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ORIGINAL ARTICLE

Diagnosis of Cytomegalovirus Anterior Uveitis in Two European Referral Centers

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ABSTRACT

Purpose: To evaluate diagnostic methods and clinical signs of CMV anterior uveitis (AU), a rarely described entity in Europe.

Methods: We included patients with clinical characteristics of CMV AU and positive PCR and/or Goldmann-Witmer coefficient (GWc) for CMV.

Results: We report 21 patients with unilateral uveitis (100%) and signs of Posner-Schlossman syndrome (PSS) (n = 20, 95.2%), Fuchs uveitis syndrome (FUS) (n = 1, 4.7%), and endotheliitis (n = 4, 19,04%). PCR was positive in 15/21 (71.4%) and GWc in 8/9 patients (88.9%) in aqueous for CMV. GWc was the only positive test in 6/9 patients (66,6%). When PCR alone was performed (without GWc) in the first tap, repeated aqueous taps were needed, twice in five cases and thrice in one case.

Conclusion: Combining PCR and GWc were very helpful to confirm the clinical diagnosis of CMV AU. In case of very high clinical suspicion and negative results, repeated tap seems to be recommended.

Keywords: Anterior uveitis, cytomegalovirus, endotheliitis, glaucoma, Goldmann-Witmer coefficient, hypertony, PCR, viral uveitis

Viral etiologies represent only 10% of anterior uveitis cases, while the majority of anterior uveitis (AU) are non-infectious.[1] The diagnosis of uveitis, including infectious uveitis, is based on clinical features of the patient, in combination with the medical history, serological laboratory tests, and radiographic studies. Patients with anterior inflammation from different viral etiologies may share similar clinical characteristics. However, the exact etiology of AU sometimes remains unknown, especially when viruses are involved. Rapid distinction between infectious and non-infectious AU is essential in order to quickly adapt the treatment strategy and to improve the visual prognosis. Aqueous humor analysis contributes to this goal.

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Two types of tests can be performed on aqueous humor to detect a causative viral agent in AU. The first test is based on detection of specific antibody production in aqueous humor, known as Goldmann-Witmer coefficient (GWc). It compares the levels of intraocular antibody to that in the serum, as measured by enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay. The coefficient is defined as GWc = X/Y, where X = specific antibody in aqueous or vitreous divided by total IgG in aqueous or vitreous; and Y = specific antibody in serum divided by total IgG in serum. A GWc ratio > 3 lead to a diagnosis of local antibody production to a specific microbial pathogen. The second method is the direct detection of the viral genome by using the polymerase chain reaction (PCR) technique on aqueous humor. PCR and GWc analysis are complementary for the diagnosis of infectious uveitis.[2–5]

By performing these diagnostic methods, it has recently been shown that cytomegalovirus (CMV), a member of the Herpesviridae family, can be responsible for an AU in immunocompetent individuals.[6,7]

A range of clinical presentations of CMV AU, has since been described, varying from recurrent iritis with raised intraocular pressure (IOP) resembling Posner-Schlossman syndrome (PSS), to chronic anterior uveitis mimicking Fuchs uveitis syndrome (FUS), both patterns that may be accompanied by corneal endotheliitis.[8]

The primary outcome of our study is to determine the relative contribution of the GWc and PCR in the diagnosis of CMV AU in patients with clinical signs of CMV uveitis. The secondary outcome of the study is to characterize the clinical signs of CMV AU.

MATERIALS AND METHODS

We retrospectively reviewed the charts of patients with CMV AU between January 1st, 2006 and 30th June 2016 in 2 tertiary referral centers in Europe: CHU Saint-Pierre in Brussels, Belgium, and University Medical Center Utrecht (UMCU), the Netherlands. Twenty-one patients, of which 20 did not have any history of immunosuppression and one was treated with anti-TNFα for spondylarthitis (SPA), were included in the study. All the patients presented with clinical signs of CMV AU and had a positive PCR and/or GWc for CMV on aqueous humor analysis. The study design adhered to Declaration of Helsinki and Institutional Review Board (IRB) / Ethics Committee approval was obtained.

