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DISSERTATION

**“Morphological changes and outcome in CMV anterior uveitis“**

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## Foreword

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Furthermore an abstract of a lecture titled „Biomorphologische Befunde bei CMV-assoziiierter anteriorer Uveitis“ presented at the annual meeting of Berlin-Brandenburgische Augenärztliche Gesellschaft (BBAG) in Berlin on December 7, 2018 has been published.

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## LIST OF ABBREVIATIONS

ACAID	Anterior Chamber-Associated Immune Deviation
AH	Aqueous Humor
AI	Antibody Index
AU	Anterior Uveitis
CEC	Corneal Endothelial Cell
CMV	Cytomegalovirus
DNA	Deoxyribonucleic Acid
EBV	Epstein-Barr Virus
ELISA	Enzyme-Linked Immunosorbent Assay
FUS	Fuchs Uveitis Syndrome
GWC	Goldmann and Witmer Coefficient
HLA	Human Leukocyte Antigen
HSK	Herpes Simplex Keratitis
HSV	Herpes Simplex Virus
IgG	Immunoglobulin G
IL	Interleukin
IOP	Intraocular Pressure
IUSG	International Uveitis Study Group
KPs	Keratic Precipitates
KSHV	Kaposi's Sarcoma associated Herpetic Virus

MANOVA	Multivariate Analysis of Variance
MCP-1	Monocyte Chemoattractant Protein-1
NAION	Nonarteritic Ischemic Optic Neuropathy
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
PCR	Polymerase Chain Reaction
POAG	Primary Open Angle Glaucoma
PSS	Posner-Schlossman Syndrome
RNFL	Retinal Nerve Fiber Layer
SUN	The Standardization of Uveitis Nomenclature
TM	Trabecular Meshwork
VEGF	Vascular Endothelial Cell Growth Factor
VZV	Varicella Zoster Virus
$\eta^2$	Eta Squared

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# 1. ABSTRACT

## 1.1 Abstract English

### Introduction:

Cytomegalovirus (CMV) associated acute anterior uveitis (AU) has been detected in individuals diagnosed with Posner-Schlossman Syndrome (PSS). It is a rare disease with little published data and was previously labelled as “idiopathic”.

In immunocompetent individuals it appears as an inflammatory process in the anterior segment, often leading to a hypertensive unilateral AU marked by coin-shaped keratic precipitates (KPs) and mild anterior chamber activity. Since molecular techniques have been available to detect viral pathogens, antiviral treatment has been applied to reduce virus load and thus control the inflammation and the elevated intraocular pressure (IOP). We investigated if CMV AU can be determined by morphological changes in the endothelium and the optic disc, and if there is a relation between length of remission and systemic antiviral therapy with valganciclovir.

### Methods:

A retrospective study of 52 CMV-positive patients confirmed by specific intraocular antibody synthesis in the aqueous humor (AH). To detect morphological changes an analysis of a corneal endothelial microscopy and a peripapillary Spectral Domain Optical Coherence Tomography (SD-OCT) scan were performed. The fellow eye served as the control group. Furthermore, we analyzed the outcome of oral valganciclovir therapy in preventing recurrences.

## **Results:**

We performed endothelial microscopy on 29 (56%) of 52 patients. Endothelial microscopic examinations revealed a significantly lower CEC density ( $p < 0.01$ ) of the affected eye compared to the fellow eye. Additionally, we conducted a peripapillary RNFL SD-OCT scan on 38 (72%) of 52 patients, imaging the affected and fellow eye. We observed a significantly lower peripapillary RNFL ( $p < 0.01$ ) of the affected eye compared to the fellow eye. In addition, we investigated differences of the SD-OCT results of the affected eye in the course of the disease based on a mean follow-up of 24.6 months of 17 patients ( $p < 0.05$ ). Furthermore, we found a significant correlation between the length of antiviral therapy and the length of remission after discontinuing therapy ( $p < 0.01$ ).

## **Conclusions:**

Our results indicate that morphological changes in the CEC and peripapillary RNFL play a crucial role in CMV AU. These changes include peripapillary RNFL thinning and loss of CEC density. Our data substantiate the need for endothelial microscopy even in early stages of the disease while SD-OCT scans are essential in early detection of secondary glaucoma. Both techniques should be frequently repeated to monitor early changes. Furthermore, long-term oral treatment with valganciclovir appears to extend the length of remission periods in patients with CMV AU.

## **Keywords:**

CEC, CMV, corneal endothelial cell density, Cytomegalovirus, OCT, Posner-Schlossman Syndrome, PSS, RNFL, Uveitis anterior, Valganciclovir

## 1.2 Abstract Deutsch

### **Einleitung:**

Die CMV assoziierte akute anteriore Uveitis wird oft synonym als Posner-Schlossman-Syndrom (PSS) bezeichnet. Es handelt sich um eine seltene Erkrankung mit nur wenigen publizierten Daten, welche bisher als "idiopathisch" galt.

Bei immunkompetenten Individuen hingegen zeigt sich eine Entzündungsreaktion im vorderen Augenabschnitt, welche oftmals zu einer unilateralen hypertensiven anterioren Uveitis führt. Charakteristisch sind hierbei rezidivierende Episoden, in denen feine münzförmige Hornhautpräzipitate auffallen sowie ein milder Vorderkammerreizzustand festzustellen ist. Seit der Einführung molekularbiologischer Diagnostik und dem Nachweis viraler Antigene als Ursache der Erkrankung ermöglichte der gezielte Einsatz von antiviraler Therapie eine Kontrolle der Entzündungsreaktion und des erhöhten intraokularen Drucks.

Ziel dieser Arbeit war es daher, Schädigungen am Hornhautendothel und an der Papille genauer zu evaluieren und die Wirkung systemischer antiviraler Therapie mit Valganciclovir auf die Dauer der Remission der Erkrankung zu eruieren.

### **Methoden:**

In dieser retrospektiven Studie wurden 52 Patienten analysiert, die im Rahmen einer Vorderkammerpunktion eine intraokulare Antikörpersynthese gegen CMV aufwiesen.

Beurteilt wurden morphologische Veränderungen sowohl von Papille mittels Spectral Domain Optical Coherence Tomography (SD-OCT) als auch die Hornhautendothelzellen mittels Spekularmikroskop. Als Kontrollgruppe diente das Partnerauge. Außerdem untersuchten wir die Wirkung von oral verabreichtem Valganciclovir auf die Dauer der Remission.

## **Ergebnisse:**

Eine Endothelzelldichtemessung führten wir in 29 (56%) von 52 Patienten durch. Dabei zeigte sich eine signifikant niedrigere Endothelzelldichte am betroffenen Auge im Vergleich zum Partnerauge ( $p < 0.01$ ).

Zur Beurteilung der retinalen Nervenfaserschichtdicke (RNFL) am Sehnervenkopf führten wir bei 38 (72%) von 52 Patienten ein SD-OCT durch. Im Vergleich des betroffenen Auges mit dem gesunden Partnerauge imponierte eine signifikant dünnere RNFL. Mittels Kontroll-SD-OCT im Krankheitsverlauf bei einer mittleren Beobachtungsdauer von 24.6 Monaten konnte bei 17 Patienten eine signifikante Verschlechterung der globalen RNFL nachgewiesen werden ( $p < 0.05$ ). Weiterhin konnten wir eine signifikante Korrelation zwischen der Dauer der antiviralen Therapie und Remissionsdauer belegen ( $p < 0.01$ ).

## **Zusammenfassung:**

Diese klinische Studie belegt, dass im Rahmen einer CMV assoziierten anterioren Uveitis morphologische Veränderungen an den Endothelzellen sowie an der Sehnerv-Papille auftreten können. Diese Veränderungen umfassen sowohl eine Abnahme der Endothelzelldichte als auch eine globale peripapilläre RNFL Ausdünnung.

Unsere Ergebnisse belegen, den Nutzen von Endothelzellmessungen und SD-OCT Untersuchung des Sehnervs besonders in frühen Krankheitsstadien. Daher empfehlen wir bei Patienten mit CMV assoziierter anteriorer Uveitis bereits zur Diagnosestellung die Erhebung von Ausgangsbefunden mittels Endothelzellmikroskopie und Papillen-SD-OCT sowie engmaschige Verlaufskontrollen, um frühzeitig morphologische Schäden zu erkennen.

Außerdem scheint die systemische Langzeit-Therapie mit Valganciclovir die Remissionsdauer von CMV assoziierter anteriorer Uveitis deutlich zu erhöhen.

**Schlüsselwörter:**

CEC, Endothelzellichte, SD-OCT, Posner-Schlossman-Syndrom, PSS, RNFL, Uveitis anterior, Valganciclovir, Zytomegalievirus

## 2. INTRODUCTION

### 2.1 Uveitis – definition and classification

The term uveitis refers to an inflammation of the uvea, which consists of iris, ciliary body and the choroid.

The Standardization of Uveitis Nomenclature (SUN) Working Group Guidance on uveitis terminology categorizes uveitis anatomically in four groups (Figure 1) [1]:

- Anterior uveitis: the anterior chamber is the primary site of inflammation
- Intermediate uveitis: the vitreous body including pars planitis is the primary site of inflammation
- Posterior uveitis: the choroid and/or retina is the primary site of inflammation
- Panuveitis: all uveal structures are involved

Based on etiology the International Uveitis Study Group (IUSG) has developed a clinical classification to distinguish three different types [1]:

- Infectious: related to bacterial, viral, fungal and parasitic infections
- Non-Infectious: related to systemic diseases or immunodeficiency syndromes
- Masquerade: related to various neoplastic and non-neoplastic diseases

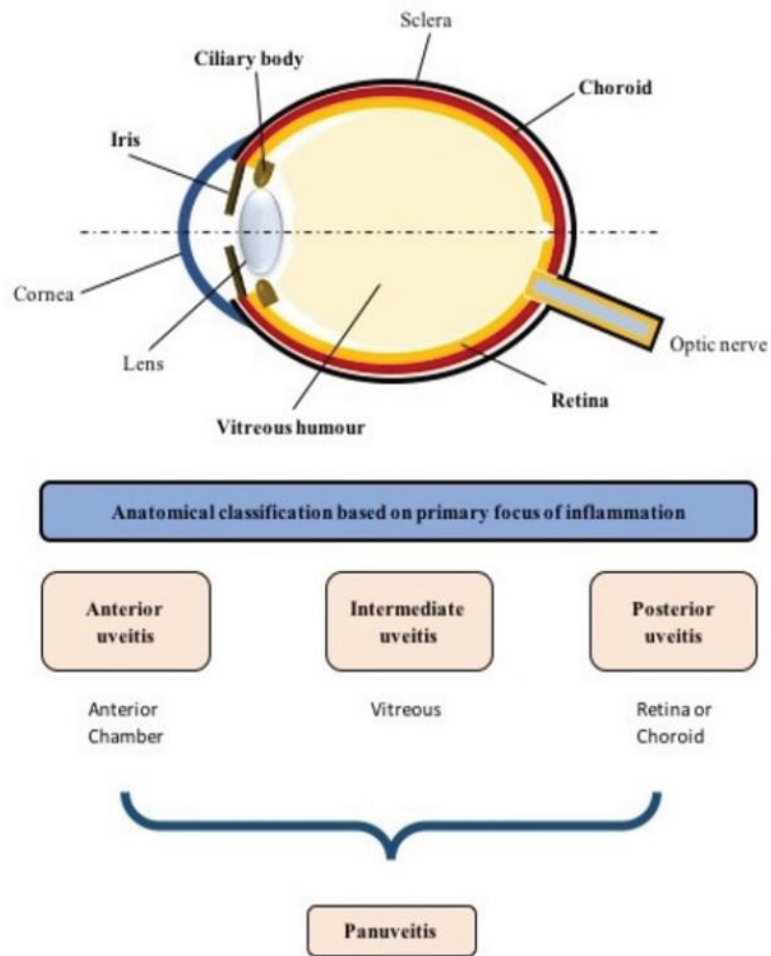


Figure 1: Anatomical classification of uveitis [2].

## 2.2 Infectious uveitis

Uveitis is an intraocular inflammatory disease caused by infectious, non-infectious or autoimmune disorders. A multi-center study by the Japanese Ocular Inflammatory Society has published that 16.4% of enrolled uveitis cases are of infectious genesis [3,4]. In many cases infectious uveitis is not a primary ocular disease. It can be related to a systemic disorder. Infectious uveitis covers a vast variety of potential pathogens including viruses, bacteria, fungi and parasites. In recent decades advancements in molecular analysis have indicated that viruses – especially herpes viruses – are a common cause of uveitis.



