.

According to the patient, her vision got worse gradually and progressively. Best corrected visual acuity (BCVA) of the right eye was 1.0 with +3.5 D and blurred vision; BCVA of the left eye was 0.2 with +4.5 D correction. Intraocular pressure was in normal range and slit lamp examination did not show any alterations of the anterior segments of both sides. We did not see any cells in the anterior chamber.

With dilated fundusoscopic examinations, there was mild vitritis on both sides probably because of the “spilled over” cells from the anterior chamber. The optic disc was normal on both sides, and no swelling was detected. Multifocal, flat, and grayish-white placoid lesions in the retinal pigment epithelium (RPE) level of the retina on both sides were revealed. On the left side, the macular region was involved.

Multiple evanescent white dot syndrome (MEWDS) is one of the diagnoses within the family of white dot syndromes. The white dot syndromes produce yellow-white retinal lesions classically located at the retinal pigment epithelium or outer retina. Symptoms of MEWDS include unilateral/bilateral blurred vision, visual field loss, photopsias, and floaters.

MEWDS is rarely bilateral, and in these cases, the ocular involvement is usually asymmetric. In our case, only the left eye was symptomatic due to the macular involvement [6]. Optical coherence tomography (Heidelberg Spectralis) showed inflammatory lesions in the level of the outer retina. The disruption of the ellipsoid zone could be seen and that could make the foveal area granular. Furthermore, optical coherence tomography showed swelling of the outer retinal layers and granules at the level of RPE [7].

Figure 1. Discontinuities in inner segment-outer segment junction and mild attenuation of external limiting membrane have been reported in acute phase. Recurrent episodes may result in the thinning of the outer nuclear layer.

Wide field fluorescein angiography (FLAG; Optos, California) was performed, showing early and late hyperfluorescence of the white spots. Diffuse and patchy late staining was detected at the level of RPE and retina. The wreath-like hyperfluorescence corresponded to the dots and could be seen clinically. After resolutions of the acute lesions, window defects could be noted, corresponding to the clinical granularity seen. No vasculitis could be detected. We performed Optos FLAG to get to know more information about the periphery of the eyes.

The initial autofluorescence images (fundus autofluorescence, (Optos, California)) showed hyperautofluorescence corresponding to the white dots. Figure 2. In the recovery phase, the areas of hyperautofluorescence became less and smaller [8, 9] Figure 3.

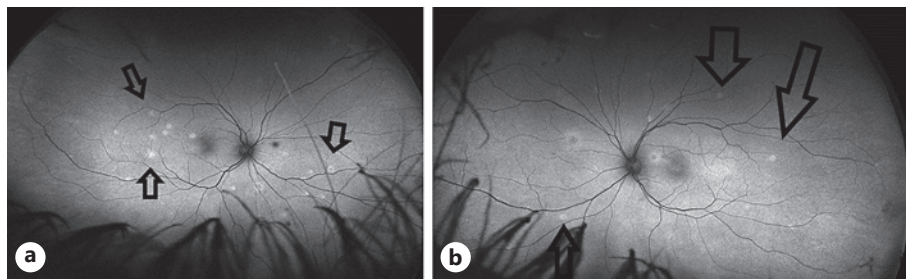


Fig. 2. Optos, California – autofluorescent pictures: before treatment. **a** Inflammatory whitish lesions on the right fundus before the therapy. **b** Inflammatory whitish lesions on the left fundus.

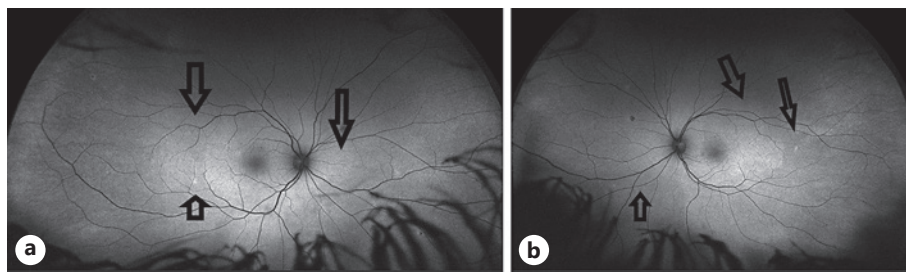


Fig. 3. **a** Optos, California – autofluorescent pictures after treatment the white spots are getting disappeared on the right eye. **b** The left fundus after therapy.

