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Akių toksoplazmozė - literatūros apžvalga ir klinikinis atvejis
Ocular Toxoplasmosis - Literature Review and Case Report

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
T. gondii	Toxoplasma gondii
OT	Ocular Toxoplasmosis
PU	Posterior Uveitis
ARF	Automated Refractive Findings
OD	Oculus dexter
OS	Oculus sinister
OCT	Optical Coherence Tomography

FAG	Fluorescein Angiography
PORT	Punctuate Outer Retinal Toxoplasmosis
ICGA	Indocyanide Green Angiography
FAF	Fundus Autofluorescence
TRC	Toxoplasmic Retinochoroiditis
CSF	Cerebrospinal Fluid
TMP-SMZ	Trimethoprim-Sulfamethoxazole
VA	Visual Acuity
FCP	Fundus Color Photography (FCP)
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ILM-OS/RPE	Internal Limiting Membrane-Outer Segment/Retinal Pigment Epithelium
RPE	Retinal Pigment Epithelium

4 Keywords

Toxoplasma gondii, Ocular Toxoplasmosis, Posterior Uveitis, Recurrence, Treatment

5 Abstract

Background: Toxoplasmosis is an illness caused by Toxoplasma gondii. Ocular infection frequently manifests as acute necrotizing retinal chorioretinitis. In the following, a description of a case of ocular toxoplasmosis with retinal chorioretinitis caused by Toxoplasma gondii, as well as the review of the pathogen itself and its treatment will be delivered. The optimal treatment remains debated with no strict guidelines.

This review aims to provide a comprehensive overview of the clinical presentation, diagnostic strategies, and current treatment options for ocular toxoplasmosis, emphasizing mainly on the postnatally acquired form of the disease. The second part of the thesis presents a detailed case report illustrating these aspects in a clinical context.

Methods: A thorough literature search was performed in the PubMed database. An additional search was made in Elsevier Science Direct and Google Scholar to complete the collected items. In regards of the case report, a retrospective analysis was conducted. Ophthalmological examinations were performed repetitively from 2021-2025. Blood sera were collected and analyzed. Moreover, diagnostic tests were performed, including Toxoplasmosis IgG and avidity, OCT, OCT-Angiography and Fundus Photographs.
Results: Toxoplasma gondii is a zoonotic infection that has the ability to infect the whole retina, possibly causing visual impairment up to the total loss of vision; thus, rapid reference to an ophthalmologist and rapid diagnosis and therapy must be implemented to enhance the prognosis, in case of vision-threatening Toxoplasmosis. This narrative literature review has presented the current knowledge and has shown existing gaps, such as the absence of standardized clinical management. The presented descriptive case report highlights the clinical findings, the course of disease, and the clinical management of an adolescent patient with ocular toxoplasmosis.
Conclusion: To conclude, in the future, further research is needed to bridge gaps in the current knowledge, like optimal treatment in different groups of patients and drugs with the ability of curative effect.

6 Introduction

Toxoplasmosis is worldwide distributed with 30 % global population infected. It often manifests as an asymptomatic illness (1). Ocular Toxoplasmosis is one of the most common causes of posterior uveitis worldwide, marking its significance in clinical practice (2). In Germany, the protozoan is the leading cause of posterior uveitis (3). It can potentially cause the clinical picture of acute and chronic Toxoplasmosis. Especially Ocular Toxoplasmosis can be debilitating as it can lead to forms of posterior uveitis, impacting the vision and cause permanent visual impairments for many patients (2).
This review has the purpose of collecting the current knowledge about the pathogen causing the clinical disease named Toxoplasmosis, focusing on Ocular Toxoplasmosis.
This literature review will point out the postnatally acquired form of the disease. Furthermore, this will be illustrated with a detailed case report of a 14-year-old patient affected by posterior uveitis caused by Toxoplasma gondii.

7 Methods

The basis for this narrative literature review are several databases such as PubMed, with the key words (MeSH terms) “human ocular toxoplasmosis”, “retinochoroiditis”, “treatment” or

"toxoplasmosis", Elsevier Science Direct, Conchrane and Google Scholar. Publishing dates of references used in this literature review range from 1991 to 2024, with the majority of literature published in 2015 or more recent. Only references available in the English language were included. This resulting narrative literature review contains several randomized controlled studies, systematic reviews, meta-analyses, case reports, books, articles from ophthalmologic journals, prospective clinical studies and many other publications mentioned therein, where full-text access could be retrieved. The information given was evaluated based on the experience of the author.
Methods regarding the case report was a retrospective analysis and description of the findings. To confirm ocular Toxoplasmosis serology and diagnostic workup were performed. Several imaging studies were performed, evaluating the development of the lesions. Pictures used in the case report, were retrieved from the patients archive.
After explaining the aim of the case report, an informed written consent was obtained from the patient's legal guardian, granting approval for the conduct of this case report. Efforts were made to disclose no personal data of the patient.

Literature Review: Ocular Toxoplasmosis

7.1 Pathogen: Toxoplasma gondii

Often described as a highly infectious parasite, Toxoplasma gondii, is an intracellular protozoan and it is worldwide distributed as it has the capacity to infect warm-blooded animals, such as humans, mammals and birds. Its definitive host are members of the feline family, like cats (4,5).
It is related to Plasmodium and Cryptosporidium species which also belong to the Apicomplexa Phylum (6).
The pathogen is meticulously studied, especially the tachyzoites can be maintained indefinitely in in vitro cultures and are used as a model to study features of the Apicomplexa Phylum. Additionally, the parasite functions as an important model for studying the interaction between hosts and parasites.
T. gondii was first described as a parasite infecting rabbits and rodents in the early 20th century. The development of a serological test named respectively Sabin-Feldman Dye Test, showed that the parasite is a after on parasite, contrary to the belief at that time (4).
Humans beings can be affected through vertical transmission, parenterally and via the enteral pathway (7,8). The enteral pathway includes ingestion and handling of undercooked or raw meat or drinking water containing oocysts. The differences in seroprevalence of T. gondii lie with

differences in hygiene and eating habits in populations, which supports the idea that the oral route is the major source of infection (1,9).
Efforts are made on public health levels to control the parasite epidemiologically and scientific efforts are made to develop novel chemotherapeutic agents with low toxicity and high specificity.

7.1.1 Life Cycles

T. gondii exists in three forms: the tachyzoites, the bradyzoites, and the sporozoites (10).
Tachyzoites, also named Endozoites or Trophozoites, but less commonly so, indicate an active infection and are the fast-replicating form of T. gondii. Usually, they are crescent-shaped and 5 μm in length and 2-3 μm in width. An example of a Tachyzoite can be seen in Figure 1, adapted from Dubey et al. (10). With a pointed end also called Conoid, the parasite is invading the host. cell. This dynamic structure makes the Tachyzoites polarized (11).

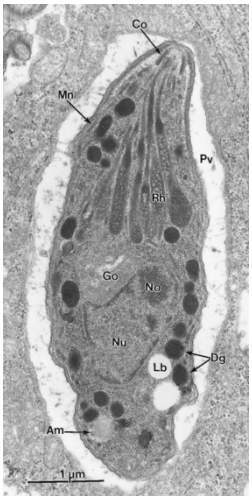

Figure 1: Transmission electron micrograph of a tachyzoite, Micrograph by Dubey et al.

In its Tachyzoites form the parasite is motile independently from external factors. It uses its actomyosin-based motor complex and uses most commonly its helical gliding movement by which it can move at a speed of several mm per hour. In this form, it can enter cells with a nucleus by active penetration (1) (12). Then they replicate within the cell in the so-called cytoplasmic vacuole. After multiple replications, the host cell is disrupted and the tachyzoites disseminate in a hematological way to many tissues, like the eye, CNS, heart and skeletal muscle (1,9). Intracellular Tachyzoites nested in the so-called parasitophorous vacuole, transform into virtually quiescent forms known as bradyzoites (13).

The dormant or latent stage of T. gondii is called Bradyzoites, also known as Cystozoites. As bradyzoites they exist encysted within the host's tissues in the brain, skeletal and heart muscle. Mature cysts may be housing thousands of bradyzoites and act as a protective barrier from digestion within the host animal. Currently, it is impossible to eradicate Toxoplasma gondii from the host, because of the ability to form tissue cysts (13).
These tissue cysts are seen in Figure 2 by generated by Dubey et al. where a section of the brain of a mouse that was inoculated 8 months earlier with oocysts of Toxoplasma gondii. This section of the cyst is showing

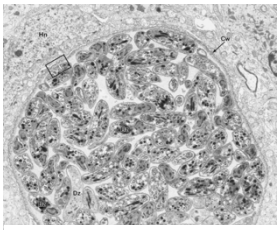
Figure 2: Tissue cysts containing bradyzoites by Dubey et al.

approximately 110 bradyzoites. The tissue cyst is surrounded by a thin cyst wall and is situated within the host cell cytoplasm near the host cell nucleus (10).
Bradyzoites can transform back to the infective and active stage of the tachyzoite, when released from the cysts. Then, it can cause the recurrence of infection (9). It prompts the parasite opportunity to spread to new hosts via intermediate hosts , without the need for sexual reproduction, which is exclusive to felids (13).
Another dormant, but highly infectious form are sporozoites. They can be found within sporocysts. The sporocyst itself is located within an oocyst. These oocysts are highly resistant to various conditions, like harsh outer environment, and standard disinfections and survive and remain infectious for up to years. This is thought to be because of its robust wall mechanics (10,14) (15) (1).
T. gondii has two life cycles. The sexual life cycle and the asexual life cycle. The sexual life cycle takes place in its definitive feline host, where the cat ingests the protozoan in one of its three forms (13). The three forms are: tachyzoites, bradyzoites, and sporozoites as aforementioned. When a bradyzoite enters the intestines via the epithelial cells, it undergoes a complex development. The fertilized zygote is dividing several times. Then sporulation occurs outside of the feline body, taking place in its feces within 1 to 5 days, producing an oocyst containing eight sporozoites. During active infection of a feline, millions of oocysts (10x12µm) are shed in their feces for 7 to 21 days. When oocysts, containing sporozoites are ingested by mammals such as pigs or mice, tachyzoites develop, which are the hallmarks of active infection (1).
Endodyogeny is the process crucial for the asexual life cycle, enabling the reproduction to new hosts via intermediate hosts in which the. Endodyogeny describes the asexual division whereby two daughter cells form within a single maternal cell (13).
There are three major strains of T. gondii, which participate in sexual recombination. This natural process has driven the natural evolution of Toxoplasma gondii virulence. The acquisition of the direct oral transmission via the enteral route has led to the widespread transmission of the protozoan.
The parasite genotypes are associated with differences in the pathogenicity and virulence. This is demonstrated in animal models.

Human ocular toxoplasmosis has been associated with 3 major strains.
The type II strain is predominantly in Europe and North America, typically causing milder forms, compared to type I strains. Type I strain showed high virulence in animal models and is associated with severe forms of ocular toxoplasmosis in humans. Lastly, the type III strain has shown milder disease presentation in animal models. The impact on humans is less defined.

There are differences in geographical distributions. Severe forms of ocular toxoplasmosis are linked to atypical strains, most commonly found in South America. Due to factors such as genetic predisposition and host immunity the correlation between clinical severity and the parasite's genotype remains a complex matter (16) (17) (18).

The parasite reaches the human retina by one of three modalities. The first one is called Leukocyte taxis, where the parasite enters especially monocytes and dendritic cells. Once these cells are infected, their mobility is enhanced and they can cross the retinal vascular endothelium.

Also, the protozoan parasite can directly navigate through the retinal endothelial cell layer. Lastly, they can infect the retinal epithelial cell and subsequently cross it. When T. gondii reaches the retina, it prefers the Müller cells as initial hosts. After that the parasite subsequently infects other cells (16).