### 2.2.1 Herpetic uveitis

There are more than 130 different known species of herpes viruses, though not all of them infect humans. The most relevant human pathogenic types of herpes viruses are Herpes Simplex Virus (HSV), CMV, Varicella-Zoster Virus (VZV), Epstein-Barr Virus (EBV), human herpes virus type 6 and the Kaposi's Sarcoma associated Herpetic virus (KSHV). All herpes viruses are easily transmitted. They may reside inside the human organism in a state of latency for long periods of time without ever causing symptoms of disease [5]. According to Rowe *et al.* [6] up to 90% of the human race is infested with herpes viruses. Concerning the most common types of herpes viruses involved in ocular disease – HSV, VZV and CMV – other studies have also reported prevalence rates of 60 to 90% [7–12]. Different types of herpes viruses produce different symptoms of disease – both systemically and locally in terms of the eye. Nevertheless, the patient's individual immune status has a significant impact on the clinical course and may allow for reactivation of the virus from latency. Herpes virus can affect all compartments of the eye as well as attached tissues. Concerning affections of the anterior segment, typically conjunctivitis is seen which involves the eyelid and also shows lesions of the corneal epithelium [6]. Generally, it can be stated that in immunocompetent patients the anterior segment is involved, while in immunocompromised patients the posterior segment is more frequently affected. In the posterior segment signs of retinitis, with or without inflammation of the vitreous body, are observed [13]. During the course of disease this may lead to severe complications such as neurotrophic keratopathy and ulcers. Epithelial lesions are marked by punctuate vesicular eruptions and dendritic ulcers [14]. Staining the basement membrane with fluorescein dye helps visualize them (Figure 2).

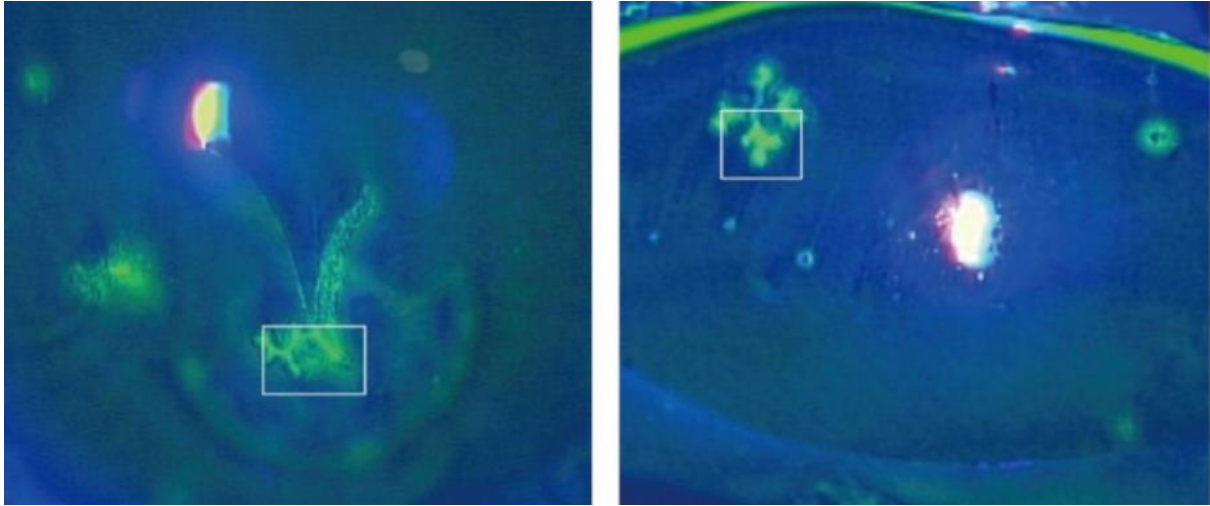


Figure 2: Fluorescein slit-lamp images of dendritic ulcers (frame) in HSK [5].

Treatment with topical corticosteroids and/or antiviral agents suppresses the inflammation, but may not always prevent scarring and blindness [14,15].

### 2.3 Anterior uveitis determined by CMV

AU is the most common type of uveitis worldwide [16] and subclassified into acute or chronic form.

Epidemiological studies are rare and often consist of small cohorts. Rodriguez *et al.* [17] reviewed the referral patterns of uveitis and described the common causes of AU (Table 1). In their cohort, PSS was responsible for 0.9% (n=6) of all AU cases (n=637). Another German study by Jakob and colleagues [18] analyzed 1916 patients with inflammatory eye disease. They found a higher frequency of 45.4% for AU cases and 2.6% for PSS (Table 2). However the majority of AU is of non-infectious etiology – an infectious viral etiology is responsible for only 10 % of all cases [19].

Cause	No. (%) of Patients (n=637 [51.5%])	Sex Distribution, No. (%)		Mean Age at Uveitis Onset, y
		M (n=248 [38.9%])	F (n=389 [61.1%])	
Idiopathic anterior uveitis	241 (37.8)	94 (39.0)	147 (61.0)	42.5
HLA-B27 negative	200 (31.3)	76 (37.6)	124 (62.4)	43.3
HLA-B27 positive	47 (6.4)	18 (43.9)	23 (56.1)	35.7
Seronegative arthropathies	138 (21.6)	76 (55.0)	62 (45.0)	36.1
Nonspecific arthropathy (HLA-B27+)	45 (7.0)	20 (44.4)	25 (55.6)	32.0
Ankylosing spondylitis	47 (7.4)	31 (66.0)	16 (34.0)	37.0
Reiter's syndrome	26 (4.0)	19 (73.0)	7 (27.0)	33.2
Psoriatic arthropathy	5 (0.8)	1 (20.0)	4 (80.0)	45.2
Inflammatory bowel disease	15 (2.4)	5 (33.4)	10 (66.6)	37.3
Juvenile rheumatoid arthritis	69 (10.8)	13 (18.9)	56 (81.1)	12.9
Herpetic keratouveitis (herpes simplex and herpes zoster viruses)	62 (9.7)	30 (48.4)	32 (51.6)	52.2
Sarcoidosis	37 (5.8)	9 (24.3)	28 (75.7)	40.8
Fuchs' heterochromic iridocyclitis	32 (5.0)	15 (46.8)	17 (53.2)	35.4
Systemic lupus erythematosus	21 (3.3)	1 (4.8)	20 (95.2)	45.6
Intraocular lens-induced persistent iritis	8 (1.2)	2 (25.0)	6 (75.0)	62.5
Possner-Schlossman syndrome	6 (0.9)	2 (33.4)	4 (66.6)	49.0
Rheumatoid arthritis	6 (0.9)	0 (0.0)	6 (100.0)	54.2
Others*	17 (2.7)	6 (33.3)	12 (66.6)	...

Table 1: Common causes of AU [17].

Uveitis with an Ocular Syndrome, n = 388	Total, n (%)
HLA-B27-positive anterior uveitis*	136 (35.1)
Fuchs uveitis syndrome	133 (34.3)
Ocular sarcoidosis**	22 (5.7)
Multifocal chorioretinitis	15 (3.9)
Birdshot retinochoroidopathy	14 (3.6)
Acute posterior multifocal placoid pigment epitheliopathy	14 (3.6)
Serpiginous chorioretinitis	12 (3.1)
Punctate inner choroidopathy	10 (2.6)
Posner-Schlossman syndrome	10 (2.6)
ANA + chronic anterior uveitis	6 (1.5)
Multiple evanescent white dot syndrome	5 (1.3)
Eales' disease	4 (1.0)
Lens-induced uveitis	3 (0.8)
Acute zonal occult outer retinopathy	2 (0.5)
Acute retinal pigment epitheliitis	2 (0.5)
Acute idiopathic blind spot enlargement syndrome	1 (0.3)

Table 2: Common causes of AU according to a German interdisciplinary uveitis center [18].

Viruses such as HSV, CMV and VZV are identified as causative factors for AU. CMV in particular has been postulated since the 1980s as an etiological cause of hypertensive AU in immunocompetent patients [20–25]. Knox *et al.* [26] reported that up to 22.8% of AU cases were tested positive for CMV DNA.

Typical ocular findings are iridocyclitis, with or without endotheliitis, marked by granulomatous, fine or stellate KPs and corneal edema [13,26–29]. In immunocompromised individuals, CMV leads to opportunistic ocular infections – often manifesting as necrotizing retinitis [30].

CMV is found as latent infection in the majority of the adult population. The seroprevalence of ocular CMV infection in an age bracket of 6-49 years old in several European states ranges between 49.5% and 73.3%, while in the USA it is 50.4% [31]. CMV is one of the infectious agents of AU. Most reports of infectious AU come from Asia, mainly involving Chinese and Japanese individuals with a CMV seroprevalence of approximately 69.1% to 98.6% [26,28,39–41,29,32–38]. Acute CMV infection has been detected in individuals diagnosed with PSS – a disease that was previously labelled “idiopathic” [42,43]. In some cases CMV AU may manifest as a self-limiting iritis with sectorial atrophy, or a chronic AU with vitreous body inflammation labelled as Fuchs Uveitis Syndrome (FUS) [44]. Chee *et al.* [23,25] reported that 52.2% of PSS patients, 41.7% of FUS patients and 83.0% of endotheliitis patients were tested positive for CMV in aqueous samplings. In 2006 Koizumi *al.* [24] reported cases of CMV-induced corneal endotheliitis by detecting CMV DNA in AH by polymerase chain reaction (PCR). CMV endotheliitis appears isolated or associated with AU [45], is characterized by corneal edema, and leads to destruction of the endothelium and severely blurred vision [46]. It can appear acute or chronic, and frequent recurrence is typical.

However, the role of CMV infection in the etiology and subsequent damage of the eye is not completely understood. There is a lack of information about morphological changes and effects of CMV AU on clinical findings such as CEC density and optic disc neuropathy in the course of the disease.

### 2.3.1 Posner-Schlossman Syndrome – a glaucomacyclitic crisis

In 1948, PSS was first described as a type of unilateral glaucoma with recurrent episodes of increased IOP characterized by mild AU, while during an acute attack the iridocorneal angle remains open, and the visual field appears normal with no damage of the optic disc [47–49]. Diagnosing PSS is challenging and based on clinical findings like minimal conjunctival injection, and small to medium-sized coin-shaped KPs (Figure 3) on the inferior and central cornea, combined with mild anterior chamber activity of 1+ cells and minimal flare [28].

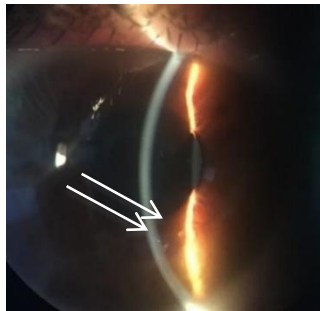


Figure 3 A: Granulomatous coin-shaped KPs (white arrows) in a patient with CMV confirmed AU.

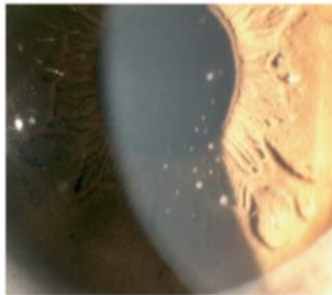


Figure 3 B: Inferiorly located and medium-sized KPs in a patient with PSS [27].

Clinical signs may help to differentiate PSS from other causes of an increased IOP. Narrow angle glaucoma can be diagnosed by gonioscopic examination, with typical signs like a fixed and dilated pupil, combined with severe pain, nausea and vomiting. The acute and recurrent attacks, the positive response to corticosteroids, and the normal IOP in the remission period distinguish PSS from other hypertensive uveitis

entities such as FUS [44,49], or primary angle closure from iridocyclitis [50,51]. PSS typically occurs in adults. The mean age at diagnosis varies between 20 and 50 years old [49,52,53]. In children [54] and in individuals aged >60 years old it is considered an even more rare entity [55–57]. The incidence is significantly higher in men than in women [58], while the reason for the predominant distribution in male individuals is still waiting to be elucidated. Epidemiological data from Finland reveal a mean annual incidence of PSS of 0.4, and a prevalence of 1.9 per 100000 population [59].

It appears to be a benign and often self-limited disease showing good response to antiglaucoma agents and corticosteroids to control the attacks. It is only a rare cause of secondary glaucoma [60]. Only recently has it been suggested to be a viral entity linked to CMV infection of the anterior chamber [21,22,27,29,61]. Chee *et al.* [25] reported that PSS patients were found positive for CMV DNA by PCR. This knowledge has changed therapeutic strategies to assigning antiviral agents for short-term or long-term periods [62]. Nevertheless, general aim of the treatment during an acute attack is to control the inflammation and the increased IOP. Recurrent attacks of elevated IOP are particularly dangerous and lead to loss of vision by progressive visual field defects, up to cupping of the optic disc and damage to the peripapillary RNFL [60,63,64]. In a clinical trial of PSS cases, Jap *et al.* [60] found that 14 (26.4%) of 53 eyes had glaucomatous optic nerve damage after attacks. PSS eventually mimicks the clinical picture of primary open-angle glaucoma (POAG) [55,65]. Another study by Sobolewska *et al.* [62] found that 54.5% of patients with manifest anterior segment inflammation by CMV had glaucomatous optic disc damage before diagnosing AU. Additionally, Kim *et al.* [56] and Irak *et al.* [66] reported that nonarteritic ischemic optic neuropathy (NAION) was a complication of PSS cases. Despite considerable progress in the understanding of the pathogenesis of PSS, and the availability of advanced diagnostic techniques, the morphological changes caused by the disease still remain undetermined.