We suspected infectious (viral) and immune-related origin, complicated by macular involvement so the patient underwent haematological and serological examinations for uveitis. According to the European Reference Network's recommendations for patients with uveitis during the COVID-19 pandemic, we started local therapy. The European Reference Networks are virtual networks connecting healthcare professionals around Europe with expertise in rare diseases, which allows them to discuss patient's diagnosis and care. This network helps to make any decision in treating uveitis during COVID-19 pandemic. This included corticosteroid injection (1 mg, dexamethasone, ratiopharm) into the orbital floor of both sides, every other day, all together five times. We gave corticosteroid drops because we were positive that there was an anterior uveitis. Beside corticosteroid eye drops (5 times a day), dilatation of the pupil was initiated (cycloplegic eye drops 5 times a day) in order to prevent severe ciliary spasm and synechiae formation. Additionally, we gave acyclovir orally 5 × 800 mg/day.

The clinical symptoms regressed completely in 4 weeks and at the 1-month follow-up visit, the whitish inflammatory dots regressed but did not disappear totally. The macular involvement on the left eye resolved. The patient's visual acuity returned to 1.0 with hyperopic spherical correction.

The laboratory data, as reported in Table 2, excluded antinuclear antigen-associated uveitis, HLA-B27 positivity, lupus anti-coagulant (LAC), toxoplasma, cytomegalovirus, Borellia, Toxocara, and Epstein-Barr antibodies-associated uveitis. We examined the patient after COVID infection, the lab values were taken at her first visit at the Department of Ophthalmology.

The Herpes simplex IgM and IgG levels were elevated. Table 2 shows the laboratory findings.

Table 2. Laboratory findings

Laboratory tests	Value
SARS-CoV-2 IgM	Negative
SARS-CoV-2 IgG	Positive
Borellia IgM Western blot	Negative
Borellia IgG Western blot	Negative
Anti-CMV IgM	Negative
Anti-CMV IgG	Negative
Anti-EBV IgM	Negative
Anti-EBV IgG	Positive
Anti-HSV-1/2 IgM	Positive
Anti-HSV-1/2 IgG	Positive
Anti-HCV IgM	Negative
Anti-HCV IgG	Negative
<i>Toxocara canis</i> antibody (IgM, IgG)	Negative
<i>Toxoplasma gondii</i> (IgM, IgG)	Negative
HLA-B27	Negative
ANA	Negative
LCA	Negative

ANA, antinuclear antigen.

The patient had elevated IgG for SARS-CoV-2 from the nasopharyngeal swab using RT-PCR (reverse transcription polymerase chain reaction) and confirmed the past infection of the SARS-CoV-2 virus. Reverse transcription polymerase chain reaction is used to prove that the patient had a past infection of SARS-CoV-2. The test is based on the extraction of SARS-CoV-2 virus nucleic acid from blood specimen, followed by combined reverse transcription of viral RNA and PCR amplification using real-time reverse transcriptase PCR (RT-PCR) methods.

Discussion

CoVs can produce many types of ocular manifestations from anterior segment pathologies like conjunctivitis and anterior uveitis to sight-threatening conditions like retinitis and optic neuritis [3, 4]. CoV creates two different phases: the first is represented by the primary infection which induces a trigger of the immune system, while the second phase is probably an autoimmune disease like reaction-based pathology [10]. The lesions presented by our patient support the hypothesis that a herpes infection can manifest after SARS-CoV-2 infection.

Multiple evanescent white dot syndrome is an acute, multifocal, and rarely bilateral retinopathy. The multiple white infiltrations or foci can be seen at the level of the outer retina. There is a strong female predominance. Recent reports revealed female predominance in MEWDS ranging from 50 to 91%; the reason is unknown.

We do not know the definite origin of MEWDS, but infectious and/or immune origin is suspected. The occurrence of MEWDS following hepatitis B, varicella, meningococcus infection, or vaccination suggests environmental triggers [4, 11, 12].

In our case, SARS-CoV-2 could trigger the inactive herpes simplex infection that caused MEWDS. Recovery of vision in a few weeks was coincident with the return of the serum IgM values to normal [5, 12].