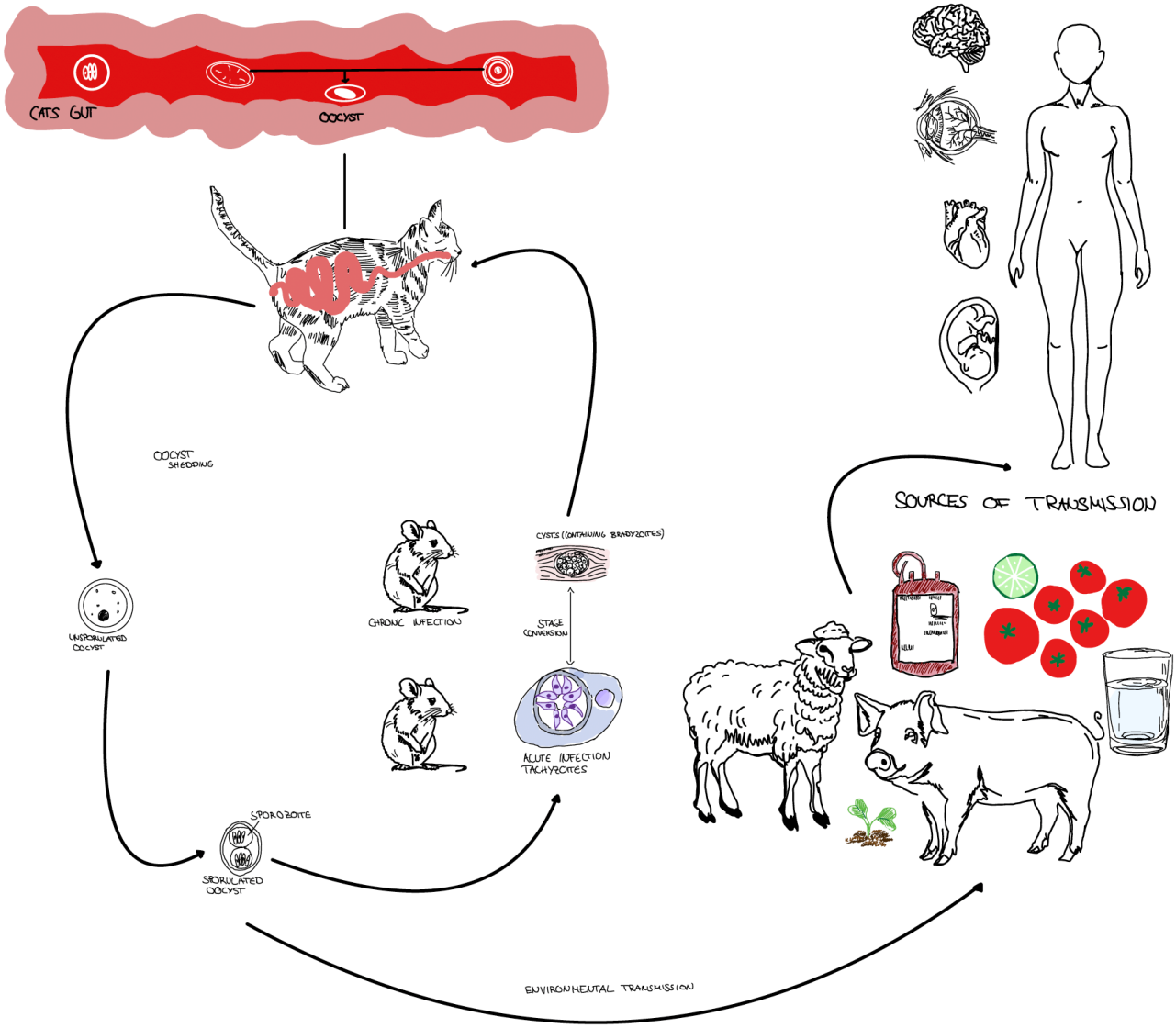

Figure 3: Schematic Representation: Life cycle of T. gondii by N. Müller

To summarize the life cycle of T. gondii, a schematic representation is provided in Figure 3.

The pathogen has ability to take part in the asexual and in the sexual life cycle. The sexual life cycle takes place in the cat's gut. The cat gets infected by an infected intermediate hosts like mice. Intermediate hosts like sheep and pigs are also crucial for the asexual life cycle. In the human the parasite can infect different organs as well as infect the fetus by vertical transmission.
Humans may get infected by different modes, for example the consumption of contaminated vegetables and meat, the unsafe handling of contaminated soil, unsafe water sources and theoretically blood products.

7.2 Forms of Toxoplasmosis

7.2.1 Acquired Toxoplasmosis

Postnatally acquired Toxoplasmosis is in 70 % of the cases clinically inapparent in immunocompetent patients. In case of manifestation, the most common clinical presentation is lymphadenopathy, with cervical lymph nodes the most commonly involved. In immunocompetent individuals it is usually a benign disease and self-limiting with duration of up to 4 weeks. Ocular manifestations do not always develop with primary infection. The time between the primary systematic disease and ocular manifestation may have an interval from days to years (5).
Distinguishing between postnatally and prenatally acquired infections is feasible only in specific clinical contexts and requires extensive laboratory investigations.
A study showed that the acute phase of Toxoplasmosis is confirmed by the presence of IgM-positive serology. Yet, in most cases of acquired infection IgM cannot be detected, which probably underestimates the percentage of acquired cases (19).
Furthermore, it is rather for academic research, than a decisive factor for treatment. Definitive determination of whether a diagnosed case of ocular toxoplasmosis is of prenatal or postnatal origin remains challenging (20).

7.2.2 Congenital Toxoplasmosis

In most cases, congenital Toxoplasmosis is asymptomatic. A new infection in early pregnancy has a very low rate of transmission with around 6 % while in the third trimester, transplacental transmission occurs in around 60-81 %. Conversely, the manifestations that occur when transmitted in early pregnancy are much graver than when transmitted in later pregnancy (21).
The most common sequela reported are cataracts, microphthalmia, optic atrophy, retinochoroidal scarring, strabismus, nystagmus and phthisis bulbi. Retinochoroiditis is the most common reported finding found in 10-80 % of infected newborns after birth. Sometimes
Detected later in life with 90 % before reaching adulthood.

Also, systematic manifestations are possible with encephalitis, myocarditis, cutaneous rash, anemia, hepatitis, splenomegaly and thrombocytopenia (5).
This form is acquired by the transplacental hematogenous spread of an actively infected woman to the fetus (22).
The retrospective, observational case series by Delair et al. suggests that active lesions with primary congenital toxoplasmosis acquisition are seen at an earlier age than in cases of acquired infection. The mean age when active lesions are seen is at the mean age of 13.7 ± 9.0 years. In cases of acquired infections the mean age is 21.8 ± 13.3 years ($p = 0.01$). Primary ocular toxoplasmosis was more frequently observed in acquired infections (29 cases) than in congenital infections (four cases) ($p < 0.0001$). Bilateral ocular toxoplasmosis was more frequent in congenital infections with 43.5%. In contrast, only 4 % showed bilateral ocular involvement in acquired infections. A statistically significant difference was found with ($p < 0.001$) (19).

7.3 Clinical Presentation of Ocular Toxoplasmosis

Ocular Toxoplasmosis usually presents itself as retinochoroiditis, an inflammatory eye condition. The infection leads to local inflammatory reaction with scarring of the retinal and choroidal layer. The symptoms and signs vary with age. While children may be referred to an ophthalmologist because caregivers complain of strabismus, microphthalmia, leukocoria, nystagmus, decreased visual acuity or choroidal coloboma, adults and adolescents present themselves with complaints of floaters and blurry vision. Vision loss can occur when there is macula involvement. Complaints of photophobia, pain and conjunctival hyperemia is seen in anterior segment involvement (5).
Atypical forms of ocular toxoplasmosis include the so-called punctuate outer retinal toxoplasmosis (PORT). It is defined by multiple small focal lesions located in the deep layers of the retina and retinal pigment epithelium. The concomitant inflammatory reaction is usually low, with minimal or absent vitreous inflammation. Most patients presenting with PORT are within the first 20 years of their life. As a complication of this atypical form, optic neuropathies with vision loss are frequently reported. For diagnosis of this highly vision-threatening form, multimodal imaging is supported, using FAF, OCT, OCT Angiography and ICGA (23).

7.4 General Diagnostic Methods

7.4.1 Serological methods

The testing of immunoglobulins is useful to characterize the infection as chronic or acute.

An increase of IgG marks past exposure or ongoing infection. In contrast, IgM most commonly indicates a current and acute infection. IgM antibodies are found approximately after 1 week of infection (24). Studies showed that in some persons the IgM is detectable for months and up to several years (23).
Therefore, the sole detection of IgM serum is not sufficient to detect acute infection. The testing of IgA is a marker used complementary to other sensitive methods to underscore the diagnosis of acute infection (23).
IgG is the final antibody to appear earliest one week after IgM. The climax is reached after 6-8 weeks with a gradual decrease over 2 years. IgG persists lifelong (23).
Other methods like IgG avidity testing or PCR can be useful to differentiate further.

7.4.2 IgG Avidity testing

In clinical practice, the preferred method is IgG avidity testing to detect the correct stage of ocular toxoplasmosis in the absence of IgM or in the persistence of high IgM. It has a tolerable specificity and a high negative predictive value. A high avidity result effectively rules out acute toxoplasmosis (25). It excludes a recent infection of less than 3–5 months (24).

7.4.3 PCR based testing

PCR testing hold its significance especially in maternal toxoplasmosis. In cases where an intermediate avidity is shown, a prospective study demonstrated that additional PCR from the peripheral blood or amniotic fluid can give negative signals. The PCR targeted the B1 and the P30 genes, demonstrating higher sensitivity with nested PCR for the B1 gene. This is especially important for treatment decisions in pregnant women with borderline results as the PCR might suggest the necessity of treatment and prevent overtreatment (26).
PCR testing has the ability to determine the presence of DNA and not the response to the infectious agent by the immune system.
Another use of PCR is also in immunocompromised patients, such as those battling cancer or undergoing dialysis, this test is used to detect the potentially dangerous opportunistic infection (27).
PCR may also be performed on anterior chamber taps or diagnostic vitrectomies in uncertain and selected cases, like in AIDS patient as multiple simulating entities are possible (28).

7.4.4 Ophthalmoscopy

In the acute phase of illness, usually a yellowish-white or gray exudate with ill-defined margins, sometimes also described as fuzzy borders, is seen (18).

The undefined margins are caused by edema. The size of the lesions can vary from small punctual lesions smaller than the optic disc up to lesions covering two quadrants of the retina.
When the lesions begin to heal and the vitritis subsides, the lesion will be whitish-gray to brown with an elevated central area. After some variable period scarring occurs. The period depends on factors, such as the immune status of the patient and the applied treatment regimen.
A healed toxoplasmosis scar is well-defined at its borders, presenting central retinal atrophy. In the periphery retinal pigment epithelial hyperplasia can be seen as dark border (5) (13). Recurrent lesions are often adjacent to old lesions or scars and are termed satellite lesions (18).
When there is vitritis present focal or diffuse exudates may be observed. These exudates can be made up of inflammatory cells, pigment and erythrocytes.
When severe vitritis is present, the active lesion may appear unclear and the vision for the examiner may appear as often described as "foggy". This is also referred to as the "headlight in the fog" phenomenon as seen in Figure 4 indicated by the red arrow by Teng Siew et al. (29).(5,18).

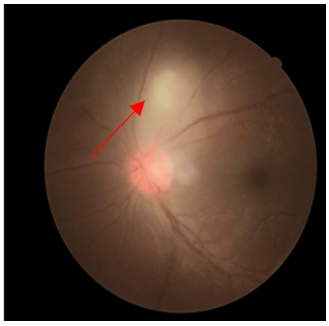

Figure 4: Headlight in the fog phenomenon

7.4.5 Slit lamp

Also, the anterior segment of the eye can be involved in the inflammation process, even without present retinochoroiditis. Important to note is that the inflammation appears to be rather reactive to the parasite's antigens than demonstrating an active infection in the retinal tissue. It might be concluded that the anterior segment involvement might reflect a systemic or local immune response rather than direct damage by T. gondii. (30).
An observation that can be made in the anterior chamber may be "mutton fat keratic precipitates", posterior synechia, fibrin deposition and Busacca and Koeppe nodules (5). It needs to be remarked that Busacca and Koeppe nodules are not exclusive to Anterior Uveitis in Toxoplasmosis, but can also present in Fuchs uveitis, Sarcoidosis or even side effects of some medications. The underlying mechanism is an inflammation (31–33). In Figure 5 the iris can be observed showing Busacca (red arrow) and Koeppe nodule (yellow arrow), adapted from Kanski's Clinical Ophthalmology (22).