### **2.3.2 Pathophysiology of CMV anterior uveitis and the risk of secondary glaucoma**

CMV is a large-envelope DNA virus and a ubiquitous beta herpes virus. Transmission occurs by contact, urine and saliva. The site of viral DNA replication is the cell nucleus of the host cell. The course of infection by CMV depends on the integrity and differentiation of the infected cell [67,68]. It leads to lifelong latency in CEC, macrophages, lymphocytes [69] and granulocyte progenitor cells [70]. In the event of reactivation a cascade of gene expression leads to production of virus particles, which are released for example into the AH [67]. It is not yet understood why CMV AU typically appears as a unilateral ocular manifestation without affecting the partner eye.

However, since molecular techniques have been available to detect these specific viral antigens in the AH antiviral treatment has been applied to reduce virus load and hence control the inflammation and elevated IOP. However, despite specific antiviral treatment recurrences cannot be completely prevented and have been associated with intraindividual stress [71], chronic inflammation [72,73] and immunosuppressive systemic corticosteroid therapy [74,75]. The frequency of relapses combined with elevated IOP may lead to secondary glaucoma in 8-26% of cases [25,60,76]. In a retrospective study by Takahashi and colleagues [77] secondary glaucoma was found in 18.3% of different uveitis cases. The majority of these uveitis cases suffered from AU and PSS specifically. Currently the underlying mechanisms of the increased IOP during an attack are still subject to investigation. However, viral trabeculitis and obstruction of trabecular meshwork (TM) by inflammatory debris have been recognized as vital causes [29]. Human TM cells may play a key role as the focus of inflammation in the pathogenesis of hypertensive AU related to CMV infection [78]. In a study by Choi *et al.* [63], human TM cells and their effect on CMV replication were analyzed, and the question raised whether or not CMV infection in TM cells alters the expression of Transforming Growth Factor (TGF)- $\beta$ 1. As a result, TM cells were found to be permissive to CMV proliferation and presented a CMV-induced disorganization, characterized by swelling and ballooning, as well as an increased number of stress fibers (Figure 4). According to Mendez-Samperio *et al.* [79] these stress fibers lead to cell rigidity and increased outflow resistance, followed by an elevated IOP. Furthermore Choi *et al.* [80] observed significantly elevated TGF- $\beta$ 1

levels in CMV-infected TM cells. TGF- $\beta$ 1 is a cytokine controlling proliferation and cellular differentiation and is responsible for an increased resistance of the outflow pathway in human TM cells.

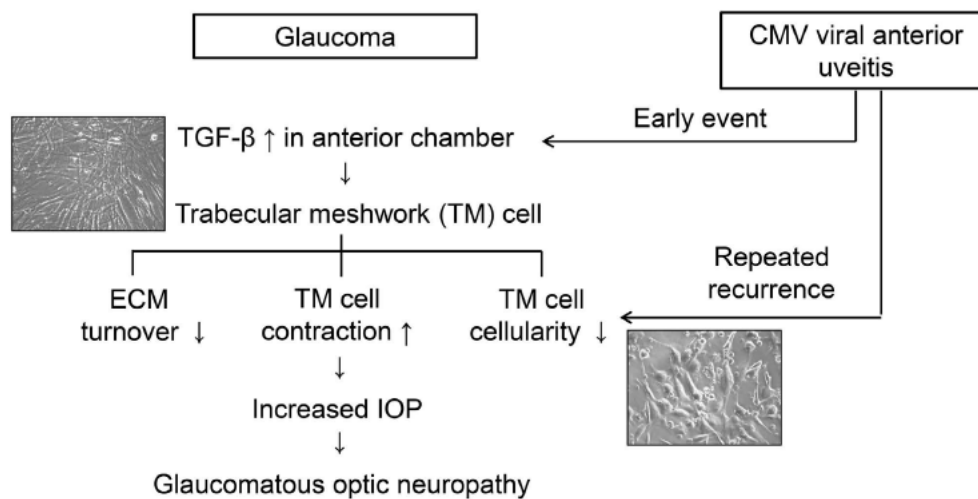


Figure 4: Elevated IOP and glaucomatous optic neuropathy caused by TGF- $\beta$ 1 in CMV AU. Immune mediator TGF- $\beta$ 1 stimulates TM cells to introduce extracellular matrix increases, triggers the contraction of TM cells and inhibits TM cell proliferation. The resulting increase of IOP induces an obstruction of the outflow pathway. Consequently, this leads to glaucomatous optic neuropathy [63].

Apart from TGF- $\beta$ 1, other authors have investigated additional immune mediators found in the AH of different uveitis entities, and their impact on viral intraocular inflammation and IOP [81–86]. In 2016, Ohira and colleagues [87] found that levels of Interleukin (IL)- 6, Monocyte chemoattractant protein-1 (MCP-1) and vascular endothelial cell growth factor (VEGF) in the AH of AU patients were higher than those in POAG patients. Just recently Pohlmann *et al.* [88] determined the composition of immune mediators in patients with CMV confirmed PSS and Rubella confirmed FUS. They found a significant increase of different immune mediators in both PSS and FUS patients. However, more importantly they found significantly higher activities of specific immune mediators such as IL-1RA, IL-5, IL-8, IL-10 and Chemokines (Eotaxin) in PSS patients compared to FUS patients. It was concluded, that higher levels of these cytokines in PSS patients imply a distinctive acute inflammation



triggered by CMV, while the relatively moderate rise of cytokine levels observed in FUS patients may account for the chronic rather than acute course of the disease. Similar findings of increased cytokine changes in CMV-positive PSS patients were reported by Lacomba *et al.* [85].

Consequently, CMV may appear as an activator of these proinflammatory cytokines and could lead to activation and exacerbation in PSS patients [82].

In conclusion, the increase of IOP is explained as a result of decreased outflow of AH caused by an obstruction of the outflow pathway, caused by CMV-induced immune mediators [89,90]. Essentially – if untreated – this may lead to secondary glaucoma and glaucomatous optic neuropathy [63]. Therefore, early therapy is essential in the clinical management of hypertensive AU, and in preventing morphological changes.

### **2.3.3 Molecular analysis – detecting viral pathogens**

The diagnosis of uveitis – particularly of infectious etiology – is not only based on clinical signs, but furthermore requires carefully utilizing patient history, laboratory testing, advanced imaging techniques and radiological examinations. Differentiating infectious agents – and particularly specifying a certain viral agent – inevitably requires specific analysis as the clinical symptoms are often very similar. The cultivation of viruses so as to reveal active infection takes long periods of time. There are two established approaches to prove the presence of a virus. On the one hand, this may be accomplished by detecting the viral DNA itself, utilizing the PCR technique. On the other, this may be accomplished by investigating for specific antibodies formed by the organism in reaction to the presence of the virus, by employing the ELISA technique [91–93]. Bloch-Michel *et al.* [20] proposed the involvement of CMV in the pathogenesis of PSS by reporting evidence of local production of CMV-specific antibodies in the AH.

### **2.3.3.1 Verifying diagnosis in CMV anterior uveitis by PCR**

PCR analysis is capable of detecting even small numbers of viral DNA copies by in vitro amplification. This method was already described in 1985 by Saiki *et al.* [94], and was confirmed as a standard method for proving CMV infections by Boeckh *et al.* [95]. They found a sensitivity of 80.1% and specificity of 93% for blood samples diagnosing systemic CMV infections. Furthermore, several studies have proven that PCR is also a valuable approach for the early detection of viral ocular infections [61,96]. Recently Miyazaki and colleagues [97] determined the efficacy of quantitative real-time PCR – particularly in CMV AU.

### **2.3.3.2 Verifying diagnosis in CMV anterior uveitis by ELISA targeting IgG**

Due to its distinctive anatomic and physiological features, the eye is one of only a few organs with an immunologic privilege. This is essential in order to protect the highly specialized intraocular tissues from inflammatory effects [98]. In case of an infection, the immune system responds by generating specific antibodies such as specific Immunoglobulin G (IgG) against proteins of the infectious agent [99]. In 1954 Goldmann und Witmer published an article on the intraocular synthesis of antibodies. According to this, the blood-aqueous fluid barrier effectively prevents an equalization of the IgG levels in the blood and those of the aqueous fluid [100]. Hence, the ratio of specific IgG in the AH and specific IgG in the blood allows us to distinguish whether specific IgG found in the aqueous fluid was synthesized locally in the eye, or systemically. A higher concentration of specific IgG in the eye indicates a local infection of the eye, while a higher concentration of specific IgG in the blood is characteristic of a systemic infection [101–103]. For the qualitative detection and quantitative determination of antigen-specific IgG-antibodies against viruses an ELISA is necessary. In serum and in AH antibody, units are measured after dilution and related to the corresponding absolute IgG value, by calculating the specific antibody index (AI) referring to the Goldmann and Witmer coefficient (GWC) [81,104], and as described in literature [105].

specific IgG in the eye	:	specific IgG in the serum
AI = _____		_____
total IgG in the eye		total IgG in the serum

An AI index  $\geq 3$  suggests local intraocular production of specific antibodies [106,107].

### 2.3.3.3 Comparing limitations of PCR vs. ELISA

In general, both molecular techniques are sensitive and specific. They provide instant verification of the pathogenic microorganism responsible for the disease thus allowing for specific medical therapy. However, considering the fact that the approach of detecting a specific viral pathogen by employing ELISA targeting specific IgG requires the patient's ability to synthesize IgG, the question is raised of how this may affect results in immunocompromised patients with posterior involvement, where production of antibodies is unpredictable. Not surprisingly, Arnaud *et al.* [93] found that in immunocompromised patients with posterior involvement PCR analysis of the AH with viral uveitis yields more reliable results than the ELISA-based AI. Other authors published similar findings [107,108]. While the PCR technique offers clear advantages in immunocompromised patients, it does also have its limitations: in the course of the disease, the virus load is eventually reduced to below detectability for PCR analysis, while IgG levels are still maintained. Hence, particularly in later stages of the disease, the PCR might be already negative, while AI values are still positive. Other reasons for the lack of sensitivity of PCR analysis could be the small volume of AH samples, intraindividual microorganism polymorphism, or the presence of inhibitory compounds [109]. De Groot-Mijnes *et al.* [91] showed that by only employing PCR as a diagnostic approach, a correct diagnosis of the infectious etiology would have been missed in nearly half of uveitis cases. On the other hand, when relying only on the ELISA-based approach by calculating the AI, just 9% would have been missed.

In conclusion, to confirm the diagnosis of CMV AU in cases with a very high clinical suspicion, combining PCR and ELISA is recommended [110–114]. Other studies showed that both are complementary for the diagnosis of infectious uveitis [39,91,115,116]. Unfortunately, even these highly-sensitive tests may yield false-negative results and thus may need to be repeated [117].

### **2.3.4 Morphological changes**

#### **2.3.4.1 The impact of CMV anterior uveitis on corneal endothelial cells**

The cornea consists of several cell layers. The integrity of the innermost layer – the endothelium – is responsible for the clarity of the cornea. Damages lead to blurred vision and halo effects. In severe cases keratoplastic surgery may be required [118]. The cornea in general, and the endothelium in particular, are susceptible to diverse pathogens including viruses. In 1982, Khodadoust and Attarzadeh [119] first described corneal endotheliitis as a chronic inflammatory disease and suggested an autoimmune process. Since herpes viruses – particularly CMV – were detected as a causative pathogen endotheliitis was labelled as an infectious disease. However there remain endotheliitis cases with unknown etiology referred to as idiopathic.

Endothelial microscopy – a noninvasive technique – was developed in order to examine the posterior endothelial surface [120,121]. It allows us to visualize anatomical details of the CEC and to differentiate morphological alterations.

Early studies by Brooks *et al.* [122–124] compared endothelial alterations caused by various corneal diseases such as keratopathy, stromal keratitis, AU etc. In cases of glaucomatocyclitic crisis they described numerous small dark areas in the mosaic of CEC, as well as a multitude of deposits on the corneal endothelium representing inflammatory debris. They also noted that after an acute episode, there was a complete remission of these alterations in some cases [123]. Later, as CMV became known to replicate inside the nuclei of different cells like human fibroblasts, vascular endothelial cells, macrophages as well as TM cells [125–130], the CECs were subject to further investigations in relation to CMV. Koboyashi *et al.* [131] and

Shiraishi *et al.* [132] reported intranuclear owl's eye inclusions in cells located within the CEC layer. These were detected by confocal microscopy and characterized by a highly reflective nucleus surrounded by halo signs of low reflection. These cells are pathognomonic for CMV and have been previously observed in other organs like lungs or kidneys [133]. Shiraishi *et al.* [132] concluded that KPs resemble the site of infection, as they exhibit the appearance of the viral cytopathic effects seen in cell cultures after viral replication. Yokogawa and colleagues [134] confirmed these results and presented a correlation between intranuclear owl's eye inclusion bodies and coin-shaped KPs of the corneal endothelium. Furthermore, Hosogai *et al.* [109] were able to prove that CMV is actually capable of replicating within human CEC. As a result, replicated viruses are released into the AH thus aggravating inflammation. Therefore, CMV was identified as an etiological factor in corneal endothelial changes due to hypertensive AU and endotheliitis [135–142].