An anterior chamber (AC) paracentesis was performed in all patients who presented with an active uveitis episode. The tap was performed using a sterile syringe with a 27G needle and a 0.1–0.2 ml sample of aqueous humor was collected. At the UMCU, PCR and GWc were analyzed simultaneously in the aqueous from the first tap.[2] In CHU Saint-Pierre, a quantitative PCR was done first[9], and when PCR was found to be negative for CMV while the clinical suspicion for CMV AU remained very high, aqueous tap was repeated and some aqueous samples were then sent to the Department of Medical Microbiology of the UMCU for semi-quantitative PCR and GWc in order to biologically confirm the clinical diagnosis. In both centers, PCR for HSV1, HSV2, and VZV were also performed. PCR and GWc for rubella virus were only performed for patients with clinical signs of FUS.

A Posner-Schlossman syndrome (PSS) diagnosis was made after the following features were identified: recurrent attacks of unilateral mild anterior uveitis (few keratic precipitates (KPs), flare and cells ≤1+) with highly elevated IOP and initially rapid resolution after the administration of topical steroids and hypotensive drugs. FUS was clinically diagnosed in patients presenting diffuse stellate KPs, mild anterior chamber reaction with or without Koeppe's nodules, atrophy and depigmentation of the iris, heterochromia and a variable grade of vitreous inflammation, but did not show any ciliary reaction, posterior synechiae or macular edema unless the patient had been previously submitted to surgery. CMV corneal endotheliitis was clinically diagnosed in patients presenting localized corneal edema associated with coin-shaped or linear KPs and associated or not with corneal stromal inflammation. [8]

Exclusion criteria were patients with another diagnosis of uveitis, immunocompromised patients with posterior CMV and patients with positive PCR or positive GWc for HSV, rubella virus or VZV.

Systemic and ocular history was collected for all patients as well as detailed ocular examinations. Data regarding age, gender, number of aqueous taps, type of inflammation at the time of each tap, positivity of PCR and/or GWc, and follow-up duration, were recorded. At each visit, patients also had a bilateral thorough assessment of the ocular findings, including best-corrected visual acuity (BCVA), intraocular pressure (IOP) measured by aplanation, anterior segment examination with evaluation of the endotheliitis, keratic precipitates (KPs), anterior chamber cells, and fundus examination. Intraocular inflammation was classified and graded according to the SUN working group method.[10] Glaucoma-associated uveitis was diagnosed when patients developed characteristic optic nerve cupping with corresponding glaucomatous visual field defect on automated Humphrey visual field (HVF) testing and defects in OCT RNFL as previously described.[3] The number and type of anti-glaucomatous medications were recorded as well as the number and type of glaucoma surgery.

RESULTS

Twenty-one eyes from 21 patients (15 from Brussels and 6 from Utrecht) were included in our study.

TABLE 1. Demographic and clinical features in patients with CMV anterior uveitis. Abbreviations: SD, standard deviation; M, male; F, female; PSS, Posner Schlossman Syndrome; FUS, Fuch's Uveitis Syndrome; IOP intraocular pressure; BCVA, Best corrected visual acuity.

Number of CMV related anterior uveitis (n)	21
Age at diagnosis (mean ±SD) (years)	38.57 ± 12.11
Sex:	
M	15 (71.4%)
F	6 (28.6%)
Uveitis type:	
PSS	20 (95.2%)
FUS	1 (4.8%)
Associated endotheliitis	4 (19,04%)
Lens status:	
Phakic	19 (90.5%)
Pseudophakic	2 (9.5%)
Mean IOP at diagnosis (mmHg)	32.95 ± 14.43
Initial BCVA	0.93 ± 0.21
Final BCVA	0.93 ± 0.11
Complications:	
Cataract surgery	5 (23,8%)
Glaucoma	8 (38,1%)
Glaucoma surgery	2 (9,5%)

Demographic and clinical characteristics are summarized in Table 1. Fifteen patients (71.4%) were males and six (28.6%) were females. Mean age at diagnosis was 38.57 ± 12.11 years. Uveitis was unilateral in all patients (100%). The 20 non-Asian patients (95.2%) had clinical characteristics of PSS and the only Asian patient (4.8%) had typical KPs resembling FUS with very rare cells in the vitreous (Figure 1d). No patient presented with posterior synechiae or iris atrophy. Four patients (19,0%) had associated endotheliitis (Figure 1e). Two patients (9.5%) were pseudophakic at diagnosis, and one patient developed AU 3 months after cataract surgery. Sixteen patients (76.2%) had an increased IOP at presentation, with a mean of 32.95 ± 14.43 mmHg [10–56 mmHg](median 35) and 1 patient presented initially with glaucoma (4.8%). Mean BCVA at presentation was 0.93 ± 0.21.