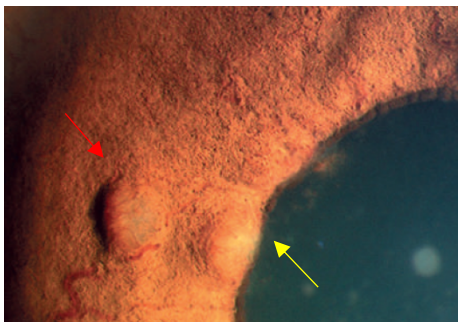

Figure 5: Koeppe and Busacca nodule

7.5 Imaging

Beyond the standard ophthalmological examination, further imaging modalities may be required to document the findings and assess possible complications of lesions. These include fundus color photography (FCP), optical coherence tomography (OCT), OCT angiography (OCTA), ultrasound (US), confocal scanning laser ophthalmoscopy (CSLO), fluorescence angiography (FAG), fundus autofluorescence (FAF), and indocyanine green angiography (ICGA) (23).
These modalities are crucial to detect retinal neovascularization, vascular occlusions, macular edema, vitreous hemorrhage, subretinal neovascularization, epiretinal membranes, as well as other ocular abnormalities. This is particularly important for longitudinal evaluation of lesions, especially essential in cases of recurrence or complications. Subsequently, imaging aids in patient consultation, offering significant information that contributes to diagnostic precision and therapeutic decision-making (23).

7.5.1 Optical coherence tomography (OCT)

As a non-invasive imaging modality, OCT enables detailed visualization of the retina, choroid, and vitreoretinal interface and has proven to be a helpful diagnostic tool in posterior uveitis, with particular relevance in ocular toxoplasmosis. Generally, retinal thinning at the active punctuate lesion site and some degree of retinal RPE−choriocapillaris/choroidal optical shadowing may be often observed (34).
On the contrary, retinal thickening is associated with focal and satellite lesions.
The posterior hyaloid may appear thickened. Focal Detachment of the aforementioned structure may be observed over punctuate lesions while attached over focal and satellite lesions. Also, findings, such as vitreomacular traction, macular edema, and maculoschisis, are seen on OCT, which cannot be seen reliably in all cases in standard ophthalmologic examination alone. It has been documented that all active retinochoroidal lesions showed increased retinal reflectivity and thickness at the lesion site. The increased hyperreflectivity of the inner retinal layers caused shadowing of the RPE and choriocapillaris.
Also, subretinal fluid accumulation has been reported.
Features like RNFL loss with a preserved neuroretinal rim has been observed in cases of ocular toxoplasmosis (34).
It enhances diagnostic accuracy by providing standardized imaging of posterior segment alterations, including hyperreflective vitreous opacities, so-called hyaloid bodies, retinal edema, epiretinal membranes, vitreoretinal tractions, and neovascular membranes.

Moreover, OCT is instrumental in quantifying macular retinal thickness, monitoring lesion evolution, and evaluating therapeutic responses. It also supports the differentiation between chronic scars and newly developed lesions (23). Moreover, OCT is a useful tool for differential diagnosis, inflammation grading and prognosis.
OCT also visualizes CNV (choroidal neovascularization), presenting as hypo-reflective choroidal back-shadowing (35).
OCT-A (OCT-Angiography) can assess the retinal and choroidal microvascular flow, without the need for contrast agent injections.
Active lesions manifest in OCT-Angiography typically with increased signal in inner retinal layers and decreased flow in outer retinal layers and in the choriocapillaris. A gradual reduction of flow signals across all retinal layers and the persistent decreased flow in the choriocapillaris may be observed as lesion progress to inactivity. The absence of flow signals may be observed in scarred or chronic lesions.
To summarize, OCT Angiography can help in assessing the status of disease activity, the vascular involvement and monitoring of the treatment response (18,36).

7.5.2 Fundus color photography (FCP)

Wide-field fundus color photography plays a vital role in tracking non-central lesions. Sequential image comparison enables early detection of pigmentation at lesion margins, indicating healing and can also highlight critical findings, such as hyperpigmented scars, that might go unnoticed in clinical evaluation. Beyond its diagnostic value, fundus photography enables comprehensive documentation of lesion localization, extent and progression in the posterior segment (23).

7.5.3 Fluorescence angiography (FAG) and indocyanine green angiography (ICGA)

Classic imaging techniques such as FAG and ICGA aid in tracking lesion development, though their necessity depends on the clinical scenario. These techniques play a significant role in identifying vascular occlusions, vasculitis, arteriovenous shunts, macular edema, and neovascular membranes (5) (23). While FAG visualizes especially the retinal circulation, ICGA better visualizes choroidal circulation, due to deeper penetration. Indocyanine green angiography serves as a valuable modality for evaluating the amount of inflammatory activity (37).

Typical described features in FAG is early hypofluorescence with late progressive leakage at lesion margins. In inactive or scar lesions an early hypofluorescence can be seen, because of pigment

blockade due to RPE proliferation or window effect, due to RPE atrophy (18) (5). FAG may also show a mottled appearance due to the irregularity of RPE hypertrophy and atrophy.
In cases of neuroretinitis or neuritis, FAG may show hyperfluorescence in the optic disc.
Furthermore, Fluorescence angiography may show associated features seen in vascular involvement, such as arterio-venous shunts in the retina, retinochoroidal shunts and choroidal neovascularization (5).

Typical, features of ICGA are hypofluorescence in inactive lesion. Occasionally there might be seen hyperfluorescence in active lesions. ICGA is also a useful diagnostic tool to assess the extent of the choroidal involvement and, in select cases, allows for tracking lesion progression over time (5,23,37).

7.6 Treatment

Ocular Toxoplasmosis is a self-limiting disease and not all retinochoroiditis lesions caused by T. gondii need to be treated, such as small extramacular lesions. Lesions that are vision-threatening however, like close proximity to the macula, the optic nerve, the main retinal vessel or small lesions that are accompanied by severe vitritis, should lead to initiating treatment (38) (39) (40).
In complications like macular pucker, a vitrectomy may be performed (41). Vitrectomy is also performed in other posterior uveitis complications (42).

Ocular Toxoplasmosis can be treated with different treatment regimens. Besides, there is no consensus on the universally optimal treatment approach.
The current mainstay of treatment is the combination of oral sulfadiazine/pyrimethamine and folinic acid for 5 to 6 weeks, which is very effective, especially gaining clinical significance in vision-threatening toxoplasmosis. To rapidly reduce intraocular inflammation, oral prednisone may be administered at 30–50 mg/day for 2–3 weeks in combination with antibiotics (38).

The possible grave side effects such as bone marrow depression in patients treated with sulfadiazine/pyrimethamine render the search for alternatives (43).
There are also side effects reported for the sulfonamide antibiotic named sulfadiazine. It can cause a hypersensitivity reaction termed DRESS-Syndrome, manifesting as an extensive morbilliform skin rash in association with visceral organ involvement, lymphadenopathy, eosinophilia, and atypical lymphocytosis. Health practitioners need to be aware of this side effect possibility (44).

In this part of the literature review a summary presented in Table 1, Table 2, Table 3 and Table 4 of treatment regimens has been collected and adapted from The Wills Eye Manual 7th Edition (28).

Table 1: Therapy

Condition	Treatment
Self-limited in immunocompetent patients	Observation for peripheral lesions
Elevated IOP	Antiglaucoma medications
Anterior uveitis	Topical cycloplegic (e.g., cyclopentolate 1% to 2% t.i.d.) with or without topical steroid (e.g., prednisolone acetate 1%)

Table 2: Classic oral therapy

Medication	Dosage	Notes
Pyrimethamine*[1]	200 mg p.o. loading dose (or two 100 mg doses 12 hours apart), then 25-50 mg p.o. daily	Contraindicated in pregnancy/breastfeeding
Folinic acid	10 mg p.o. every other day	Minimizes pyrimethamine-induced bone marrow toxicity
Sulfadiazine	2 g p.o. loading dose, then 1 g p.o. q.i.d.	Expensive; can be replaced by TMP/SMX 160 mg/800 mg b.i.d.
Prednisone*[2]	20-60 mg p.o. daily	Begin at least 24 hours after antibiotics; taper 10 days before stopping antibiotics
***[1]:** Weekly CBC to monitor for bone marrow suppression, Reduce pyrimethamine dosage if platelet count drops below 100,000, Avoid folic acid-containing vitamins, Administer with food to reduce anorexia *[2]: Systemic steroids should rarely be used in immunocompromised patients. Before use, evaluate fasting blood sugar, hemoglobin A1C, and rule out tuberculosis. (28)		

Table 3: Alternative Therapies

Alternative Regimen	Dosage	Notes
Clindamycin	150-450 mg p.o. t.i.d. to q.i.d. (max 1.8 g/day)	Use alone, with pyrimethamine (if sulfa-allergic), or as adjunct (quadruple therapy). Attention for pseudomembranous colitis.
Intravitreal Clindamycin	0.1 mg/0.1 mL	Effective for macular-threatening cases or intolerance to systemic medication. Combined with dexamethasone (0.4 mg/0.1 mL) has been reported helpful.
Atovaquone	750 mg p.o. q.i.d.	Alternative to clindamycin.
Trimethoprim/ Sulfamethoxazole (TMP/SMX)	160 mg/800 mg one tablet b.i.d.	With or without clindamycin and prednisone
Azithromycin	1 g loading dose (Day 1), then 250-500 mg daily	Can be used alone or with pyrimethamine (50 mg daily)
Spiramycin	400 mg p.o. t.i.d.	Consider in pregnancy

Table 4: Maintenance Therapy

Maintenance Therapy (for Immunosuppressed Patients)	Dosage	
TMP/SMX	160 mg/800 mg p.o. three times per week	
Clindamycin	300 mg p.o. q.i.d.	Alternative for sulfa-allergic patients, common in HIV-infected individuals

In the following part of the narrative literature review, studies regarding other treatment modalities apart from the classic oral triple therapy will be discussed.

A prospective randomized single-blind trial compared the efficacy of the classic treatment of ocular toxoplasmosis, which consists of pyrimethamine, sulfadiazine and prednisolone with another

treatment regimen consisting of co-trimoxazole (trimethoprim/sulfamethoxazole and prednisolone). Main outcome measures were visual acuity before and after intervention, visual acuity, inflammation resolution, recurrence rate and adverse drug reactions during follow up and changes in retinochoroidal lesion size after 6 weeks of treatment (45).
It was found out that the two aforementioned treatment regimens showed no statistical difference in treatment effects. Both showed improvement in VA, lesion size and inflammatory resolution. This result suggests trimethoprim/sulfamethoxazole and prednisolone as a viable alternative treatment with fewer side effects and easier management.

In 2012 a pilot, prospective, randomized, intention-to-treat study was conducted, comparing the efficacy and tolerance of two treatment regimens for non-vision-threatening and active retinochoroiditis caused by T. gondii by the study group of Balaskas, Konstantinos et al. The classic treatment of Sulfadiazine/pyrimethamine was compared with azithromycin monotherapy. Treatment outcomes were measured by assessing lesion scarring and disease inactivity. In this study there were no statistically significant differences of treatment outcomes of patients treated with Sulfadiazine/pyrimethamine or azithromycin found. The median time to achieve lesion scarring poses a difference, with a median time of 71.5 days (interquartile range (IQR) 57.5) for azithromycin versus 36 days (IQR 25.5) for sulfadiazine/pyrimethamine. Yet, no statistically significant was found. This indicates that azithromycin might be used instead of the classic oral therapy.
Furthermore, the study demonstrated a statistically significant better overall treatment tolerance in patient who received the azithromycin-containing regimen in comparison to the standard regimen. ($p=0.0005$) (43). It might be concluded that Azithromycin monotherapy poses to be an effective and safe alternative in treating non-vision-threatening forms of Ocular Toxoplasmosis.

Clindamycin is another drug of interest as it is effective against T. gondii. Its mechanism of action is by interfering with the protein synthesis of the protozoan. It can be administered intravenously, intraocular, and orally. Yet, if it is taken in any other form as an intraocular injection, the bioavailability at lesion site is low as it penetrates poorly into CSF and vitreous fluid (38).

A prospective randomized trial assessed the efficacy of intravitreal clindamycin plus dexamethasone versus the conventional oral therapy. Both forms of treatment showed efficacy with no statistically significant difference ($p = 0.83$). There was no higher rate of complications with the intravitreal administration of clindamycin in this study. Therefore, it may be an acceptable alternative due to various reasons such as fewer systemic side effects (38,46).