Recent studies have demonstrated that CMV confirmed AU is associated with severe CEC loss [25,141,143–145]. Furthermore, the viral DNA load significantly correlates with coin-shaped lesions, recurrence rates, IOP and CEC loss [41,144,146].

The exact pathogenesis is not understood yet and remains undetermined. Early studies by Suzuki [147,148] suggested an autoimmune mechanism triggered by CMV, which they refer to as anterior chamber-associated immune deviation (ACAID). Consequently, they assume that latent CMV residing in the anterior chamber become intermittently reactivated, thus inducing ACAID, resulting in release of insufficient antibodies against CMV antigen [149].

Additionally, in 2017 Miyazaki *et al.* [150] examined how CECs prime the antiviral immunity after CMV infection. They demonstrated that CMV-infected CEC induce antiviral immune responses – particularly by activating CD8+ cytotoxic T cells. These represent the acquired arm of the immune system in response to CMV infection [151]. Miyazaki *et al.* [150] also showed that the innate immune response mediated by interferon signaling is activated as well. Hence, they concluded that CECs have immune competence in responding to CMV infection.

An excessive inflammatory response, however, may lead to CEC dysfunction and CEC loss.

#### **2.3.4.2 Glaucomatous optic neuropathy in CMV anterior uveitis – quantified by peripapillary OCT scan**

Recurrent episodes of hypertensive AU may increase the risk of developing secondary glaucoma, characterized by visual field defects [52,60] and anatomical and physiological changes including progressive optic nerve cupping with corresponding RNFL loss [64]. Thus, continuous monitoring of changes to the optic disc is considered a crucial part of detecting glaucoma damage. In 1991 Huan *et al.* [152] evaluated OCT as an essential diagnostic tool to assess and quantify optic neuropathy. Numerous other studies have since validated the general importance of OCT [153,154,163–167,155–162] as well as the specific value for early detection and follow-up of different glaucomatous optic neuropathies [168–175]. So far, only a few studies exist on the effects of AU with hypertensive attacks on optic nerve head behavior in particular [60,64,65,77,176–179].

#### **2.3.5 Antiviral treatment options and risk for recurrences of CMV anterior uveitis**

Ever since molecular techniques have been able to confirm the presence of viruses as the etiology of AU, antiviral agents such as oral valganciclovir and intravenous, intravitreal or topical ganciclovir have been an integral part of the treatment strategy supplemented by topical anti-inflammatory corticosteroids [23,25,27,29,146,180–182].

Ganciclovir acts as a potent virustatic agent against the herpes virus by suppressing virus replication [181,183–186]. Several studies have shown that antiviral treatment with ganciclovir is effective in the treatment of herpetic keratitis and conjunctivitis [187,188]. Local and systemic applications of ganciclovir in the form of intravitreal injections and implants as well as oral or intravenous administration have also been evaluated [181,189–191]. Intravenous ganciclovir as an antiviral agent for CMV has proved to significantly reduce the CMV virus load in TM cells [63,192,193].

While ganciclovir has poor bioavailability when orally administered [194], valganciclovir – a prodrug of ganciclovir – has better bioavailability and rapidly converts to ganciclovir. CMV is the main indication for the application of valganciclovir. Valganciclovir is available for topical and oral application. However, oral antiviral treatment remains the standard treatment, as it is assumed that topical administration provides insufficient drug levels in the AH [67,135,188,195–201]. Thus it is also the first choice for treatment of CMV AU in Japan [146]. Other studies on antiviral treatment have also confirmed the efficacy of oral valganciclovir in CMV AU [181,182,185]. The length of antiviral treatment with valganciclovir is still subject to debate. Several studies have shown that long-term therapy is beneficial to lower recurrence [62,182,202].

### **2.3.6 Surgical treatment**

In cases where conservative antiglaucoma treatments have failed, and glaucomatous optic disc damage is evident, several surgical options are available. Zong *et al.* [203] reported the trabeculectomy as an effective method to control IOP in PSS cases. However, the efficacy of filtering surgeries is still subject to debate compared to results of glaucoma surgery in POAG patients [204–207]. A causal relation is that the inflammatory reaction may accelerate wound scarring and thus lead to failure of the glaucoma surgery. In addition, the unsuccessful filtering surgery may itself result in inflamed conjunctiva significantly boosting local lymphocytes, macrophages and the release of proinflammatory cytokines [208]. The minimally invasive ab interno trabeculotomy (trabectome) offers a suitable surgical treatment alternative to stabilize IOP [209–211]. Pahlitzsch *et al.* [212] reviewed the outcome of trabectome surgery in hypertensive glaucomacyclitic crisis and found a significant reduction in IOP. Later studies confirmed the decrease of IOP after trabectome surgery in PSS cases [209–211]. Nevertheless, IOP decompensation still remains a risk. The first choice to lower IOP is still medical treatment. But in severe cases, advanced surgical treatments are required.

### **3. PURPOSE**

An important aspect in CMV AU is the inflammatory reaction in the anterior segment of the eye, which causes KPs, corneal edema and CEC damage. Subsequently, the CECs may deteriorate [24,25,123,135,143–145,149,213]. Our research is therefore aimed at the question of how the CEC density of the affected eye relates to the CEC density of the fellow eye.

In patients with unilateral recurrent hypertensive AU caused by CMV, the inflammatory reaction and elevated IOP during an attack lead to alterations of the TM, with the risk of consecutive development of a secondary glaucoma which itself causes damage to the optic nerve [25,60,63,76–78,89,90]. In order to detect and document even minimal structural damage to the optic nerve at an early stage, high resolution imaging techniques are obligatory. OCT scans provide quantifiable data on the status of the optic nerve head by measuring the peripapillary RNFL [153,154,173–175,155–157,168–172] – both in comparison to the fellow eye or in follow-up of the affected eye. A major focus of interest is on the issue of whether there are morphologic changes to the optic disc head in patients with a unilateral disease course.

This allows for better monitoring of the clinical course. Subsequently, this may have an impact on evaluation of the therapeutic strategies applied. Our observations of the clinical course have raised the question of if, and how, the clinical outcome in terms of recurrences is affected by oral antiviral therapy with valganciclovir.



## 4. PATIENTS AND METHODS

### 4.1 Inclusion of patients

This prospective study was performed in accordance with the standards of the Declaration of Helsinki and approved by the ethics committee of Charité University of Medicine Berlin. Informed written consent was obtained from each participating patient.

From February 2007 to April 2018 a total of 52 patients (52 eyes) with confirmed CMV AU were enrolled at the Department of Ophthalmology Charité Berlin.

#### **Inclusion criteria – clinical findings:**

All patients presenting with at least one acute attack of unilateral AU and elevated IOP ( $\geq 21$ mmHg) – suspected as PSS – were included (Figure 5). The fellow eye served as control. The clinical diagnosis and grading of AU were adapted from the anatomical classification of the SUN scheme by the IUSG [1]. Based on this classification we included patients with at least four of the following clinical findings:

- low-grade AU
- fine or focal KPs
- cells 1+
- absence of posterior synechiae and vitreous inflammation
- flare

While the inflammation was active, an anterior chamber paracentesis was performed on the affected eye of all patients to confirm CMV AU. Only patients with an AI  $\geq$  3 for CMV antibodies were included. In turn, patients with positive titers for HSV, VZV, EBV, Rubella and Toxoplasma gondii were excluded, as well as patients with immunocompromising diseases such as Human Immunodeficiency Virus, Syphilis, Lyme borreliosis, Tuberculosis and Sarcoidosis. Two patients who had additional positive findings for HLA B27 remained included because of a lack of systemic disorders.

All patients underwent a complete ophthalmic examination including visual acuity, slit-lamp microscopy and ophthalmoscopy. For measurement of IOP, a Goldmann Applanation Tonometer was used.

Data including patient demographics, ocular and systemic history, clinical course and medication were systematically collected.

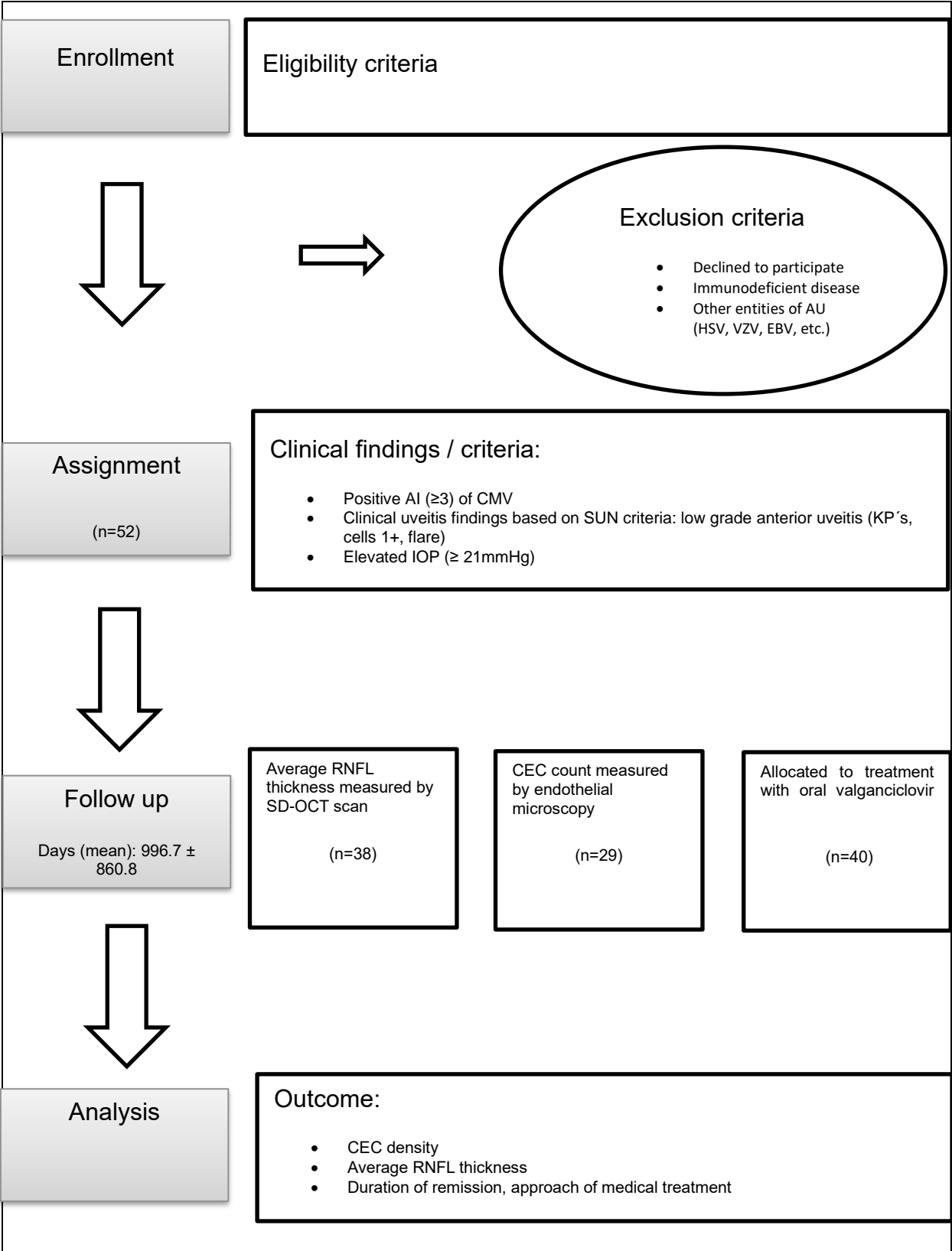


Figure 5: Flow chart of participating patients.

## 4.2 Laboratory analysis

In order to further investigate the etiology, an anterior chamber paracentesis was conducted on the affected eye of 52 patients. The anterior chamber tap was performed with a 31-gauge sterile needle in local anesthesia under aseptic conditions. Under direct microscopic view, a sample of approximately 100 µl of AH, and a blood sample taken simultaneously, were collected for laboratory analysis and examined by an ELISA (Enzygnost®, Dade Behring Marburg, Germany) for the qualitative detection and quantitative determination of antigen-specific IgG-antibodies against CMV, HSV, VZV, EBV, Rubella and Toxoplasma gondii. The assay was performed according to the manufacturer's recommendations. Serum and AH antibody units were measured after standard dilution (1 mg/dl), and related to the corresponding absolute IgG value by calculating the specific AI referring to Goldmann and Witmer [81,104]. We calculated the AI as a ratio according to the following formula:

$$\text{AI} = \frac{\text{specific IgG in the eye}}{\text{total IgG in the eye}} : \frac{\text{specific IgG in the serum}}{\text{total IgG in the serum}}$$

An AI index  $\geq 3$  suggests local intraocular production of specific antibodies [106,107].

In the current study we included patients with a positive AI ( $\geq 3$ ) for CMV targeted by ELISA.

### 4.3 Endothelial microscopy

The CEC density in cells/mm<sup>2</sup> was measured with an endothelial microscope (NIDEK, CEM-530 Specular Microscope). The CEM-530 records paracentral images with an auto tracking mode. It automatically sorts images based on quality and ability to be analyzed [214].