The HLA locus maybe important; a preliminary study found the frequency of HLA-B51 haplotype to be 3.5 times more common in patients with MEWDS than in normal group. Our patient was negative for HLA-B27.

The natural course of MEWDS is excellent, and no intervention is required, but in the time of SARS-CoV-2, local steroid therapy is recommended to keep the best visual acuity [13]. Periocular and intraocular corticosteroids are not suitable for recommendation in management of MEWDS, but in time of SARS-CoV-2 pandemic, it is recommended although there is no abundant evidence to prove whether the resolution of MEWDS is self-limiting or relays on corticosteroid.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. We state that written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Information revealing the subject's identity is avoided. All patients can be identified by numbers or aliases and not by their real names. Human subjects have been performed with the approval of Regional and Institutional Review Board of Human Investigations in University of Szeged and with appropriate participant's informed consent in compliance with the Helsinki Declaration. This study protocol was reviewed and approved by Regional and Institutional Review Board of Human Investigations in University of Szeged, approval number 5053.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this study.

Author Contributions

Lilla Smeller: patient examination, photodocumentation, therapy, and writing the publication. Edit Toth-Molnar: following the publication. Nicolette Sohar: patient examination and following the therapy.

Data Availability Statement

Data are available and they can be found in our department. All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

- 1 Emrani J, Ahmed M, Jeffers-Francis L, Teleha JC, Mowa N, Newman RH, et al. SARS-COV-2, infection, transmission, transcription, translation, proteins, and treatment: a review. *Int J Biol Macromol*. 2021 Dec 15;193(Pt B):1249–73.
- 2 Ocansey S, Abu EK, Abraham CH, Owusu-Ansah A, Boadi-Kusi SB, Ilechie AA, et al. Ocular symptoms of SARS-CoV-2: indication of possible ocular transmission or viral shedding. *Ocul Immunol Inflamm*. 2020 Nov 16;28(8):1269–79.
- 3 Sen M, Honavar SG, Sharma N, Sachdev MS. COVID-19 and eye: a review of ophthalmic manifestations of COVID-19. *Indian J Ophthalmol*. 2021 Mar;69(3):488–509.
- 4 Le Bal'h P, Pinceaux K, Pronier C, Seguin P, Tadié JM, Reizine F. Herpes simplex virus and cytomegalovirus reactivations among severe COVID-19 patients. *Crit Care*. 2020;24:530.
- 5 Maldonado MD, Romero-Aibar J, Pérez-San-Gregorio MA. COVID-19 pandemic as a risk factor for the reactivation of herpes viruses. *Epidemiol Infect*. 2021;149:e145.
- 6 Veronese C, Morara CMM, Armstrong GW, Ciardella AP. Bilateral multiple evanescent white dot syndrome. *Int Ophthalmol*. 2018 Oct;38(5):2153–8.
- 7 Essilfie J, Bacci T, Abdelhakim AH, Ramtohul P, Turchi F, Freund KB, et al. Are there two forms of multiple evanescent white dot syndrome? *Retina*. 2022 Feb;42(2):227–35.
- 8 Furino C, Boscia F, Cardascia N, Alessio G, Sborgia C. Fundus autofluorescence and multiple evanescent white dot syndrome. *Retina*. 2009 Jan;29(1):60–3.
- 9 Seah I, Agrawal R. Can the Coronavirus Disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in humans and animals. *Ocul Immunol Inflamm*. 2020;28(3):391–5.
- 10 Maddur MS, Vani J, Lacroix-Desmazes S, Kaveri S, Bayry J. Autoimmunity as a predisposition for infectious diseases. *PLoS Pathog*. 2010 Nov 4;6(11):e1001077.
- 11 Tartari F, Spadotto A, Zengarini C, Zanoni R, Guglielmo A, Adorno A, et al. Herpes zoster in COVID-19-positive patients. *Int J Dermatol*. 2020;59(8):1028–9.
- 12 Beltrán-García J, Osca-Verdegal R, Pallardó FV, Ferreres J, Rodríguez M, Mulet S, et al. Sepsis and coronavirus disease 2019: common features and anti-inflammatory therapeutic approaches. *Crit Care Med*. 2020;48(12):1841–4.
- 13 Smith JR, Lai TYY. Managing uveitis during the COVID-19 pandemic. *Ophthalmology*. 2020;127(9):e65–7.