A large multicenter study compared the effectiveness of three treatment modalities with triple therapies each. The following groups and therapies are: group 1 with pyrimethamine, sulfadiazine, and corticosteroids; group 2 with clindamycin, sulfadiazine, and corticosteroids; and group 3 with trimethoprim, sulfamethoxazole and corticosteroids. Active peripheral lesions were not treated with systemic medications. The first group also received supplemental folinic acid 5 mg twice a week. The results showed that with the trimethoprim-treated group, the lesions significantly decreased in size ($p<.01$) compared to the untreated group. Yet, the most frequent occurrence of side effects was observed in the trimethoprim group. Side effects were of hematologic nature, which is rooted in the antagonistic action of trimethoprim. A side effect was for example thrombocytopenia.
Folinic acid substitution reduces the risk, but some participants experienced adverse drug reactions even with folinic acid substitution at the given dose. When the dose of folinic acid was increased, the thrombocytopenia normalized within 2 weeks (40).

However, the optimal treatment strategy for ocular toxoplasmosis, particularly the role of corticosteroids, remains unclear. A systematic review investigating the efficacy of corticosteroid adjunct therapy versus anti-parasitic treatment alone has identified no relevant multicentered randomized controlled trials. The absence of robust evidence highlights the necessity for well-conducted randomized-controlled studies. The role, optimal timing, and dosage of corticosteroids in managing ocular toxoplasmosis remains unclear. Evidence-based guidelines based on high-quality studies would improve the quality of treatment (47) (48).

Generally, it can be concluded that larger sample sizes could improve the statistical value of the studies. It can be concluded that there are alternative treatment modalities in different forms of application, showing effectiveness, granting the possibility for individualized treatment.

7.7 Prevention

7.7.1 Primary Prevention & Risk Factors

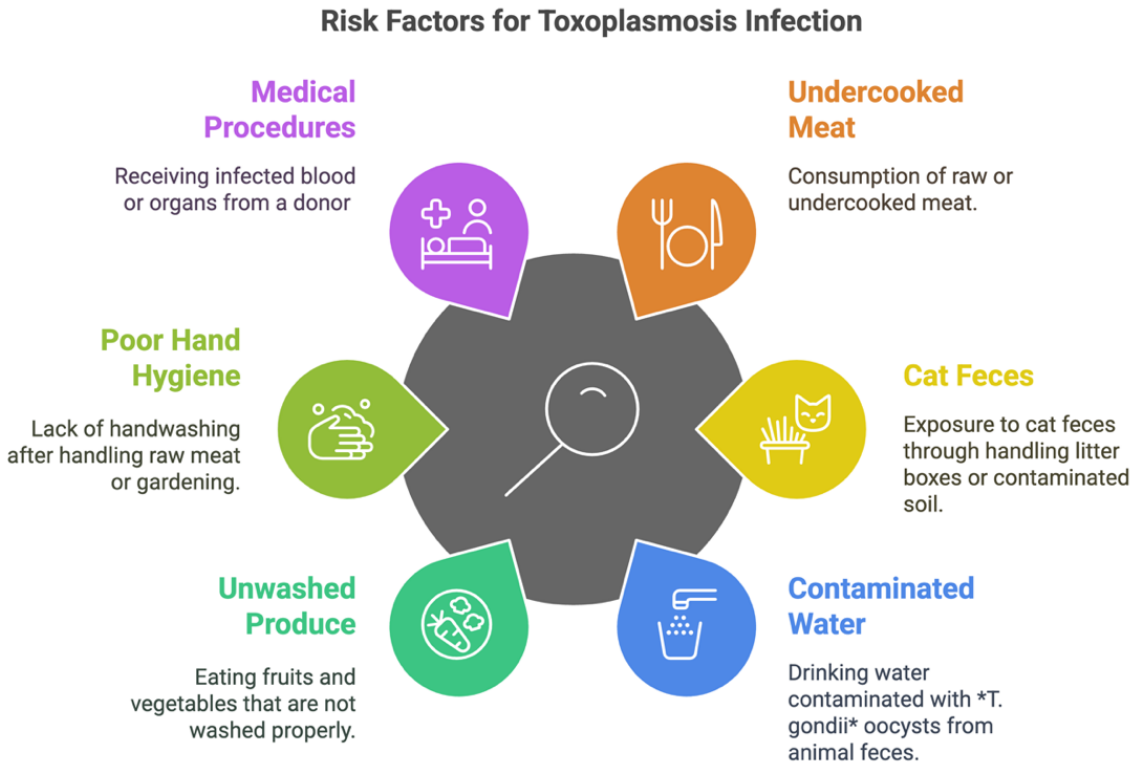

Figure 6: Risk Factors for Toxoplasmosis Infection

Prevention is the mainstay of managing Toxoplasmosis when it comes to primary infection, especially when recalling the life cycle of this pathogen. Affecting different intermediate hosts, the presence in water and soil, as well as possible transplacental spread, there are also many risk factors associated with this disease summarized in Figure 6.

Seroprevalence is increasing with increased age. One study conducted in Germany found that 20% in the 18-29 age group and up to 77% in the 70-79 age group showed seroprevalence (49). Also, studies from South America, for example from Brazil, showed significant associations between increased age and increased seroprevalence. The former mentioned study also showed statistically significant increase of seroprevalence in adults, the elderly, illiterates, unemployment and the lack of a safe water source. Merely owning a cat showed no significant association with higher seroprevalence (50).
Yet safe handling with cat feces and emptying litter boxes daily prevents the sporulation.

Moreover, the consumption of undercooked or cured meat is the risk factor most strongly predictive for acute infection. Thus preventive strategies should include the prevalence of infection in meat products, and inform consumers about farming and processing methods like “farmed indoors” or “frozen meat” (9). Studies have shown that freezing meat for 3 days below -20 °C effectively eliminates the infectivity of present T. gondii (51).
The prevalence of Toxoplasma gondii in pigs can be reduced, simply by hindering access of cats to the farm animals (52). Also, the consumption of unpasteurized milk products is attributed to transmission (9).
Cats play a key role in the life cycle of T. gondii, but direct contact with them is less of a risk for infection than consuming contaminated food, especially meat.
Several studies showed that the ingestion of oocysts is the main form of transmission and not the handling of cats or their feces, showing that, especially this route of infection is important to emphasize, to increase compliance in patients. Especially with recent changes in consumer habits, with increased consumption of organic meat like pork. Pork meat carries a higher risk of T. gondii infection than poultry or beef (9).
A study from the Netherlands demonstrated that the seroprevalence of T. gondii is higher in pork meat from free-range farming than from intensive farming, with statistical significance and odds ratio of 15.8 (53).
A drug-eliminating tissue cysts does not exist; therefore chronic infections cannot be banished. This highlights the importance of preventing the transmission of the highly environmentally resistant oocysts (15). Non-safe water resources are a contributing risk factor for Toxoplasmosis infection, as a study found that the consumption of unfiltered water is associated with increased risk of seropositivity for the lower and middle socioeconomic populations in Brazil (54) .

The control of Toxoplasmosis focuses on prevention, by addressing the key risk factors, especially contaminated food sources as a primary strategy. While felines are critical in the pathogen’s lifecycle, literature review has shown that direct contact with cats or their litter poses minor risk. Instead, the consumption of undercooked meat is significantly more predictive of infection. Moreover, the seroprevalence notably increases with age and is higher in vulnerable populations. As there are strong differences seen geographically, national preventive strategies may aim toward their individual national risk factors.
Given the absence of curative therapies, with ability to eliminate tissue cysts, public health measures emphasizing on food hygiene and safety remains essential.

Table 5: Main hygiene recommendations for prevention of Toxoplasmosis. Adapted from (16)

Main Hygiene Recommendations for Prevention of Toxoplasmosis
• Avoiding undercooked meat
• Hygiene practices (gloves and handwashing)
• Drink only filtered or boiled water
• Cat-related precautions

7.7.2 Secondary prevention

According to Gilbert and Peckham (2001), prenatal screening for toxoplasmosis is discussed in the section of the narrative literature review below.
The estimated birth prevalence of congenital toxoplasmosis ranges from 1 to 5 per 10.000 life births in northern parts of Europe and North America. The majority of newborns appear asymptomatic at birth, with potential symptoms emerging later in life, particularly retinochoroiditis. Neurodevelopmental presentations such as intracranial lesions are rare, with many lesions disappearing spontaneously or with treatment (55). More severe manifestations include permanent neurological impairment, seizures and blindness (56).
The presence of randomized controlled trials that clearly demonstrate the efficacy of prenatal antiparasitic treatment are lacking. There are several observational studies from France and Austria, that suggests a decrease in congenital toxoplasmosis, since the introduction of prenatal treatment with agents such as spiromycin.
Testing is not only beneficial, but it also harbors risk as diagnostic procedures like amniocentesis come with a 0.9% miscarriage risk. Also, the drug therapy or in the neonatal and infant period poses risks of side effects.
A screening for all pregnant woman cannot be made universally, as there is no evidence to support the implementation of it, especially considering the potential clinical risk (55).

Another patient group where prophylaxis is used includes individuals with immunosuppression. Reactivation of Toxoplasmosis in AIDS patients can have debilitating effects. Central system disease, most commonly in the form of toxoplasmic encephalitis, occurs especially in AIDS patients with a CD4 count <100/mm^3. All forms of prophylaxis are usually implemented in these cases. Prophylactic regimens like trimethoprim 160 mg plus sulfamethoxazole 800 mg; one tablet twice daily and 2 days per week are used (56).

To encapsulate the previous passage, there are possibilities of secondary prevention if it is indicated.

7.7.3 Recurrence

It is estimated that two-thirds of all patients with ocular toxoplasmosis will have at least one recurrent episode (5,57).
Findings suggest that there are specific clinical factors contributing to the risk of recurrence exist. Clinically, advanced age (>40 years), newly diagnosed lesions, early-stage disease (<1 year after the initial episode), macular involvement, large lesions (>1 disc diameter), congenital toxoplasmosis, and bilateral compromise were linked to increased recurrence risk (58).

Environmental and parasitic variables, such as precipitation levels, geographic origin of infection, and highly virulent strains, also played a significant role. Given these associations, patients exhibiting these risk factors may derive benefit from prophylactic therapy (58).
In postnatal acquired ocular toxoplasmosis, also age < 21 years and male sex show a higher tendency of recurrence (3).
During active treatment the combination of corticosteroids and antibiotics may reduce the risk of permanent visual impairments and potentially delay recurrence. The recurrence within the first two years after infection is around 12-15 % and then diminishes. There are recurrences observed even up to 49 years after active infection (59).

A two-double-blind study investigated the impact of administering antibiotic prophylaxis with 160 mg trimethoprim in combination with 800 mg sulfamethoxazole three times a week for twelve months. The results showed that there was a reduction of the occurrence of relapses from 22% to 3 % for up to three years. Yet, after three years, patients who have never received prophylaxis do not have a higher risk of a recurrence than those who received the chemical prophylaxis. It can be concluded that relapses can be effectively prevented if it is medically indicated. Also, considering the location of the lesion, immunocompetence as well as frequent relapses (59).

Another study conducted in Brazil underlines the effectiveness of treatment in preventing recurrence. The cohort study published in 2020 by Fernandes Felix, João Paulo et al. compared the effects of 1 year of treatment with trimethoprim-sulfamethoxazole vs placebo with the aim of reducing the risk of recurrent Toxoplasma gondii retinochoroiditis. The primary outcomes were the recurrence of ocular toxoplasmosis within the first year and in the 6 years of follow up. Up to 27, 5 % of cumulative probability of recurrence in the placebo group was observed after 6 years, while in

the patients treated with TMP-SMZ for 1 year, only 1,4 % cumulative probability of recurrence was observed with statistically significant p values ($p < 0.001$) (60).

Limitations of this study include that there is a lack of prior evidence-based research to support the dosage used in this study. Another limitation, potentially limiting the applicability, is the particular ecology of T. gondii strains in South America, and particularly Brazil. The strains differ from other regions.
The combination therapy of Trimethoprim-sulfamethoxazole for 1 year after treatment of active lesions may be used for prophylaxis of recurrent retinochoroiditis caused by T. gondii (60).

A factor that need to be taken into consideration when giving antibiotics as prophylaxis of recurrence is that the antibiotics employed for long-term prophylaxis of toxoplasmic retinochoroiditis must exhibit a favorable safety profile and high tolerability, as extended therapy may be accompanied by adverse effects (61).