### 4.4 Peripapillary OCT scan

An SD-OCT (Heidelberg Engineering, Spectralis® Tracking Laser Tomography) using the confocal scanning laser ophthalmoscope was utilized prospectively to measure the entire papilla and the peripapillary RNFL thickness. It was determined at 256 points around a set diameter (3.4mm) circle using the Fast RNFL program. A circular chart (Figure 6) visualized the classification results for the global average (G) and the six sectors - Temporal (T), Temporal-Superior (TS), Temporal-Inferior (TI), Nasal (N), Nasal-Superior (NS) and Nasal-Inferior (NI). Based on a comparison with a normative reference database, the results are color indicated as normal (green), borderline (yellow) or beyond normal limits (red). The global average sector of the RNFL thickness, provided using the Heidelberg Engineering software (Version 6.3.2.), was used for data evaluation.

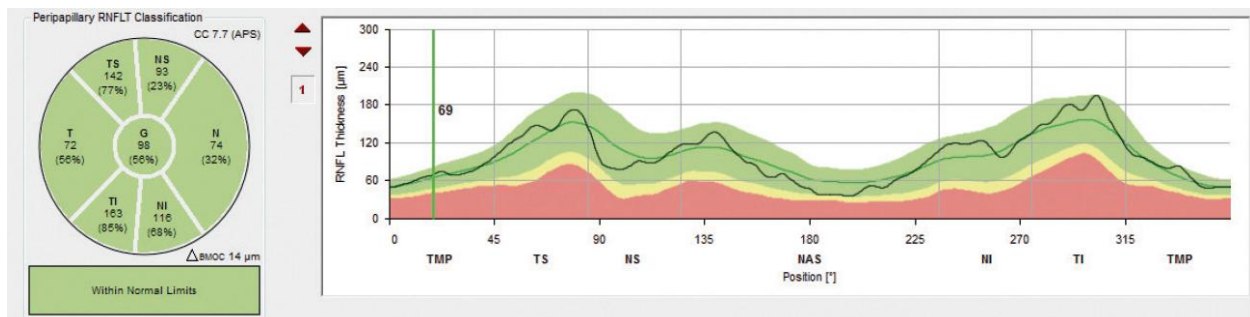


Figure 6: OCT circular chart visualizing the RNFL (in µm) classification in sectors: Global (G), Temporal (T), Temporal-Superior (TS), Temporal-Inferior (TI), Nasal (N), Nasal-Superior (NS) and Nasal-Inferior (NI) based on a comparison with a normative reference database [19].

Eyes with a myopic refractive error exceeding -8 diopters and eyes with a swelling of the optic nerve were excluded because of their altered optic disc morphology.

#### **4.5 Treatment of CMV anterior uveitis**

Upon completion of the diagnostic tests specific anti-CMV therapy was started following a standard induction course for at least 2 weeks of oral valganciclovir 900 mg twice daily. After this induction each patient received a maintenance scheme of valganciclovir 450 mg twice daily for a time period ranging from approximately 3 months to more than 12 months. We split patients into subgroups based on length of oral valganciclovir therapy (Table 7): 3 months as short-term therapy regimen, 4 to 12 months as intermediate-term therapy regimen and > 12 months as long-term therapy regimen. We also examined the length of remission after confirmed diagnosis. Accordingly, we defined 3 time frames for remission intervals after the stopping of valganciclovir therapy: 0-6 months, 7-24 months and more than 24 months. Response to treatment was characterized as absence of inflammation and normalization of IOP while antiglaucoma medication is applied [181].

Glaucoma treatment was initiated step-wise depending on the level of elevated IOP during an attack. The therapy was based on topical antiglaucoma medication (beta-blocker, alpha-2-agonists, acetazolamide and prostaglandin), in some cases intensified by systemic acetazolamide. Glaucoma surgery was needed for only a few patients, when glaucomatous optic disc damage was evident and conservative antiglaucoma agents were ineffective.

## 4.6 Statistical analysis

The collected data were analyzed using SPSS (Software IBM Statistics, Version 15.0). A p-value of  $<0.05$  was considered statistically significant.

For this purpose, the empirical data were processed by descriptive statistics and presented in the form of tables and charts including the relevant statistic parameters such as mean, median and range.

Furthermore, a statistical model was established to evaluate morphological damage to the optic nerve head and the CEC layer. Accordingly, a multivariate analysis of variance (MANOVA) was applied. This is an extension of the univariate analysis of variance (ANOVA). While an ANOVA examines statistical differences on one continuous dependent variable by an independent grouping variable, the MANOVA extends this analysis by taking into account multiple continuous dependent variables and bundles them together into a weighted linear combination or composite variable. Hence the MANOVA essentially compares whether or not the independent grouping variable simultaneously explains a statistically significant amount of variance in the dependent variable.

In order to reveal the relevance of statistically significant results the effect size eta squared ( $\eta^2$ ) was calculated. The effect size describes the ratio of variance explained in the dependent variables by the predictor as the independent variable. According to Cohen [215] the following guidelines help in interpreting Eta-squared:

<b>Effect size</b>	<b><math>\eta^2</math></b>	<b>Explained variance</b>
small	.01	1%
medium	.06	6%
large	.14	14%

Furthermore, a covariance analysis was performed to evaluate the impact of a covariate (age, gender and IOP) on the dependent variable (SD-OCT and CEC results).

Finally, a Chi-Squared Test was employed to estimate the correlation between length of oral antiviral therapy and length of remission.



## 5. RESULTS

### 5.1. Baseline demographics

We identified a total of 52 patients (52 affected eyes) with unilateral hypertensive AU (Table 3) fulfilling the inclusion criteria.

All patients underwent an AH analysis of the affected eye and were tested positive for CMV antibodies determined by calculating the specific AI. No patient had bilateral eye involvement.

There were 18 (35%) female patients and 34 (65%) male patients.

The mean age when CMV AU was first diagnosed was  $42.0 \pm 16.9$  years old (median age: 40, range: 19-78) (Figure 7).

At the time of initial examination 41 patients (79%) suffered from blurred vision, 32 (62%) complained of unilateral ocular pain, 27 (52%) presented with conjunctival redness, and 13 (25%) had halo signs.

The mean of the highest recorded IOP during an episode of CMV AU (with or without IOP-lowering agents) was  $45.4 \pm 10.7$  mmHg.

The affected eyes were treated with a number of IOP-lowering eye drops (median of 3, range 0-4). Only 2 (4%) eyes received no IOP-lowering therapy. Initially 43 (83%) patients were orally treated with acetazolamide for IOP control (Table 4).

<b>CMV anterior uveitis</b>	
<b>Variables</b>	<b>N=52 (%)</b>
Affected eye	
Right	34 (65%)
Left	18 (35%)
Gender	
Female	18 (35%)
Male	34 (65%)
Age in years	
Mean $\pm$ SD	42.0 $\pm$ 16.9
Median (range)	40 (19-78)
Signs and symptoms	
Blurred vision	41 (79%)
Ocular pain	32 (62%)
Conjunctival redness	27 (52%)
Halo signs	13 (25%)
Highest IOP in mmHg	
Mean $\pm$ SD	45.4 $\pm$ 10.7
Median (range)	46.5 (21-74)

Table 3: Baseline characteristics, clinical features of eyes with CMV AU.

	<b><i>CMV anterior uveitis</i></b> <b>N=52</b>
<b>No IOP-reducing eye drops</b>	2 (3%)
<b>Number of IOP-reducing eye drops</b>	
Median (range)	3 (0-4)
Mean (SD)	2.8 ( $\pm$ 0.9)
IOP-reducing eye drops (1 agent)	2 (4%)
IOP-reducing eye drops (2 agents)	11 (21%)
IOP-reducing eye drops (3 agents)	25 (48%)
IOP-reducing eye drops (4 agents)	12 (23%)
<b>Oral acetazolamide</b>	43 (83%)

Table 4: IOP-reducing therapy during follow-up.

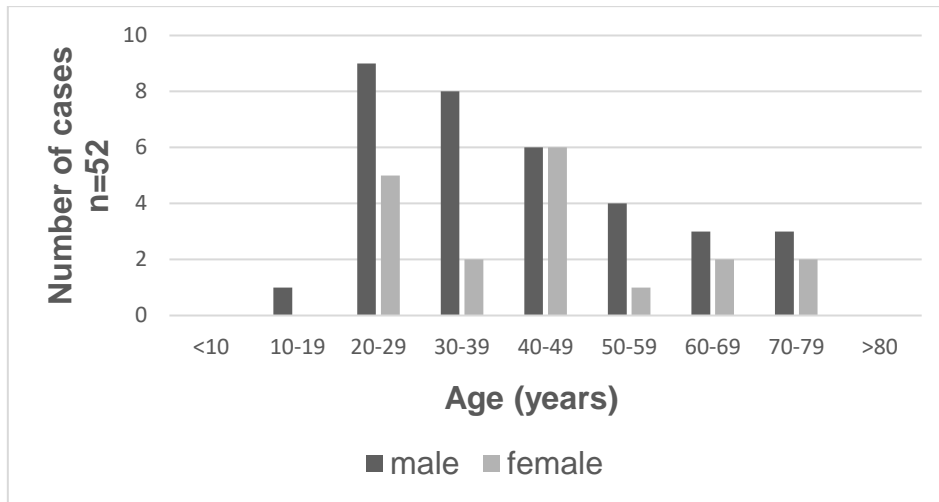


Figure 7: Age and gender of patients with CMV AU. The mean patient age was  $42.0 \pm 16.9$  years old, 18 (35%) cases were female and 34 (65%) were male.

The mean duration (Table 5) from onset of first symptoms to laboratory proof of CMV AU was  $1069.5 \pm 1347.2$  days. The follow-up period varied from 60 to 3850 days, while the mean follow-up period was  $996.7 \pm 860.8$  days. In 5 (10%) cases clinical findings for AU were presented for the first time, while in 47 (90%) cases previous recurrent episodes were recorded (Table 6).

<b><i>Disease duration (days)</i></b>	
Disease duration from onset to laboratory proof of diagnosis, mean days (median; range)	1069.5 ±1347.2 (461; 2 - 5627)
Duration of follow-up, mean days (median; range)	996.7 ± 860.8 (796; 60 - 3850)

Table 5: Disease duration.

<b><i>Number of patients with recurrences</i></b>	
No previous episode	5 (10%)
Recurrent episodes	47 (90%)

Table 6: Number of patients with recurrences.

## 5.1 Changes in the anterior segment and value of CEC microscopy

We applied endothelial microscopy in 29 (56%) of 52 patients by imaging the affected and fellow eye simultaneously. The fellow eye served as control. None of the controls had had previous ocular surgery. The mean CEC density at baseline of the affected eyes was  $2229.07 \pm 384.80$  cells/mm<sup>2</sup>, while CEC density of the fellow eye was  $2534.7 \pm 342.0$  cells/mm<sup>2</sup>. Specular microscopic examinations revealed significantly lower CEC density (MANOVA, within subjects,  $F=20.56$ ;  $DF(1;28)$ ;  $p<0.01$ ,  $\eta^2 = 0.42$ ) of the affected eye compared to the fellow eye. Notably, the mean CEC density of the affected eyes was 305.6 cells/mm<sup>2</sup> lower than that of the non-affected eyes (Figure 8).

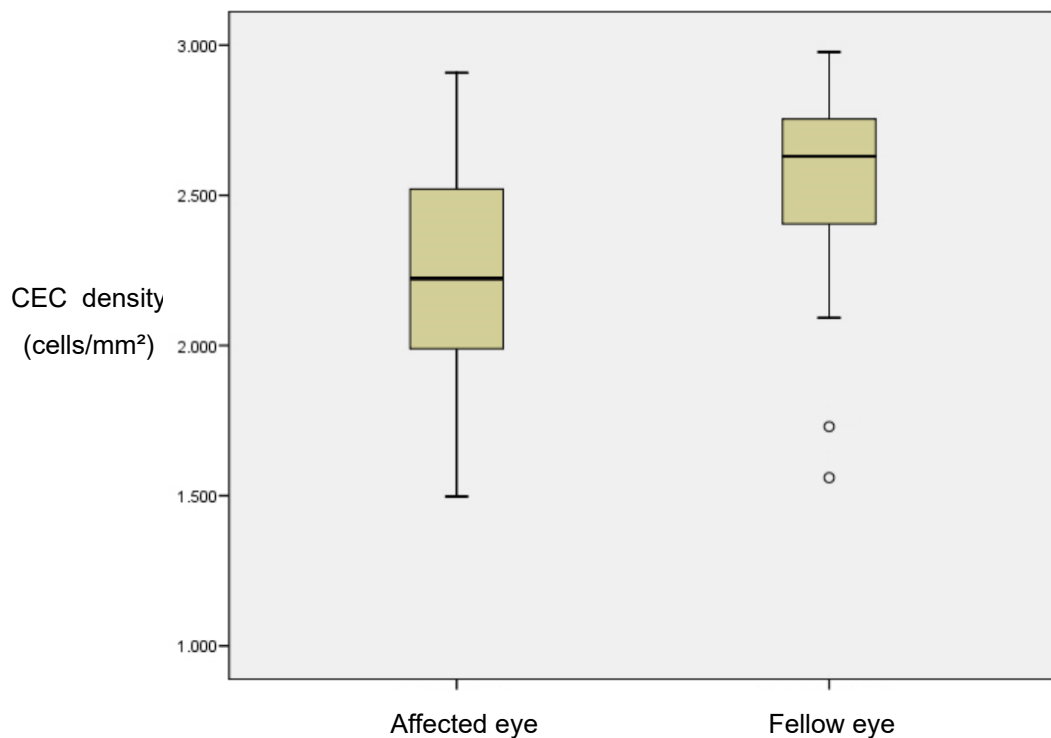


Figure 8: Lower CEC density for CMV AU of the affected eye. The mean CEC density of the affected eye was compared to the fellow eye by MANOVA,  $*p<0.01$ .