In the past, many programs focused mainly on pregnant women. Nowadays, knowledge points to the fact that intraocular infections are mostly acquired postnatally (62).
Hence, an emphasis on preventive strategies postnatally should be implemented.
Novel treatments such as vaccines are researched and if effective could have long-term benefits (63) (64).

8 Case Report

8.1 Clinical Presentation

In this part of the review, a case of Toxoplasmic retinochoroiditis, which has resulted in grave reduction of visual acuity upon initial presentation will be discussed.
A 14-year-old adolescent patient suddenly experienced vision impairment in the left eye due to an active lesion of toxoplasmic retinochoroiditis.
A 14-year-old male patient presented to the emergency department of Pediatric Ophthalmology after reporting blunt facial trauma due to a snowball impact into the left side of the face on 04/12/2021. Because of the stable visual acuity and no other visual disturbances, such as metamorphosis, redness or pain in the eye, the patient went home with no need to seek medical treatment.
Two days later, on 06/12/2021 the patient noticed that the visual acuity of the left eye decreased, with the description of blurry vision. Therefore, the patient went on 07/12/2021 to an ophthalmologist, who referred him to the pediatric ophthalmology department at the University Hospital of Vilnius, for further examination for retinal involvement.

8.2 Patients History

In early childhood, the patient underwent a preschool medical examination in which the visual acuity was tested with 1.0 on both eyes. It is also presumed that he had red fundus reflex testing as a newborn with no abnormalities detected. Approximately two years prior, the patient experienced a transient black dot in his visual field which resolved after the administration of topical artificial tears. Besides this episode, there was no significant ophthalmologic history reported. The patient had no history suggestive of immunosuppression and was presumed to be immunocompetent, had no additional past medical or ocular history nor was taking any medication.

8.3 Clinical Findings

The first visual acuity test on 07/12/2021 upon first presentation shows that the visual acuity on the right eye (OD) was 1.0 with unremarkable findings. On the contrary, the left eye (OS) showed an uncorrected visual acuity of 0.1.
The automated refractive findings showed in the OD a mild hyperopia with minor astigmatism (cylinder -0,5) at an axis of 3 °. In the OS there was no spherical error found, just a minor astigmatism with a cylinder of -0.25 at an axis of 164 °.
On both eyes the intraocular pressure was in the normal range (10-21 mmHg) with 18 mmHg in the OD and 17 mmHg in the OS, measured with the iCare tonometer.

In OD fundoscopy showed a regular optic nerve disc with clear boundaries and a healthy pink color. Also, there were no abnormalities in the macula observed.
In the right eye, the fundoscopy examination revealed a small, dark lesion at 6 o'clock position.

In the left eye, the fundoscopy showed a regular optic nerve disc. The macula showed a fluffy yellowish, pronounced lesion accompanied by swelling and hemorrhage of the retina. Adjacent, to the macula, there is an older, well-defined dark lesion. The dark lesions with defined margins is most probably an old scar of retinochoroiditis caused by T. gondii. The lesion in the left eye can also be seen on the fundus photography in *Figure 7b.*
The green arrow demonstrates the hemorrhage. The black arrow demonstrates the yellowish-white new lesion in proximity of the old, scarred lesion. The new lesion can be described as satellite lesion. The red arrow indicates an old scar of ocular toxoplasmosis as it has defined margins. The yellow arrow in the OS shows a blurry view of the optic nerve indicating inflammatory process, most probably vitritis. This can be compared with the OD, where the optic nerve is seen as defined and sharp with no overlaying vitreous haze.

a) b)

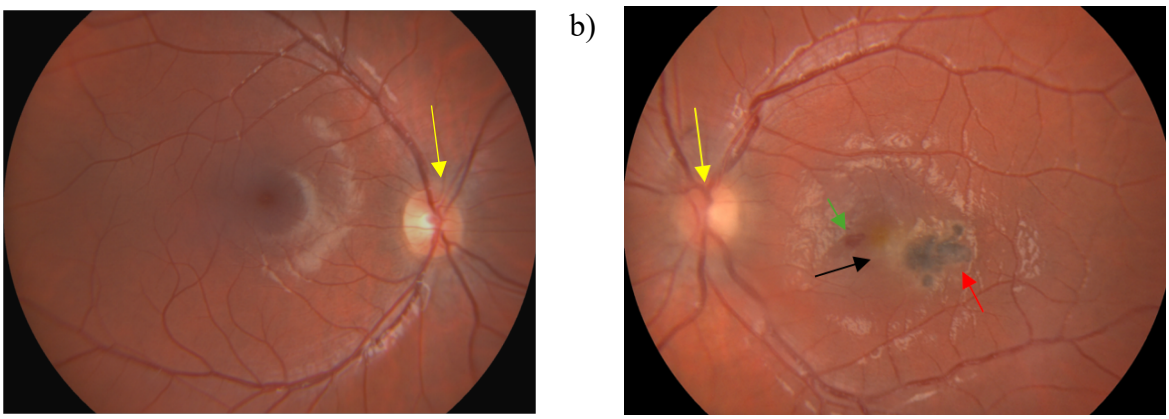

Figure 7: Fundus photography from 12/2021, a) OD b) OS

To carry out more diagnostics regarding the acute retinochoroiditis an OCT was performed with different modalities. In Figure 8 a) you can see the typical lesion seen in posterior uveitis caused by T. gondii, as described in detail above. In Figure 8 c), the red arrow indicates the subretinal fluid and the white arrow indicates the intraretinal fluid. The yellow arrow indicates hyperreflectivity as a result of the scarring of the adjacent old lesion of toxoplasmic retinochoroiditis. The yellow line shows the thickened choroid.
These clinical findings are suggestive for toxoplasmic retinochoroiditis and support its diagnosis.

Also, the average thickness is increased with 304,4 µm. Moreover, the center thickness is increased with 277 µm. These findings are suggestive of an inflammatory process and may explain the decrease of visual acuity in the OS. The increased in thickness is demonstrated in the color mapping Figure 8 b), d) and f) in Figure 8 b) and f) can see also dark green/black areas indicated by the black arrow, in areas of the scar, indicating retinal atrophy.

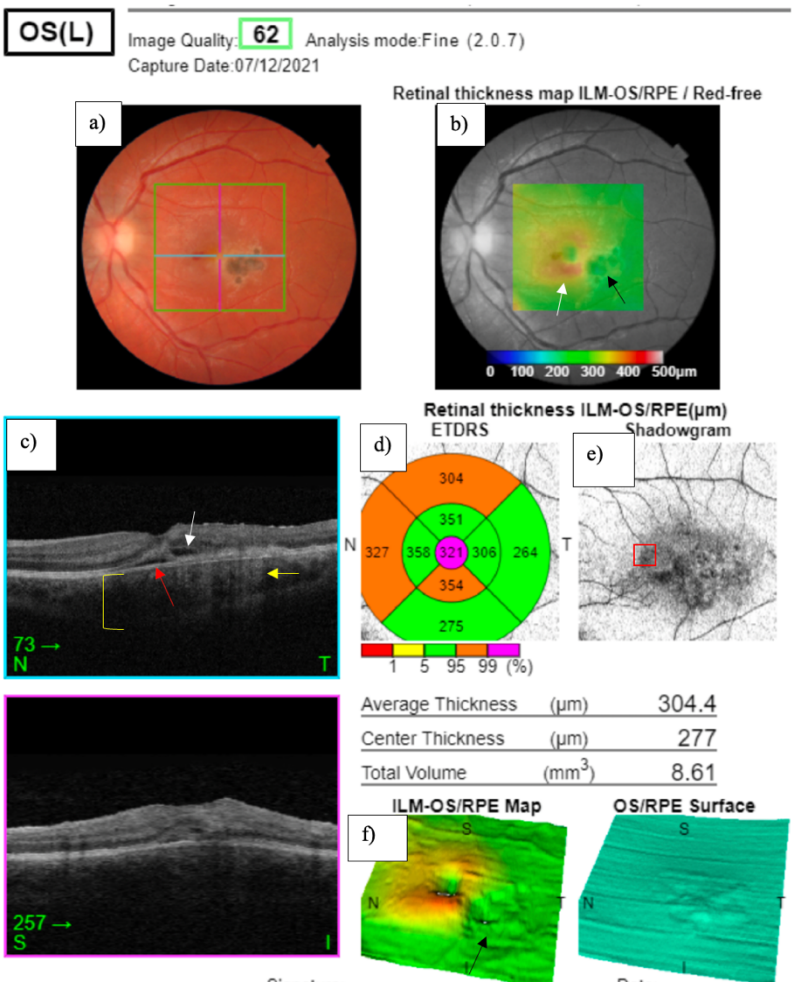

Figure 8: OCT 07/12/2021, a) Fundus image b) Retinal thickness map ILM-OS/RPE/Red-free c) OCT-B d) ETDRS e) Shadowgram f) ILM-OS/RPE

To underline the diagnosis of Toxoplasmic retinochoroiditis and to rule out Differential Diagnosis a serological search was performed seen in *Table 6*.

Table 6: Laboratory Results from 07/12/2022

Parameter	Result	Reference Range
Toxo-IgG (IU/ml)	112,8	<1,6
Toxo-IgG	positive	
Toxo-IgM (s/co)	0,22	<0,83
Toxo-IgM	negative	
Toxocara canis IgG (U)	7,4	positive: >11; borderline: 9-11; negative: <9
Toxocara canis IgG	negative	Negative
Toxo IgG avidity test	88,9110	low: <50 borderline: 50-59.9 high: =>60

The serologic search for Toxoplasma gondii infection was positive for immunoglobulin G (112,8 IU/mL, reference value <1,6 IU/mL), whereas immunoglobulin M levels were normal, indicating prior exposure to Toxoplasma.
The combination of clinical picture, history of the patient and positive IgG levels were conclusive for an active ocular Toxoplasmosis. The negative IgM indicate past exposure of Toxoplasmosis, with no possibility to know with certainty when exactly the infection occurred.
Information regarding the serological status of the mother could not be verified.
A consultation with the Infectious Disease department revealed that the family previously owned multiple cats as pets, but there is no contact with cats in the household at the moment. Furthermore, the consumption of uncooked meat was denied. Information about other risk factors is not known.
With consultation a treatment plan was established as well as further diagnostic tactics.
The clinical abdominal examination was without pathologies. There was no significant organomegaly found, just a mild splenomegaly with 131,4 mm. (Reference range in 14-year-old male: approx. 90-120 mm) (65). Moreover, the neurological examination was without abnormalities.
The plain chest radiography from 09/12/2021 showed no significant findings. It was performed to exclude other foci of infection before starting therapy. There were no infiltrations or other pathologies detectable in the lungs. The bronchial tree was not expanded. The absence of air or fluid in the pleural cavity was shown and the radiographic silhouettes of the heart and mediastinum did not demonstrate significant enlargement. The diaphragm contours were smooth with normal anatomical positioning.

8.4 Treatment

Treatment was initiated after the consultation with the infectiologist. The infectiologist advised to start the treatment with Pyrimethamine with an initial dose of 100 mg per day. This should be followed with 25 mg once a day. This should be complemented with an initial dose of Sulfadiazine 3g as a single dose, followed by Sulfadiazine 1g thrice daily. Also, Leucovorin, a folinic acid supplement was advised to use 10mg per day for 6 weeks. Finally, oral corticosteroid therapy 40 mg once daily orally should be used, after 3 days of antimicrobial treatment. After one week of 40 mg once daily, the dose should be gradually reduced (e.g. 5 mg every week) so that after the end of antibacterial treatment the remaining dose of prednisolone does not exceed 10 mg/d.
Before the start of treatment a laboratory test with complete blood count, liver enzymes (ALT, AST, GGT) was performed. During the treatment a CBC was performed every 1-2 weeks to monitor leukocyte count, hemoglobin levels and platelet count.