There was no effect on the CEC density - whether by gender, age, or elevated IOP (Table 7).

<b>Variable</b>	<b>df</b>	<b>F</b>	<b>p-Value</b>	<b><math>\eta^2</math></b>
Age (in years)	1;27	0.010	0.923	0.0003
Gender	1;27	0.016	0.900	0.001
Mean of the highest IOP (in mmHg)	1;27	0.223	0.641	0.008

Table 7: Effect of clinical variables on CEC density by MANOVA and covariance analysis.

In 8 (28%) of 29 cases we were able to follow-up CEC microscopy in a mean of  $31.8 \pm 37.4$  months. There was no significant effect of further deterioration of the affected eye (Figure 9). However, we noted a tendency that during the course of the disease the CEC density declines further.

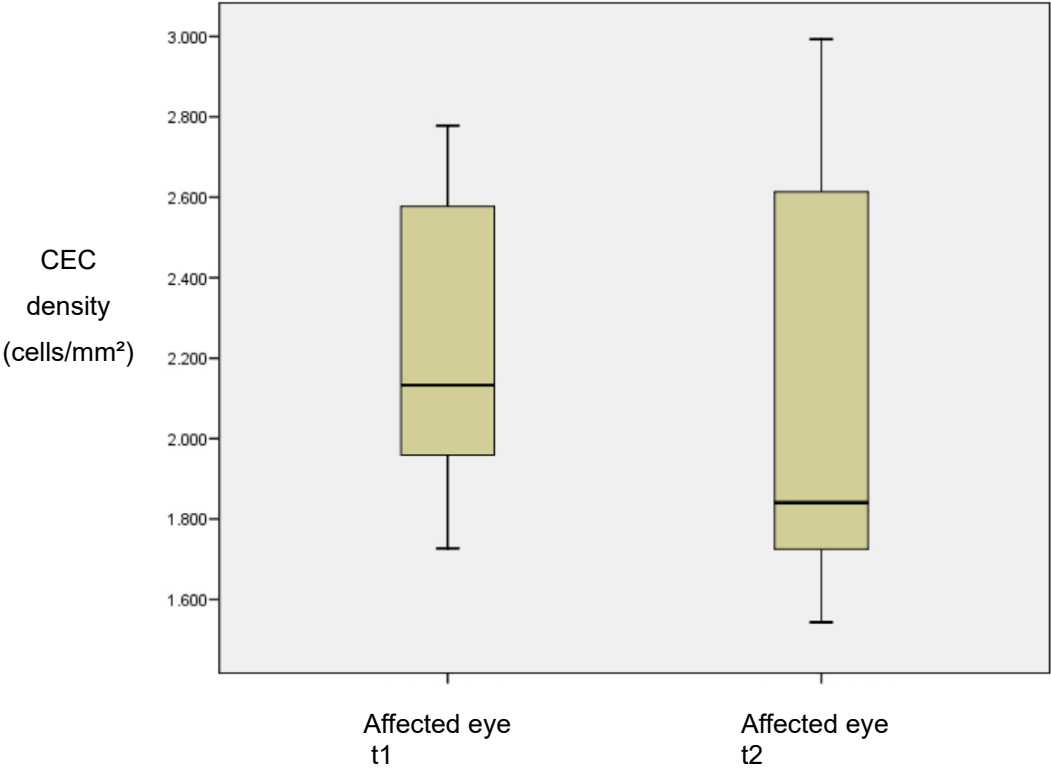


Figure 9: CEC density of the affected eye during a mean follow-up of  $31.8 \pm 37.4$  months. The mean CEC density was compared at timepoint t1 (initial CEC density) vs. t2 (CEC density at last check-up) by MANOVA, \* $p > 0.05$ .



## 5.2 Value of peripapillary RNFL thickness by SD-OCT scan

We employed a peripapillary RNFL SD-OCT scan provided by Heidelberg Engineering in 38 (72%) of 52 patients by imaging the affected and fellow eye simultaneously. The global average sector of peripapillary RNFL thickness in  $\mu\text{m}$  was used for the data evaluation. The mean peripapillary RNFL thickness of the affected eye was  $86.3 \pm 29.3 \mu\text{m}$  while the mean peripapillary RNFL thickness of the non-affected eye was  $99.3 \pm 12.5 \mu\text{m}$ .

To evaluate the validity of SD-OCT scan diagnostics for distinguishing morphologic changes to the optic disc head in patients with a unilateral course of disease, we compared global RNFL of the affected vs. the non-affected eyes serving as control (Figures: 10,11).

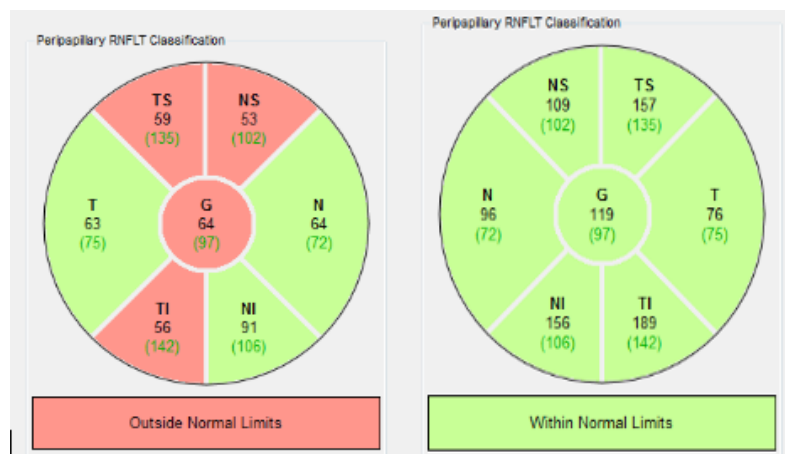


Figure 10: Representative example: Comparison of SD-OCT findings of a 46-year-old patient with an IOP of 42 mmHg at initial presentation. Peripapillary RNFL (in  $\mu\text{m}$ ) of the affected eye (left image) vs. the fellow eye (right image) showing significantly lower global (G) RNFL of the affected eye.

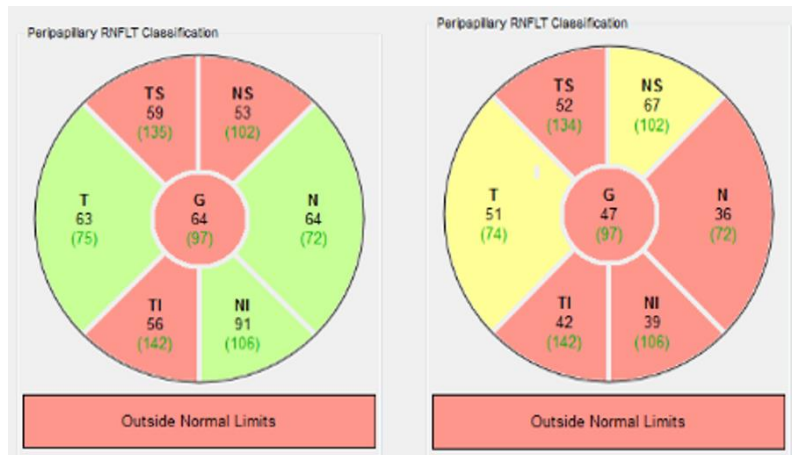


Figure 11: Representative example: Comparison of SD-OCT findings of the affected eye of the same patient at initial presentation (left image) vs. follow-up after 31 months (right image). Peripapillary RNFL (in  $\mu\text{m}$ ) showing significantly lower global (G) RNFL of the affected eye in the course of the disease as a sign of progressing damage.

We found a significantly lower RNFL thickness (MANOVA, within subjects,  $F=9.11$ ;  $DF(1;38)$ ;  $p<0.05$ ;  $\eta^2=0.193$ ) of the affected eye. The mean RNFL of the affected eye was reduced by a mean of  $12.6 \pm 2.7 \mu\text{m}$  (Figure 12).

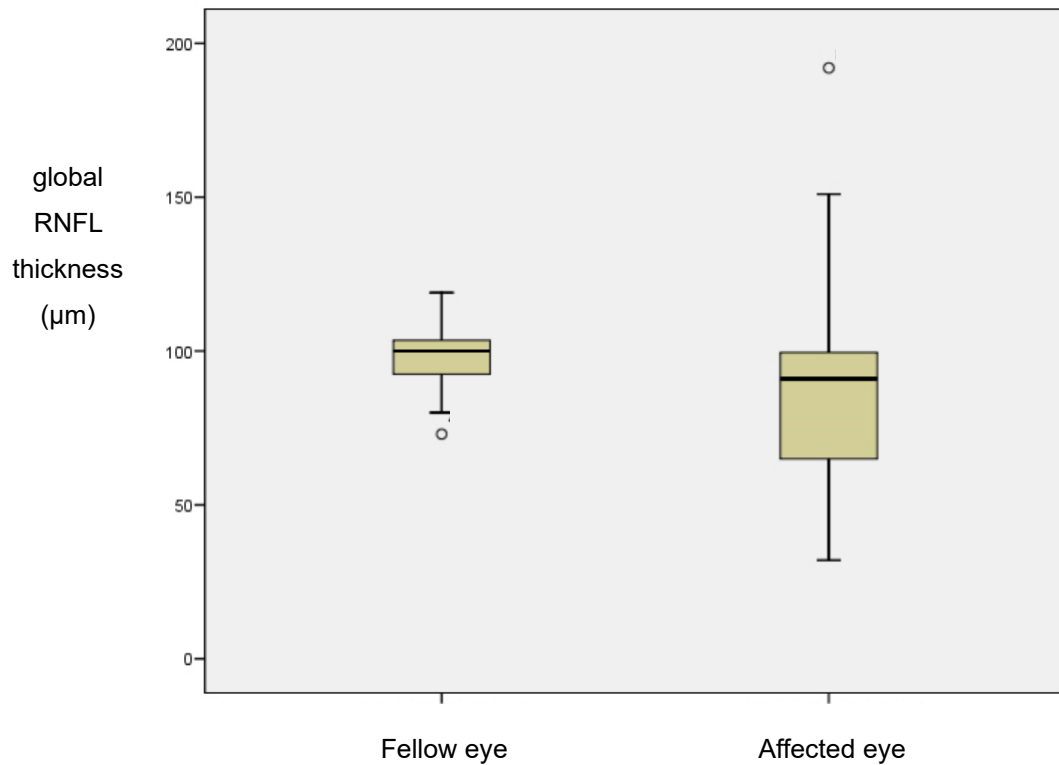


Figure 12: Average RNFL thickness in  $\mu\text{m}$  measured by SD-OCT scan. Lower RNFL thickness for CMV AU of the affected eye. Mean RNFL thickness of the affected eye was compared to the fellow eye by MANOVA,  $*p<0.01$ .

There was no effect on the RNFL thickness, whether by gender, or by elevated IOP. As expected, we recorded a reduction of RNFL with age (MANOVA; within Subjects;  $F= 6.80$ ;  $p<0.05$ ;  $\eta^2=0.155$ ) (Table 8).

Variable	df	F	p-Value	$\eta^2$
Age (in years)	1;38	6.797	<b>&lt;0.05*</b>	0.155
Gender	1;27	0.016	0.900	0.001
Mean of the highest IOP (mmHg)	1;36	0.216	0.645	0.006

**\*significant**

Table 8: Effect of clinical variables on RNFL thickness by MANOVA and covariance analysis.

Subsequently, we investigated differences in the SD-OCT results of the affected eye during the course of the disease, based on a mean follow-up of  $24.6 \pm 13.2$  months of 17 patients (Figure 12). Although we did find a statistically significant decrease of the peripapillary RNFL thickness by  $3\mu\text{m}$  on average (MANOVA; within subjects;  $F=6.13$ ;  $DF(1;16)$ ;  $p<0.05$ ;  $\eta^2=0.28$ ), these results should be interpreted cautiously, due to the considerably reduced number of cases (Figure 13).