Table 7: Treatment

Pyrimethamine per os.	First dose 100 mg per day, then 25 mg 1 time per day
Sulfadiazine per os.	First dose 3 g once, then 1g, 3 times per day
Prednisolone per os.	40 mg, 1 time per day, per os., treatment should be started 2-3 days after the start of antibacterial treatment. After a week (treatment with prednisolone), the dose can be gradually reduced (e.g. 5 mg every week) so that after the end of antibacterial treatment the remaining dose of prednisolone does not exceed 10 mg/d.
Leucovorin per os.	10 mg per day
Nevanac (Nepafanac Ophthalmic Suspension) intraocular	3xd to OS for 2 weeks
Treatment with these drugs is prescribed for 6 weeks	

Moreover, the cardiologists were consulted because the mother of the patient reported that after initiation of treatment, the boy had higher blood pressure for some time. These findings were not conclusive for increased arterial blood pressure. ECG and Echocardiography were performed on 21/12/2021 and showed normal findings. A systolic functional murmur and AV block I degree with QTc prolongation of 0.383 seconds were found. These findings were considered physiologic, as the patient is asymptomatic. Regular evaluation is advised in I-degree AV blocks as they may progress. At the moment, it is thought that in adolescent patients a higher parasympathetic tone is a factor for the development of this conduction disturbance (66) .

As seen below, the urinalysis Table *8*: Urinalysis from 08/12/21 showed normal findings, except for the ketonuria, which was valued without significance for the Toxoplasmic oculopathy.

Also, the CBC is demonstrated and shows normal blood values. Furthermore, liver enzymes were obtained. These tests seen in *Table 8* and *Table 9* were made before initiating the treatment and are important in case the patient develops side effects, for example thrombocytopenia.

Table 8: Urinalysis from 08/12/2021

Parameter	Result	Reference Range
Glucose (mmol/l)	Not detected	3.9-5.8 mmol/L
Glucose (-, 1+, 2+, 3+, 4+)	-	Negative
Bilirubin (µmol/L)	Not detected	< 17 µmol/L
Bilirubin (-, 1+, 2+, 3+, 4+)	-	Negative
Ketones (mmol/L)	1.5	< 0.6 mmol/L
Ketones (-, 1+, 2+, 3+, 4+)	2+	Negative
Specific Gravity	1.025	1.005–1.030
pH	6.00	5.0–8.0
Protein (g/L)	Not detected	< 0.15 g/L
Protein (-, 1+, 2+, 3+, 4+)	-	Negative
Urobilinogen (µmol/L)	Not detected	0.2–1.0 µmol/L
Urobilinogen (-, 1+, 2+, 3+, 4+)	-	Negative
Nitrites	Not detected	Negative
Erythrocytes (/µL)	Not detected	< 10/µL
Erythrocytes (-, 1+, 2+, 3+, 4+, 5+)	-	Negative
Leukocytes (/µL)	Not detected	< 10/µL
Leukocytes (-, 1+, 2+, 3+)	-	Negative
Color	Amber	Yellow to amber
Clarity	clear	clear

Table 9: Complete Blood count from 08/12/2021

Parameter	Result	Reference Range
WBC (*10^9/l)	6,24	4.0 -10.0
RBC (*10^12/l)	5,4	4.2 - 5.4
HGB (g/l)	152	120-160
HCT (%)	45,7	37- 47
MCV (fl)	84,6	80 - 96
MCH (pg)	28,1	27-33
RDW-SD (fL)	40,6	36 - 46
MCHC (g/l)	333	320 - 360
RDW-CV (%)	12,9	11-15
PLT (*10^9/l)	0,19	0.11-0.28
NEUT (%)	56,3	40-75
LYMPH (%)	33	20-45
MONO (%)	6,7	2-8
EOS (%)	3,4	1-6
BASO (%)	0,6	<1
IG (%)	0	<0.5
CRP (mg/l)	<0.6	<5.0
ALT (U/L)	10	7-56
AST (U/L)	17	5-40
GTT (U/L)	10	10-60

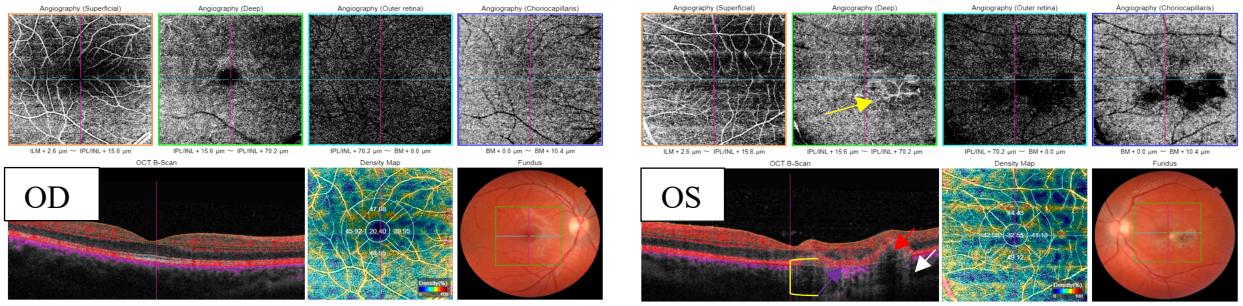

Figure 9: OCT Angiography 21/12/2021, OS) changes supporting the diagnosis of retinochoroiditis

In the following section of this case report, the OCT-A seen in Figure 9 is described. It is a great tool to assess the retinal and choroidal microvascular flow (36).

It was used to provide images of the retinal and choroidal vasculature non-invasively. The scan is divided into four vascular layers, an OCT B-scan, a density map, and a fundus image. On the right side we can see the retina of the OS represented. On the left side we can see the retina of the OD represented.

The OCT images in the OS show several findings supporting an inflammatory process involving retina and choroid, hence termed retinochoroiditis.

In the OS, the affected eye, the superficial capillary plexus has a uniform, interconnected capillary network. It is noticeable that a clear presentation of the fovea with the typical image of a small round circle like in the unaffected eye is not observed.

The Deep Capillary Plexus (DCP) visualizes the deeper retinal microvasculature. The affected area appears larger than in the superficial capillary plexus, suggesting inflammatory damage extending deeper. In this layer hyperintense vascular is seen indicated in Figure 9 by the yellow arrow. This could possibly indicate vascular remodeling of the scar, as there is no such vasculature usually seen.

The outer retina, also called the avascular zone, shows an even bigger affected area than the deep capillary plexus layer, demonstrating the depth of inflammatory involvement. Hypointense changes are visible and suggest either inflammatory or degenerative processes.

This indicates structural loss of photoreceptors and the retinal pigment epithelium. This correlates with retinal atrophy secondary to retinochoroiditis.

The choriocapillaris refers to the choroid vasculature. The choriocapillaris is the layer crucial for supplying blood to the outer retina and retinal pigment epithelium. in healthy eyes it should appear densely perfused without dark voids as seen in OD for comparison. In the picture, from our patient, large dark zones also described as vascular voids or hyporeflectivity are corresponding to decreased flow are seen.

This finding is consistent with choriocapillaris damage from inflammation (18).

The OCT-B scan in Figure 9 shows the retinal lesion in cross-section, with color-coded segmentation. We can see disruption of the retinal layers. The retinal pigment epithelium is irregular and hyperreflective, indicated by the purple arrow pointing to the outermost retinal layer. These findings are suggestive for an active inflammation.

Also, focal hyporeflective thickening of the choroid can be observed indicated by the yellow bracket. The yellow brackets mark the thickened interface between the retinal pigment epithelium and the choroid-scleral interface. The violet arrow indicates disorganization of the retinal pigment epithelium. These finding are suggestive for underlaying choroidal inflammation beneath the retinal inflammation. Indicated by the red arrow, there is the typical view of choroidal neovascularization. The white arrow points to hyperreflective zones, representing scarring, most probably from the adjacent older scarred lesions.

Sub- or intraretinal fluid is not observed, which excludes retinal detachment at this stage. Retinal detachment is a complication seen more commonly in the acute phases of systemic infection (67).

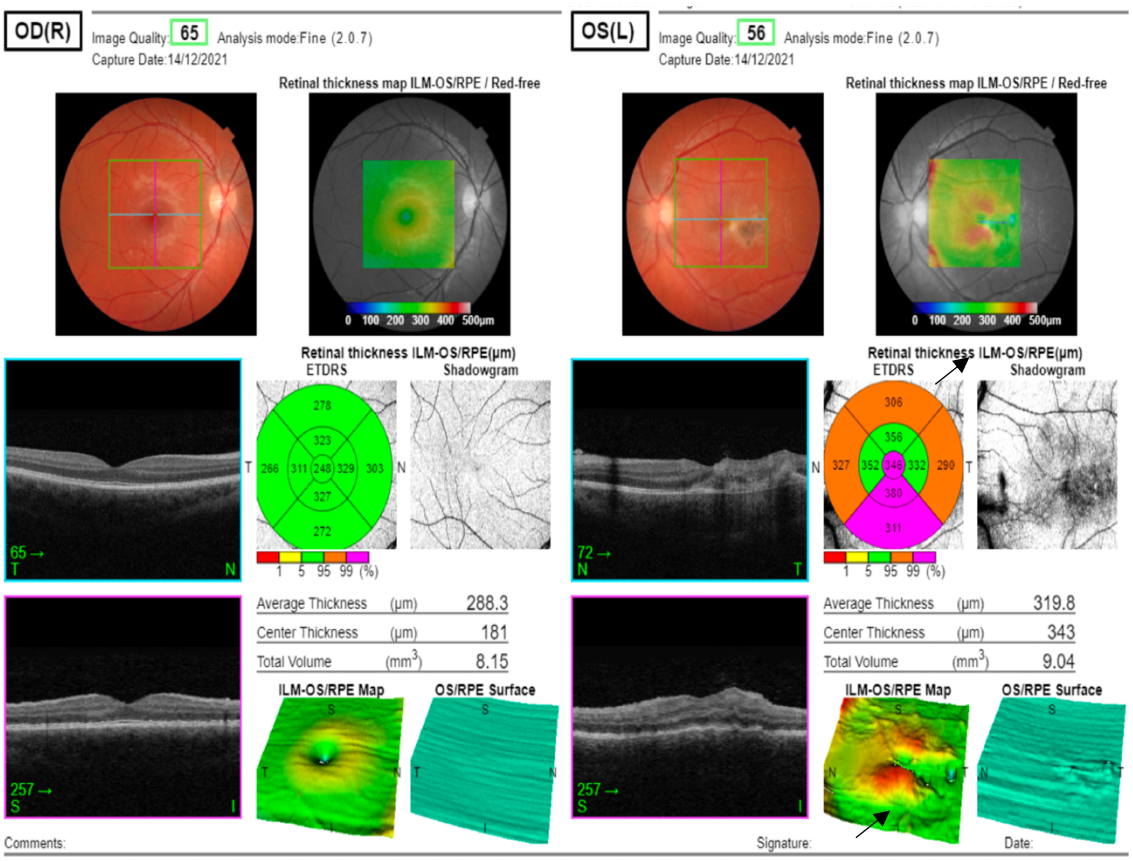

Figure 10: OCT from 14/12/2021

The OCT seen in Figure 10 was made several days after initiating the treatment. When looking at the picture of the OS it is noticeable that there is an increase in center thickness with 343 µm and average thickness with 319,8 µm. Compared to the values of the OD with an average thickness of 288,3 µm and center thickness of 181 µm. Also, it is visible that the hemorrhage which was present upon the first presentation is not noticeable anymore in the fundus photograph. The ILM-OS/PRE map shows an increase of thickness especially in the region inferior to the macula, visible in the red color and indicated by the black arrows.

Only 3 days later, there is a stark reduction of the average thickness and the center thickness visible with values of 299,9 µm and 238 µm in Figure 11. This indicated the reduction of inflammation. In the ILM-OS/RPE there are new areas of retinal thinning visible. Also, the vitreous fluid has cleared, with less prominent vitrous haze, as the optic nerve is visible, compared to Figure 10. This indicates also a reduction in vitritis.