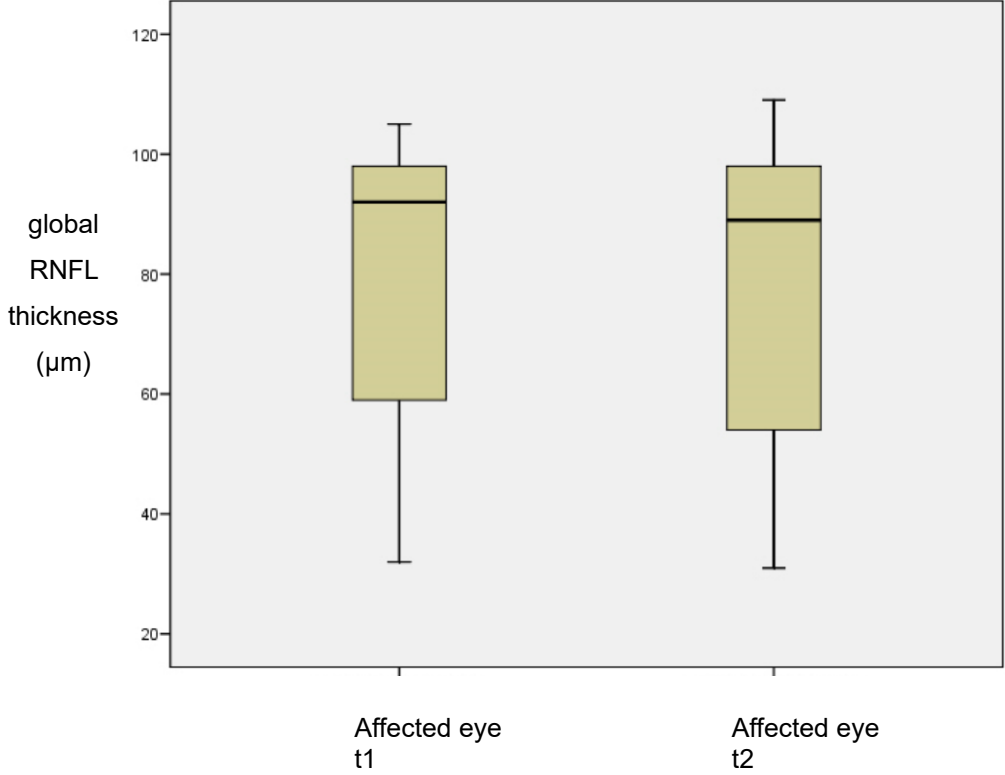


Figure 13: Follow-up after  $24.6 \pm 13.2$  months of average RNFL thickness in  $\mu\text{m}$  measured by SD-OCT. The mean global RNFLs were compared at timepoint t1 (initial SD-OCT examination) vs. t2 (SD-OCT at last check-up) by MANOVA,  $*p<0.05$ .

**5.3 How does antiviral therapy affect clinical outcome?**

Oral valganciclovir as antiviral therapy was administered to 40 (77%) of 52 patients. Oral antiviral therapy was refused by a total of 12 (23%) patients. The patients who agreed to follow a therapy regimen obtained a loading dose of oral valganciclovir 900 mg twice daily for at least 2 weeks, maintained by a scheme of oral valganciclovir 450mg twice daily for at least 3 months. Further administration was based on clinical course, tolerability and patient adherence. We split patients into subgroups based on length of oral antiviral therapy received (Table 9). Short-term oral treatment with antiviral therapy for approximately 3 months was applied to 6 (15%) patients, 20 (50%) patients received oral treatment for up to 12 months, and 14 (35%) patients had oral treatment for a long-term period lasting longer than 12 months.

	<b>Duration of valganciclovir medication</b>		
	<b>in months</b>		
	<b>0-3</b>	<b>4-12</b>	<b>&gt;12</b>
	<b>short-term</b>	<b>intermediate-term</b>	<b>long-term</b>
<b>Number of patients with oral therapy</b>  <i>n=40 (%)</i>	6 (15%)	20 (50%)	14 (35%)

Table 9: Duration of oral antiviral treatment.

We reported recurrence episodes in relation to the oral treatment regimen (Table 10). In 12 (30%) cases recurrences were reported under ongoing oral treatment. In 14 (35%) cases recurrences with highly elevated IOP and anterior segment inflammation were seen after stopping oral treatment during follow-up.

<b>Recurrent CMV anterior uveitis</b>	
<b>Recurrence in relation to treatment (n=40)</b>	<b>Patients</b>
Under oral treatment	12 (30%)
After oral treatment	14 (35%)

Table 10: Recurrence episodes in relation to oral treatment.

Recurrences during and after therapy were recorded to document the length of remission period in months. Accordingly, we defined 3 time frames of recurrence free periods: 0-6 months, 7-24 months and more than 24 months. All patients (n=52) were referred to one of these three subgroups – independent from oral antiviral therapy. Remission intervals of up to 6 months were recorded in 17 (33%) cases, longer remission intervals of 7 to 24 months were observed in 15 (29%) cases, and 20 (38%) patients had no recurrence for more than 24 months (Table 11).

	Time interval until recurrence (remission interval) in months		
	0-6	7-24	>24
<i>n</i> =52 (%)	17 (33%)	15 (29%)	20 (38%)

Table 11: Time interval until recurrence independent from oral valganciclovir treatment.



These remarkable differences in length of remission led to the hypothesis that different therapeutic regimen resulted in different outcomes. In the next step, we were able to prove a significant correlation between length of oral antiviral therapy and length of remission period afterwards (Pearson Chi-Squared Test 14.9; DF (1;4);  $p < 0.01$ ). Consequently, 5 patients with short-term therapy were relapse free for only a short period of less than 6 months, and none of the patients with short-term therapy remained recurrence free for more than 24 months. Within the subgroup of patients with intermediate therapy we found 11 patients with an intermediate recurrence free interval, while 5 patients remained relapse free for more than 24 months. Within the subgroup of patients with long-term therapy, the majority of patients remained without recurrences for more than 24 months (Table 12).

Length of valganciclovir therapy in months		Remission interval in months			Total
		0-6	7-24	>24	
0-3 (short-term)	<b>Count</b>	<b>5</b>	<b>1</b>	<b>0</b>	<b>6</b>
4-12 (intermediate)	<b>Count</b>	<b>4</b>	<b>11</b>	<b>5</b>	<b>20</b>
>12 (long-term)	<b>Count</b>	<b>3</b>	<b>3</b>	<b>8</b>	<b>14</b>
Total		<b>12</b>	<b>15</b>	<b>13</b>	<b>40</b>

Table 12: Relation of length of valganciclovir therapy and remission interval in months by Pearson Chi-Squared Test 14.9;  $p < 0.01$ .

In addition to oral valganciclovir, 7 (18%) patients received topical antiviral eyedrops (aciclovir or ganciclovir), while 2 (4%) patients received only topical antiviral agents. No patient received intravenous valganciclovir or intravitreal ganciclovir.

Adverse effects were observed in 6 (15%) of 40 patients (Table 13).

<b>Systemic adverse effects under oral valganciclovir therapy</b>	n=6 (15%)
Neurological complaints	6 (15%)
Gastrointestinal complaints	3 (8%)
Leucopenia	2 (6%)
Dyspnea	1 (3%)

Table 13: Adverse effects of oral treatment, multiple nomination.

## 6. DISCUSSION

The results of the current study are based on a prospective evaluation of 52 patients (52 eyes) with confirmed CMV AU.

For confirming the CMV infection two standard diagnostic methods were established – PCR and ELISA targeting IgG. We included patients with a positive AI ( $\geq 3$ ) for CMV targeted by ELISA, rather than relying on the PCR-based detection of CMV DNA. The reason for this is the diagnostic advantage of assessing CMV antibodies vs. CMV DNA, which was demonstrated by Boer *et al.* [107]. They revealed that detecting CMV DNA by PCR is limited to the acute inflammation in terms of sensitivity, while throughout the course of the disease the detection of antibodies by ELISA is more reliable in terms of sensitivity. Similar results were published by De Groot-Mijnes *et al.* [91], who reported false-negative PCR results in 48% of uveitis cases with a positive AI. However, applying both methods could improve the reliability of test results.

Our major findings included:

- 1.) a significant CEC loss on the affected eye compared to the fellow eye
- 2.) a significantly lower peripapillary RNFL of the affected eye compared to the fellow eye at first examination, and a further reduction during follow-up
- 3.) a significant correlation between length of antiviral therapy and length of remission

These results will be discussed in the following.

## 6.1 Endothelial cell loss

A major focus of our investigation was the evaluation of CEC changes in CMV confirmed AU. Accordingly, we found a significant CEC loss on the affected eye compared to the fellow eye in CMV AU.

This is consistent with a study on 11 patients by Miyanaga *et al.* [196] describing a significant CEC loss in all patients with acute recurrent CMV AU. However, they showed a more severe CEC loss of at least 35% compared to the fellow eye. In 4 of these 11 patients, additional signs of stromal edema and endotheliitis, and even more severe CEC loss of at least 70% were recorded. In our study only 2 of 29 (7%) patients suffered a CEC loss of  $\geq 35\%$ . Looking for reasons to explain these differences, we noted a lower CEC count and signs of more severe corneal decompensation at initial examination in Miyanaga's cohort compared to our cohort (mean CEC density of the affected eye 1152.5 cells/mm<sup>2</sup> vs. 2229.1 cells/mm<sup>2</sup>). This may also be attributed to the initially lower CEC baseline. Apparently endotheliitis with stromal edema causes more severe damage to the endothelium [135]. Furthermore, we found different age distributions at onset (mean age 60.6 vs. 42.0 years old). Age has been associated with reduced CEC before - independent from CMV AU [41]. Miyanaga *et al.* [216] also found a correlation between CMV virus load and CEC loss. Kandori *et al.* [41] confirmed these results. Su *et al.* [143] published a study on 126 PSS patients. 68 Patients were confirmed CMV positive. They too found a severe endothelial cell loss in CMV AU which is in keeping with our results.

A study by Setala *et al.* [145] from 1978 reported the effect of iridocyclitis on CEC. Their cohort consisted of 60 patients with unilateral chronic or acute iridocyclitis. The etiology of this iridocyclitis remained undetermined with an unknown CMV involvement. In 7 severe cases, they found mutton-fat KPs. A lower central CEC density was observed in 5 of these 7 cases. Thus, the vast majority of the 60 patients showed no difference in CEC density compared to the healthy eye. These results do not match our results. We explain these different observations by the confirmed CMV-positive status of our cohort.

Pillai *et al.* [217] evaluated 13 patients with AU, 2 of which were labelled as PSS patients, none of whom were tested for CMV. They observed morphological changes

to the corneal endothelium by specular microscopy and found a reduction of CEC density in the vicinity of KPs. While our study cannot provide data on a correlation between KPs and CEC density, we also found a significant CEC density reduction in our cohort.

CMV AU causes various morphological abnormalities on the endothelium. The appearance of different KPs may threaten the endothelial integrity and the cornea itself. If this endothelial stress induced by inflammatory reactions or CMV replication persists, it may lead to corneal oedema, corneal decompensation, and finally CEC loss.

We were able to confirm that measurement of CEC density by specular microscopy helps detecting morphological alterations in CMV AU, and suggest initial documentation. Whether or not this technique is a reliable follow-up marker could not be confirmed based on the small patient number and should be subject to further studies. It appears reasonable to schedule follow-up examinations. Patients with CMV AU require intraocular surgery more often (e.g. cataract surgery), and may develop perioperative complications such as corneal decompensation. We suggest employing endothelial microscopy to assess this risk.

## 6.2 Peripapillary RNFL thinning

The majority of enrolled patients presented with mild blurred vision and unilateral ocular pain with a mean IOP of 45.4 mmHg. The elevated IOP is a characteristic sign of CMV AU, but is not pathognomonic [27]. It has been linked to obstruction in the TM by inflammatory debris. The expression of immune mediators (e.g. cytokines) in TM cells may be responsible for an increase of the resistance of the outflow pathway. Accordingly, CMV might appear as an activator of these proinflammatory cytokines and could lead to activation and exacerbation in PSS patients [82]. Subsequently, it can lead to secondary glaucoma in 8-26% of cases [25,60,76]. Takahashi and colleagues [77] observed that PSS patients have the highest incidence of secondary glaucoma among cases of different uveitis entities. The latest advances of confocal scanning laser tomography – especially OCT scans – allow for quantitative measurements and three-dimensional images of the optic nerve head, optic disc, cup, neuroretinal rim and peripapillary RNFL [218–220]. The assessment of topographic features of the optic disc and the peripapillary RNFL yields vital information for diagnosis and follow-up of different conditions concerning the optic nerve head [218–222].

In the current study we looked to demonstrate the benefits of employing peripapillary RNFL scan by SD-OCT for distinguishing healthy from pathologic conditions as well as for early detection and follow-up of inflammatory glaucomatous diseases. Our results provide evidence for morphologic alterations of the optic disc corresponding to a significant decrease of the RNFL thickness of the affected eye. Furthermore, our results document progress of the disease in follow-up (mean 24.6 months). Few studies on CMV AU employing the results of OCT scans have been published to date.

In a case report by Tsai and colleagues [64] on a patient with acute episodes of glaucomatocyclitic crisis, a progressively decreasing RNFL thickness was found. They also noted that the most remarkable reduction occurred within 2 months. Tsai *et al.* interpreted these findings as “secondary degeneration” of the peripapillary nerve cells continuing even in remission periods with a normal IOP. They also described a cell damaging “domino effect” on initially non-affected neurons by adjacently located impaired neurons. In our cohort of 38 patients with SD-OCT scans we can

corroborate the findings of Tsai *et al.* that the peripapillary RNFL is reduced. We cannot describe whether there are dynamics of the thinning within the first 2 months. But our cohort shows a decrease in the course of CMV AU. Another study by Jap *et al.* [60] also found glaucomatous damage in 14 of 53 (26.4%) eyes with PSS, with recurrent attacks of elevated IOP. During a mean follow-up of 10 years, 10 of these 14 patients showed progressive thinning of the neuroretinal rim and an increase of cup/disc ratio.

Darchuk *et al.* [223] evaluated retinal confocal tomography and scanning laser Doppler flowmetry in four PSS cases. They compared results of both diagnostic techniques before, during and after an attack and found significant changes in the optic nerve head. The flowmetry measurements showed normal values before an attack, while during an attack the flow was reduced, and a lower blood supply was detected particularly in the temporal and nasal sectors. Interestingly, optic nerve head topography and flowmetry presented as normal after an attack, with a recirculation of blood and normal oxygen supply. Subsequently, they demonstrated that significant morphological changes in the optic nerve head were seen during a hypertensive episode, but nevertheless these structural changes were reversible and no degeneration of RNFL was noted. However, the authors of this report also conceded that in severe cases with high IOPs and numerous recurrent episodes neurodegeneration, followed by irreversible damage to the optic nerve head, may be observed. To explain this assertion, they presumed a “baropressive” effect where the acute IOP rises to such an extent that the retinal autoregulation system might fail to maintain an adequate blood supply, which may yield to persisting hypoxic damage especially in cases with numerous recurrent episodes. Our results confirm a neurodegenerative process of peripapillary RNFL thinning in the course of the disease. However, we cannot substantiate a correlation to IOP. We have no data on a possible correlation of the number of recurrence episodes and RNFL thinning.

In contrast, Tsai *et al.* [64] did find a correlation of IOP and decrease of RNFL. However, their assumption needs to be interpreted cautiously, as it is based on the observation of a single patient presenting with an initially higher IOP (>50mmHg), while our cohort had a lower mean IOP of 45.4mmHg and included 38 patients.

In summary, we were able to confirm that the peripapillary SD-OCT scan is capable of discriminating morphological alterations of the affected eye in comparison to the fellow eye. Progressing CMV AU results in loss of the peripapillary RNFL of the entire papilla. Our results, and those of the reports cited, emphasize the importance of repeated OCT scans relating to the early detection and follow-up of glaucomatous damage caused by CMV AU. We thus recommend applying a repeated SD-OCT scan at primary diagnosis, and in the remission period, in order to closely monitor glaucomatous damage. However, the interpretation of peripapillary RNFL as a marker for progressing disease still needs to be validated with larger patient numbers in future studies.



### 6.3 Correlation between length of antiviral therapy and length of remission

CMV is identified as a cause of infectious uveitis with recurrent anterior inflammation and increased IOP. To date, only a few studies have focused on treatment outcome and therapy regimen (Table 14) [29,62,182,185,202,224–226]. Thus, there still is a lack of a specific guideline for CMV AU therapy, which is needed to improve the long-term outcome of CMV AU. The findings of our study suggest that longer periods of oral antiviral therapy with valganciclovir are able to better control ocular inflammation by decreasing recurrences. In 2018 Harada *et al.* [202] reported similar results. They followed 14 patients (17 eyes) with CMV AU on a treatment regimen of oral valganciclovir for a mean of 6.1 months (900 mg twice daily for 21 days and then tapered to 450 mg twice daily for up to 17 months). Their recurrence rate during tapering or termination was 50%. In addition, they demonstrated a correlation between CEC density and length of remission, and concluded that antiviral therapy should be extended for patients exhibiting CEC damage. Another report by Chee *et al.* [224] reviewed the outcome of antiviral treatment in 22 patients (23 eyes) with acute recurrent CMV AU. Their first-choice treatment was systemic application of either intravenous ganciclovir (for 12 weeks) or oral valganciclovir (900 mg twice daily for 6 weeks, tapered to 450 mg twice daily for another 6 weeks). In patients with contraindications to systemic therapy or recurrences, alternative treatment options were intravitreal or topical ganciclovir. They found that patients responded well to a short-term therapy of 12 weeks of systemic treatment (91% of eyes). They also revealed that the recurrence rate after stopping systemic treatment was high (80% of eyes). In keeping with these findings of Chee and colleagues, the present study also indicates that long-term therapy is beneficial in terms of long-term remission, while short-term therapy frequently results in early recurrences. Specifically corresponding to our study, 8 out of 14 patients who received a long-term valganciclovir therapy were stable for more than 24 months, while in turn 5 out of 6 patients in the short-term therapy group suffered from an early recurrence within 6 months (Table 12). Wong *et al.* [182] published long-term results of oral valganciclovir treatment for CMV AU. They followed 13 patients (13 eyes) for a mean duration of 17.2 months after administering an oral loading dose of 900 mg twice daily for a median of 4 weeks (2–9 weeks), followed by a maintenance therapy of 450 mg twice daily for 2–36 months. 5 patients (38.4%) suffered recurrence of disease within 1–4 months after stopping

therapy and required retreatment. These data are in keeping with our findings, where 48% of the patients had a recurrence after cessation of oral valganciclovir therapy. Another study by Sobolewska *et al.* [62] was based on a small cohort of 11 PSS patients who were treated with valganciclovir for a mean period of 20 months (range 10-46 months). Their results showed that in 7 of 11 (63.6%) cases, valganciclovir therapy effectively dissolved inflammatory activity and stabilized the IOP. In 2 of 11 (18.8%) cases, valganciclovir therapy was repeated because of early recurrences after discontinuation of antiviral treatment. Our findings support the results of that study as well – leading to the recommendation for a long-term oral antiviral therapy regimen.

In terms of our study, adverse effects were shown just in 6 of 40 (15%) patients, and we recorded a decent tolerance of oral antiviral treatment. Sobolewska *et al.* [62] investigated the outcome of oral valganciclovir therapy on 11 patients with PSS, and also found no significant adverse effects of systemic antiviral therapy. Wong *et al.* [182] also reported no adverse events in a group of 13 patients with CMV AU under oral valganciclovir therapy.

The fact that all currently available anti-CMV drugs – including ganciclovir and valganciclovir – are virustatic but not virucidal [227] offers a good explanation for the high recurrence rates after stopping treatment. Consequently, there is a need for safe and effective management in the antiviral treatment of CMV AU, and based on our findings we recommend a long-term valganciclovir therapy regimen to prevent recurrences and further damage to the eye.

Authors	Publication	Number of treated eyes	Treatment modality and duration in months	Outcome	Duration of follow-up (months)
Current study		40	<ul style="list-style-type: none"> <li>900 mg oral valganciclovir twice daily for at least 2 weeks, followed by 450 mg twice daily for up to 12 months</li> </ul>	13 responded for > 24 months, 15 responded for 7-24 months, 12 responded for at least 6 months, 13 had recurrences under therapy	2-126.6
Harada <i>et al.</i> [202]	2018	17	<ul style="list-style-type: none"> <li>900 mg oral valganciclovir twice daily for 21 days, followed by 450 mg twice daily for up to 17 months</li> </ul>	7 responded, 7 recurred	4-67
Sobolewska <i>et al.</i> [62]	2014	11	<ul style="list-style-type: none"> <li>900 mg oral valganciclovir twice daily for 3 weeks, followed by 450 mg twice daily for 10-46 months</li> <li>prior to oral valganciclovir treatment 10 patients had aciclovir 800 mg five times daily</li> </ul>	7 responded, 2 had recurrences	Unknown
Wong <i>et al.</i> [182]	2012	13	<ul style="list-style-type: none"> <li>900 mg oral valganciclovir twice daily for at least 2 weeks, followed by 450 mg oral valganciclovir for 2-36 months</li> </ul>	8 responded, 5 recurred	6-38
Chee <i>et al.</i> [224]	2010	11	<ul style="list-style-type: none"> <li>Intravenous ganciclovir 5 mg/kg twice daily for 6 weeks, followed by 1 mg/kg for another 6 weeks, 4 cases</li> <li>900 mg oral valganciclovir twice daily for 6 weeks, tapered to 450 mg twice daily for another 6 weeks</li> </ul>	10 responded, 8 recurred	4.9-54.8

Table 14: Overview of studies on CMV AU of systemic treatment regimen and recurrences to date.

## **7. CONCLUSION**

In our cohort of CMV AU patients, morphological changes are very common and play a crucial role, despite its often relatively asymptomatic clinical course. These changes include peripapillary RNFL thinning and loss of CEC density. Therefore, careful monitoring by initial and follow-up SD-OCT scans and endothelial microscopy is recommended. Both methods should be employed as standard monitoring procedures and should be repeated to monitor early changes. Furthermore, long-term oral treatment with valganciclovir appears to extend the length of remission intervals in patients with CMV AU.

## 8. LIMITATIONS OF THE STUDY

Certain limitations of the study need to be considered.

While a randomized controlled trial characterized by a prospective, randomized and placebo-controlled study design is recognized as the best method to approach a medical question, this might be difficult to accomplish due to low incidence. Our study combines elements of case-control studies and cohort studies. Case-control studies are primarily employed in researching relatively rare diseases, as applies for CMV AU. Accordingly, we gathered data on all cases of unilateral CMV AU at the Department of Ophthalmology Charité Berlin between February 2007 and April 2018. The non-affected eye of the same individual served as a control allowing for a perfect match between case and control, since possible disturbances are eliminated, thus allowing for homogeneous groups. Cohort studies generally require a larger number of cases, which constitute the cohort to be prospectively monitored. This follow-up is either defined by certain events or a set time schedule. However, follow-up studies naturally include the risk of cases getting lost to follow-up for various reasons. In our study we only had a relatively small number of patients available for follow-up, which indicates that our results should be confirmed by future studies with larger patient collectives.

Concerning the evaluation of the antiviral treatment regimen, further studies should also employ strict standards for dosage and length of therapy to allow for better comparison and reliability of results.

The patient's malcompliance generally adds to uncertainty of data.

Ideally a randomized double-blind placebo-controlled trial should be considered, favorably set up as a multicenter study to reach sufficient patient numbers.

Generally, it should be noted that the examinations of the RNFL thickness by SD-OCT and endothelial microscopy may vary depending on the patient's cooperation.

Other limitations of this study are related to the fact that RNFL thickness and CEC density were not always performed simultaneously at first presentation upon disease onset. This would be a prerequisite to provide valid answers to the question of

whether optic nerve damage and loss of CEC density occur simultaneously, or whether one of these morphological changes occurs more rapidly. Furthermore, it should be noted that some of the patients included in this study may have been treated elsewhere before initially presenting at our clinic, which may not always be reflected in the documented medical history.

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## 10. AFFIDAVIT AND DECLARATION OF ANY EVENTUAL PUBLICATIONS

I, Therese Walla, certify under penalty of perjury by my own signature that I have submitted the thesis on the topic “**Morphological changes and outcome in CMV anterior uveitis**”. I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE [www.icmje.org](http://www.icmje.org)) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM and are answered by me. My interest in any publications to this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

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Date and Signature doctoral candidate

## **Declaration of any eventual publications**

Publication 1: Poster: Walla T., Lenglinger M., Pleyer U.

“Morphological changes and outcome in CMV anterior uveitis.” at the conference of the Deutsche Ophthalmologische Gesellschaft (DOG), Bonn, Germany, 27.9.2018 - 30.9.2018, contribution in detail: characterization of potential optic nerve damage and corneal endothelial changes in CMV AU, independent acquisition and organization of prospective data, involvement in the statistical analysis, poster design, results and conclusion, graphic design [Figure 8, 10-13]

Publication 2: Abstract for scheduled talk and presentation: Walla T., Lengliner M., Pleyer U.

„Biomorphologische Befunde bei CMV-assoziiierter anteriorer Uveitis“ at the annual winter meeting of Berlin-Brandenburgische Augenärztliche Gesellschaft (BBAG), Berlin, Germany, 07.-08.12.2018, contribution in detail: characterization of potential optic nerve damage and corneal endothelial changes in CMV AU and outcome of oral valganciclovir therapy in preventing recurrences, independent acquisition and organisation of prospective data, involvement in the statistical analysis, graphic design

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Date and Signature doctoral candidate

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Date, signature and seal of mentoring advisor

## **11. CURRICULUM VITAE AND SCIENTIFIC PUBLICATIONS**

### **Curriculum vitae**

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

## Scientific publications

Therese Walla, M. Lenglinger, U. Pleyer.

“Morphological changes and outcome in CMV anterior uveitis” Poster on the Conference of the Deutsche Ophthalmologische Gesellschaft (DOG), Bonn, Germany, 27.9.2018 - 30.9.2018

Therese Walla, M. Lengliner, U. Pleyer

“Biomorphologische Befunde bei CMV-assoziiierter anteriorer Uveitis“ at the annual winter meeting of Berlin-Brandenburgische Augenärztliche Gesellschaft (BBAG), Berlin, Germany, 07.08.2019 - 08.12.2018

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Signature doctoral candidate



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