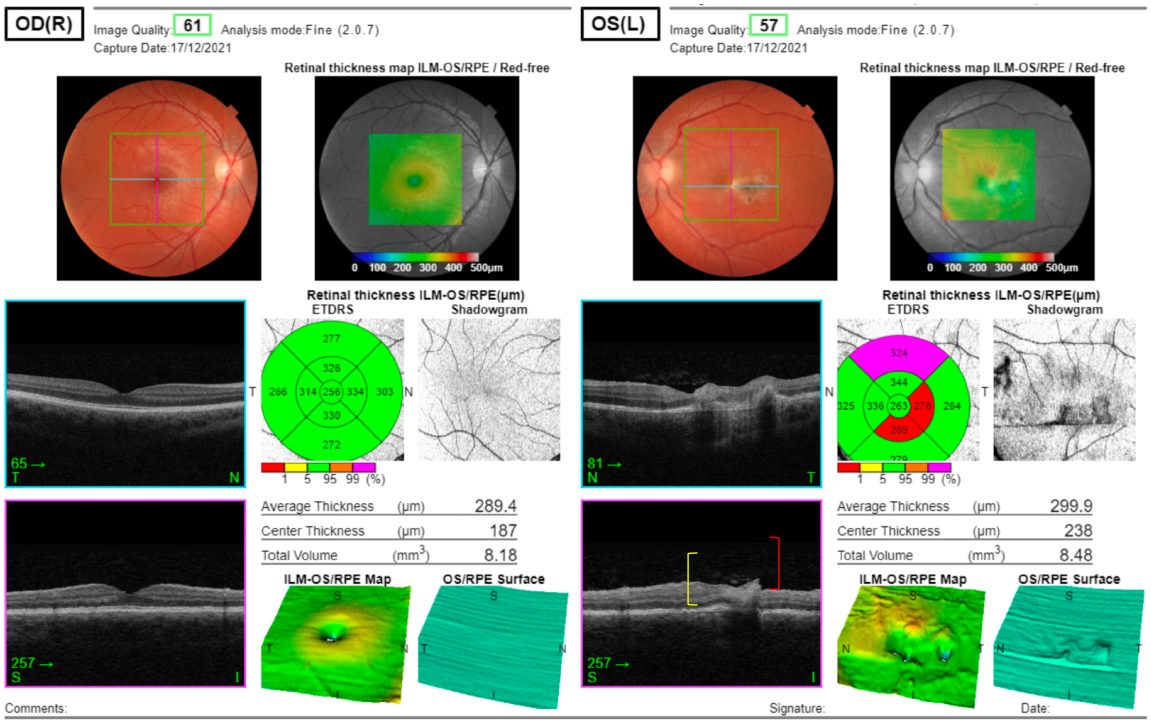

Figure 11: OCT from 17/12/21

8.5 Course of Disease

In the following part of the case report, the course of the disease will be illustrated with the use of various Optical Coherence Tomography images and Fundus Photographs, identifying changes seen during healing. From the initial presentation in December 2021 up to today, the patient was closely monitored. Monitoring hereby included the control of CBC while on medication as well as routine fundus photographs and OCT for assessment of the current retina status. The continuous monitoring of CBC values was particularly important, given the potential systemic side effects associated with the medication administered. During both treatments the patient experienced no side effects, which would cause discontinuation of treatment.
For two years the patient remained symptom-free until February 2024, when the patient presented with a recurrence in the right eye, showcasing a bilateral involvement.

Below in Figure 12 , fundus photographs are seen from November 2022. The lesion, with what the patients presented himself initially is now pigmented and has clear margins indicated by the red arrow. It is located in proximity to the fovea.
In many cases recurrence happens adjacent to an existing lesion and are termed satellite lesions, which is also seen in this case (67).

a) b)

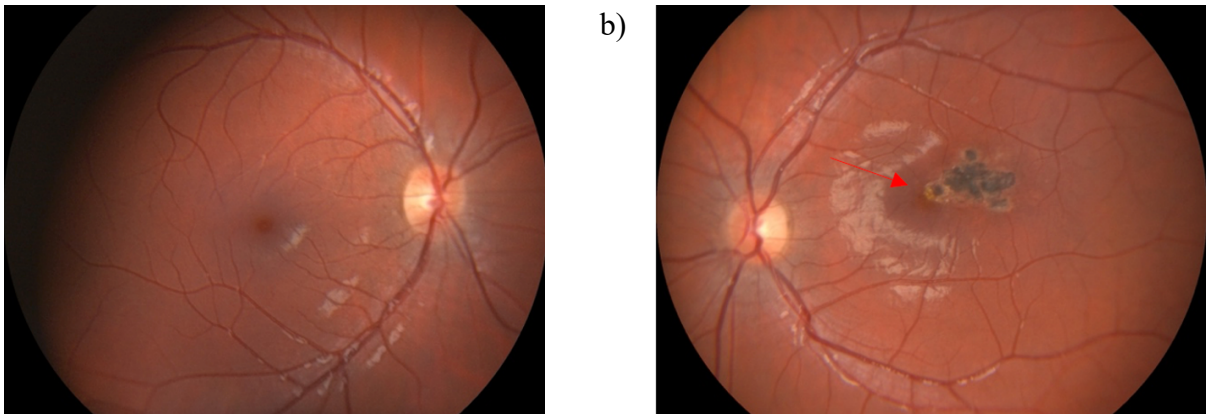

Figure 12: Fundus Photography from 09/2022

In the OCT seen in Figure 13 , the scar formation can be observed with disorganized retinal layer reflectivity beneath a thin, hyperreflective choroid. Furthermore, retinal pigment epithelium-choroid complex atrophy is seen. Additionally, minimal subretinal fluid can be seen, indicated by the green arrow. A reduced average retinal thickness with 270.7 micrometers is seen. This is also seen in the retinal thickness ILM-OS/RPE map seen as dark blue areas. Furthermore, we can see, indicated by

the red arrow, that the nerve fiber layer seems atrophied. Also, no signs of active inflammation is seen.

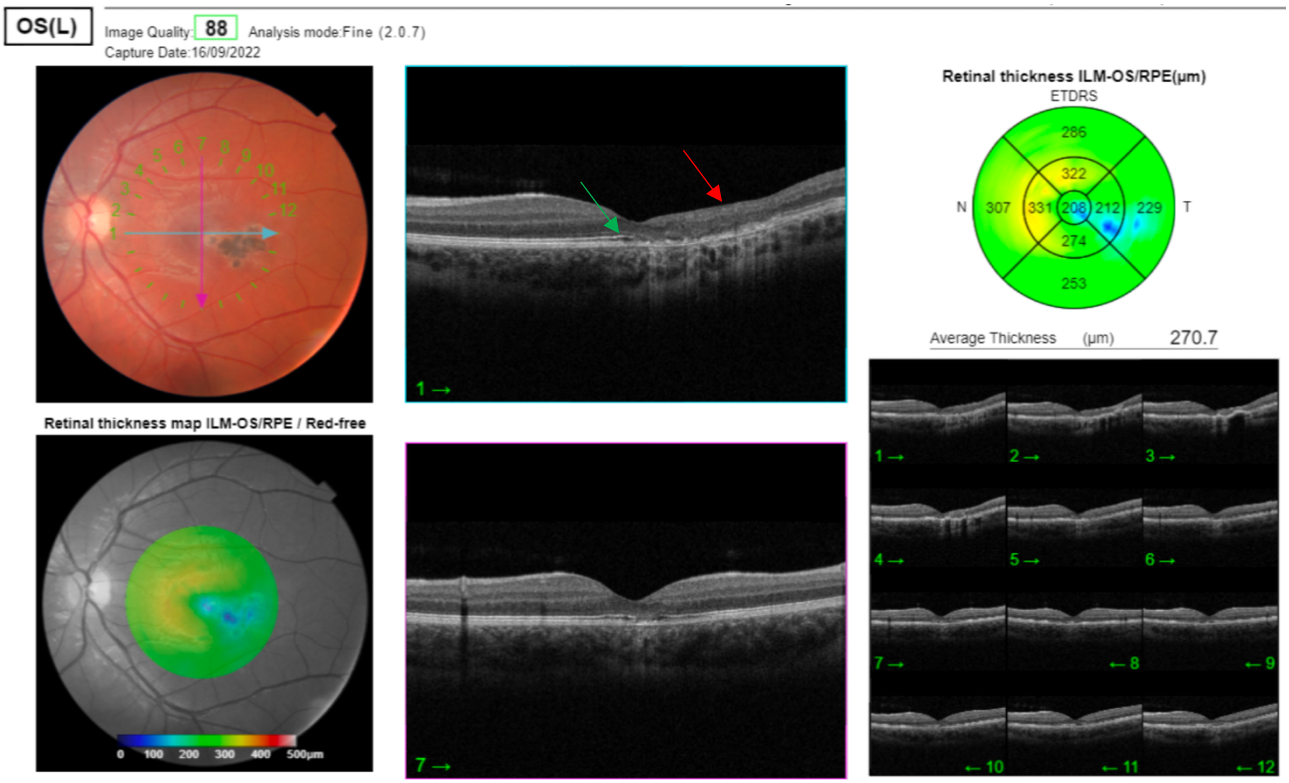

Figure 13: OCT from 16/09/2022

In the OCT from 30/10/2023 seen in Figure 14, further retinal atrophy is seen as thinning, indicated by the yellow bracket. This is also demonstrated by the retinal thickness ILM-OS/RPE map, showing blue areas. In these places the retinal thickness is not greater than 100 micrometers. This is interesting in the context that the patient has full visual acuity. This underscores the possibility that even in parafoveal lesions a high visual acuity can be regained.

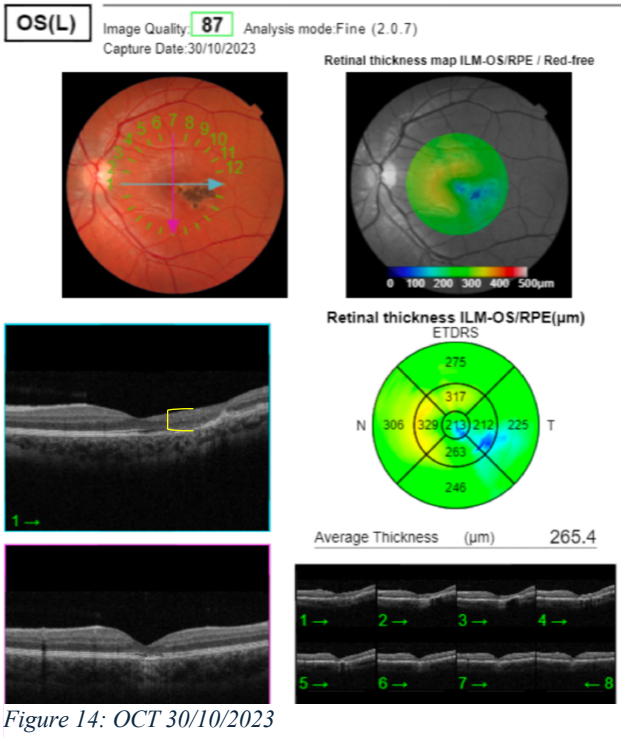

Figure 14: OCT 30/10/2023

After 2 years of stable disease, a new lesion appeared in the right eye. The patient came in with a complaint of black spots in front of the right eye. Visual acuity was tested 1.0 in OS and 1.0 in OD, despite reported floaters. The slit lamp examination showed no anterior uveitis, with no cells

in the aqueous humor. Both the cornea and lens were clear. The iris showed no signs of inflammation and pupils were dilated regularly. In indirect ophthalmoscope examination a new whitish fluffy lesion with unclear margins and neighboring hemorrhage was observed in the periphery in the right eye.

A reactivation was presumed, and the patient was hospitalized to initiate treatment. Clinically, there was no concomitant enlargement of lymph nodes. A therapy was implemented by the infectiologists with three drugs. These three drugs include, representing the classical oral therapy:

1. Pyrimethamine -100 mg on the first day, then 25 mg two times daily
2. Sulfadiazine -1000 mg four times daily
3. Folinic acid 10 mg three times per week.

The treatment was given for 6 weeks, with reassessment after the 4th week for effectivity.

The infectiologists advised that in case of an insufficient effect, prednisolone per os 60 mg should be added for one week after the 4 weeks and then tapering the dose by 5 mg every three days.

The complete blood count was checked every 10-14 days for possible neutropenia

As alternative treatment regimens, treatment with spiramycin 6g/day for 7-14 days or 7 days with azithromycin 500mg two times daily was proposed. Spiramycin is usually used in acute seropositive pregnant woman to prevent transplacental transmission to the fetus (5). This treatment should be implemented in case of neutropenia in the face of bone marrow depression which can occasionally occur with pyrimethamine (5).

The proposed alternative regimen proposed by the infectiologists was not needed, as no side effects were apparent.

As de novo foci not associated with an old scar or multiple are uncommon in immunocompetent individuals, reasons for immunosuppression should be excluded. Generally, it is estimated that within a period of 5 years, more than half of patients will experience a recurrence (22).

Generally, recurrence of latent toxoplasmosis is thought to be caused by the rupture of tissue cysts containing bradyzoites, which in turn trigger a local immune response (18).

In this case Vitamin D levels and serology for HIV was tested to exclude reasons for immunosuppression. The Vitamin D levels were decreased with values of 24,84 (25-OH) (nmol/l), therefore Vitamin D was supplemented.

Vitamin D is important for the functionality of the immune system. It is needed for modulation of several processes in different kind of immune cells, expressing Vitamin D receptors (VDR) (68).

In the Fundus Photograph seen below the new whitish fluffy lesion is observed in the right eye, indicated by the red arrow in Figure 15a. The yellow arrow indicates the neighboring hemorrhage, representing a typical picture in acute lesions (5).

a) b)

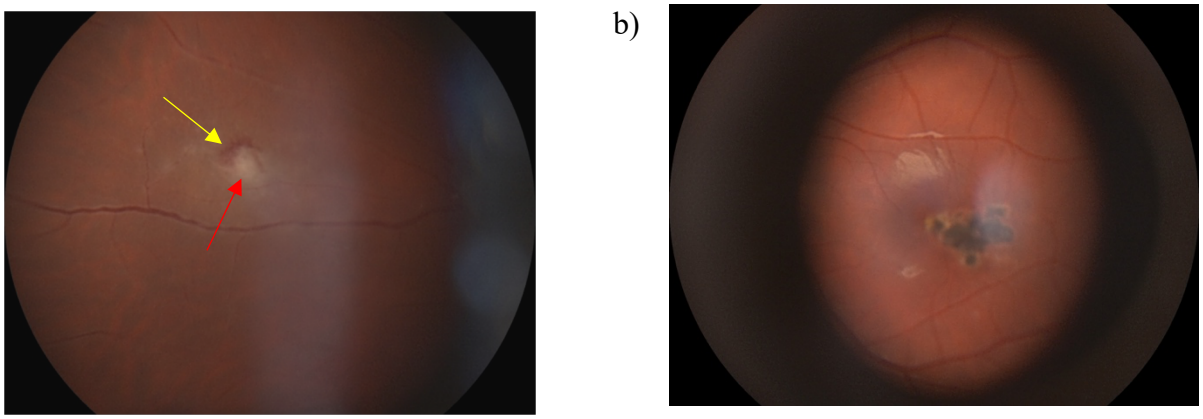

Figure 15: Fundoscopy from 02/2024, a) OD: new lesion, b) OS

The fundus in Figure *16*b shows unchanged findings in the OS. The OD is seen in Figure *16*a. There is a whitish retinal lesion with clear margins highlighted with the red arrow. The hemorrhage which was seen in February 2024 has dissolved. The yellow arrow indicates a small lesion.

a) b)

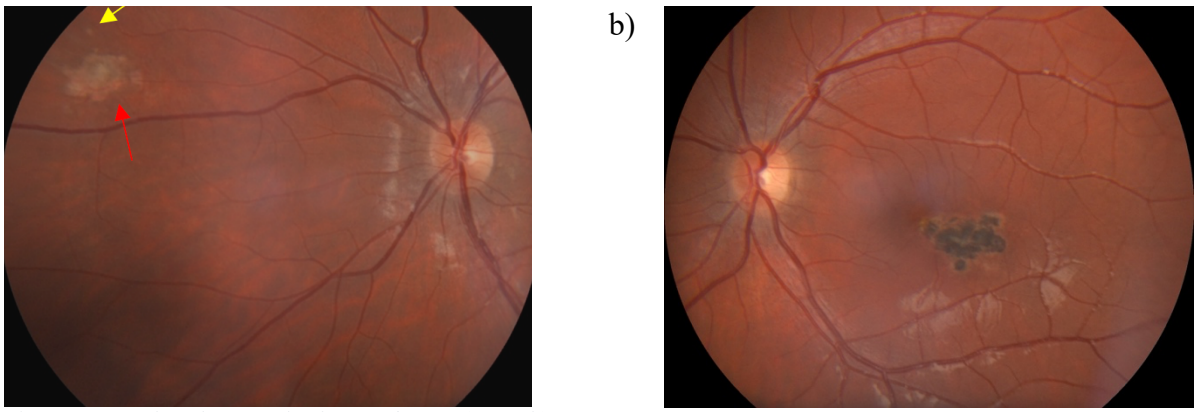

Figure 16: Fundus Photography from 04/2024, a) OD, b) OS

At the ophthalmological control appointment on the 30/05/2024, the visual acuity was tested 1.0 in both eyes. Both eyes showed a clear cornea and lenses. The pupils were reacting to light readily.

Also the vitreous fluid was clear with no cells detected in the anterior segment or the vitreous body. Ophthalmoscopy showed no new lesion. In OD a light yellowish lesion in the periphery was described with clear margins. The macula appeared flat. In the OD no new lesions were observed. The known parafoveal flat pigmented scar was described, as seen also in Figure *16*b above.

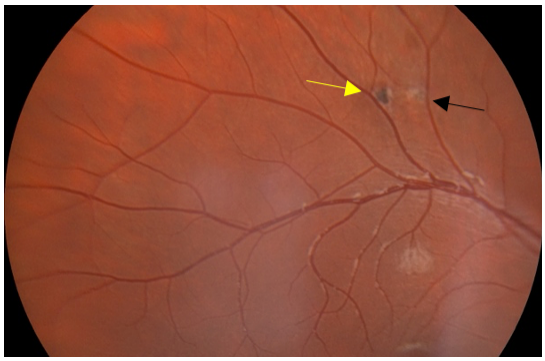

Figure 17: OS lesions from 04/2024

In Figure 17 two lesions, an older lesion indicated by the yellow arrow and a recent lesion, indicated by the black arrow are seen. Both of them are located rather in the periphery of the retina. OCT or other imaging modalities besides the fundus photograph were not performed.

The typical picture of the black lesions seen in the fundus photography below Figure 18, is thought to be caused by mechanisms induced by T. gondii as a result of interaction with retinal pigmented epithelial cells. The infection of retinal pigmented epithelial cells by T. gondii leads to altered secretion of growth factors. This stimulates the proliferation of nearby unaffected cells. Thus, we can observe a hyperpigmented scar, caused by accumulation of melatonin due to an altered cellular response.

Hyperpigmented scars are typically adjacent to areas of active retinitis as it was also visible in this case. They represent previous episodes of infection and subsequent inflammation (16).

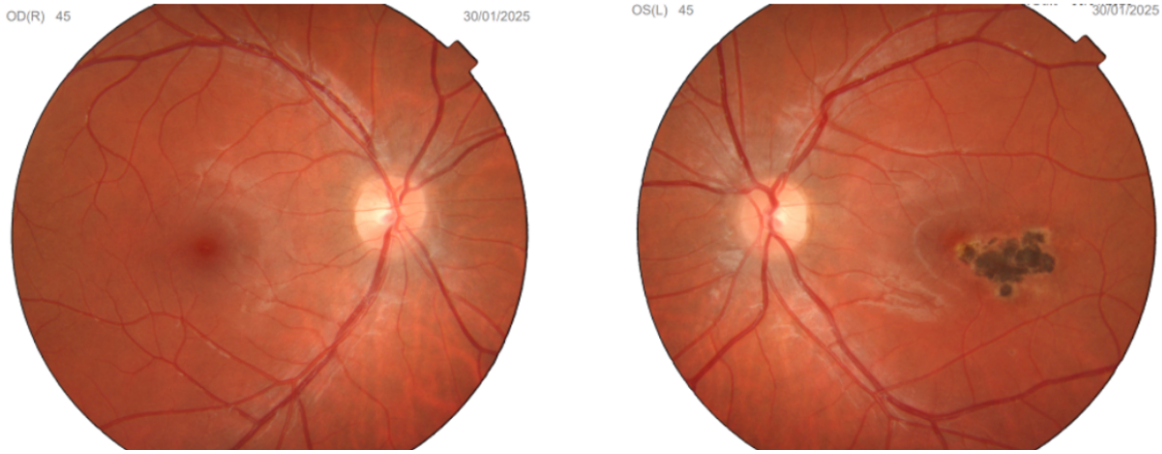

Figure 18: OD and OS

When comparing Figure 18 and Figure 19, we can see typical differences seen in acute and chronic lesions. Figure 19 represents the first fundus photograph taken, showing a whitish focus in the posterior pole with fuzzy borders. This focus is surrounded by hemorrhage and inflammation. Inflammation is also seen in the vitreous fluid as vitreous haze. Figure 18 represents the most current fundus photographs available from the patient, with well-defined pigmented margins and central atrophy (5).

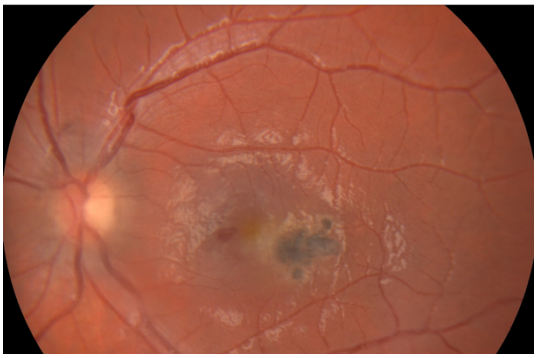

Figure 19: Fundus Photograph from 12/2021 OS

9 Discussion

The upper presented case is of particular interest as we have bilateral involvement and occurrence of a recurrence was reported.

Furthermore, when the patient was initially admitted, he was only 14 years old, favoring non-invasive diagnostic and treatment methods.

Many questions remain, like the probability of recurrence or which role the host's immunity plays in this specific case. The lesion in the left eye is vision-threatening as it is adjacent to the fovea. Studies have shown that bilateral involvement shows a statistically significant risk of recurrence (58).

Prophylaxis with trimethoprim-sulfamethoxazole every other day for 311 days has been shown to be effective in reducing recurrences compared to a placebo, as demonstrated by the randomized double-blind clinical trial conducted in Brazil (60). This regimen could be discussed to possibly reduce recurrence and therefore complications that might worsen the patient's vision.

The limitations of this case study relate mainly to the retrospective analysis of the given data. There are some questions that remain unanswered, like when exactly and how it was acquired. Serological testing revealed positive IgG with negative IgM and high IgG avidity, further corroborating a non-acute, reactivated infection.

Nevertheless, one can learn from this case study what needs to be considered in the treatment of patients with ocular toxoplasmosis. In addition, one can discuss whether prophylaxis for 1 year would be sensible due to the visually dangerous localization of the lesion in the left eye. Although prophylaxis was not initiated post-treatment, this decision should be reconsidered in the event of future relapse.

It can be concluded that restoration of high visual acuity can be achieved when immediate treatment is implemented, even in parafoveal lesions, as presented in this case. The visual acuity improved to 1.0 in the left eye during the treatment.
The presented patient was managed according to the current standards and knowledge for vision-threatening ocular toxoplasmosis, as detailed in the literature review. The patient was treated with the classic oral therapy, consisting of Pyrimethamine, Sulfadiazine and Prednisolone per os.
While several treatment modalities exist, the optimal therapy remains undetermined, especially when discussing the optimal therapy of recurrence of ocular toxoplasmosis. This case underscores that we have effective treatment regimens, presented in the literature review and demonstrated with the successfully treated patient.
In this case, prompt systemic therapy led to clinical stabilization and preserved visual acuity in the affected eye, despite initial involvement of the macula.

10 Conclusion

Toxoplasma gondii which causes ocular toxoplasmosis, is responsible for most cases of infectious posterior uveitis worldwide and is an important factor for blindness (61).
The presented case highlights the complexity of managing Ocular Toxoplasmosis as a vision-threatening disease, the necessity of regular ophthalmologic check-ups and the possibility of recurrence. It is a difficult disease in terms of patient satisfaction, due to the disease's unpredictable nature, which places a psychological and clinical burden on patients, with many questions remaining unanswered.
Although current therapies manage the immediate threat to vision, especially when initiated early, a curative treatment is not available, as there is no treatment to eradicate tissue cysts.
This review underscores the multifaceted challenges of ocular toxoplasmosis, demonstrating that there are substantial gaps in research. Therefore, further studies are necessary focusing on individual recurrence risk, novel therapeutic targets focusing on the cystic stage, individualized treatment approaches, such as intravitreal approaches and long-term management of this disease.
Until curative treatment is available, prevention on the national public health level is necessary, as risk factors are different depending on the region.
Continued interdisciplinary and international research is essential to bridge current knowledge gaps, create a deeper understanding of the disease's pathophysiology and ultimately improving long-term visual outcomes for affected patients.

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