Twenty-eight diagnostic aqueous taps were performed in order to confirm biologically the clinical diagnosis of AU in 21 patients (data summarized in Table 2). In Utrecht, where PCR and GWc were done simultaneously, PCR and/or GWc confirmed the diagnosis after the first tap in all six patients (by PCR (1/6 patient), GWc (3/6 patients) or both PCR and GWc (2/6 patients) (Table 2)). In Brussels, where only PCR was performed on the first tap, the diagnosis was obtained after 1 tap in 9/15 patients. When clinical signs still strongly suggested CMV AU (PSS, FUS, ± endotheliitis), repeated taps were performed. A second tap has been necessary to biologically confirm the diagnosis of CMV AU by PCR in three patients and by GWc in two patients. A third tap has been necessary in 1 patient, who had three successive negative PCR for CMV but GWc confirmed the diagnosis.

In summary, PCR (performed in all patients) led to the diagnosis of CMV AU in 15/21 patients (71.4%) and GWc (performed in 9 patients) confirmed the diagnosis in eight patients (88.9%), and it was the only positive test in 6/9 patients. The value of GWc was relatively high with a mean of 23.3 [4.1–83.3] and median value of 16,4.

Interestingly, we found in six patients who had only KPs and no AC cells at the time of tap, that PCR was always negative and GWc positive.

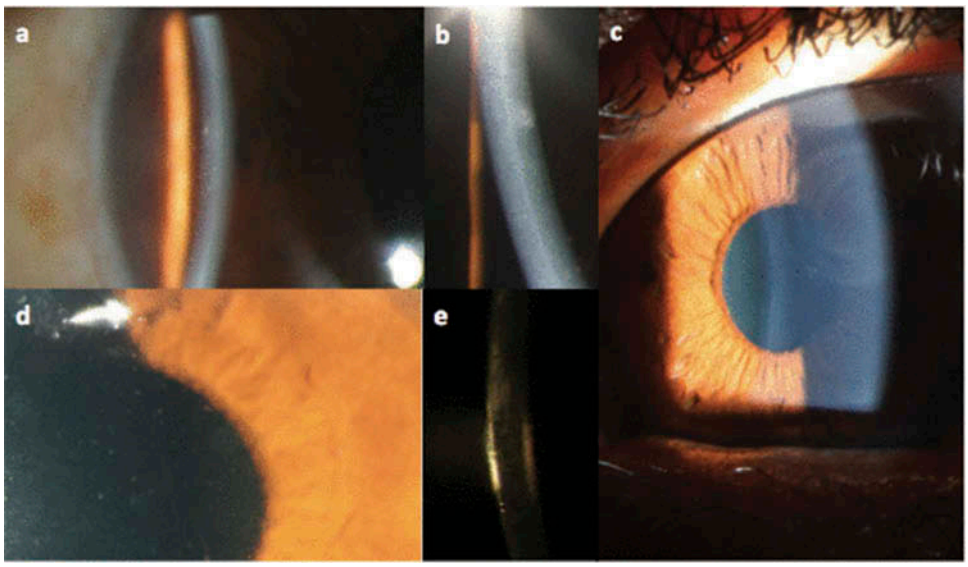

FIGURE 1. Clinical features of CMV AU. a. PSS, few little and medium size white KPs in the center of the cornea; b. Coin shaped KPs; c. immune ring formation associated with endotheliitis; d. FUS like uveitis, white stellate and medium size KPs dispersed on the whole cornea; e. endotheliitis.

TABLE 2. Real-time PCR and GWc analysis in 21 CMV anterior uveitis patients. Abbreviations: PCR -, Polymerase chain reaction negative; PCR +, Polymerase chain reaction positive; GWc ND, Goldmann Witmer coefficient not done; GWc-, Goldmann Witmer coefficient negative; GWc+, Goldmann Witmer positive; NA, not applicable.

	PCR -	PCR +	Total
GWc ND	ND	12	12 (57.1%)
GWc -	NA	1	1 (4.8%)
GWc +	6	2	8 (38.0%)
Total	6 (28,57%)	15 (71,4%)	21

At the end of the follow-up, five patients (23.8%) had cataract surgery consisting in a phacoemulsification without any complication. Eight patients (38.1%) had glaucoma and two had glaucoma surgery (9.5%) by trabeculectomy with mitomycin C. The mean final visual acuity was 0.93 ± 0.11 in 19 patients (90.5%), they reached a final VA of 0.7 to 1. However, two eyes of two patients had a final VA of counting fingers, resulting from severe glaucomatous damage of the optic nerve, despite intensive medical and surgical glaucoma treatment (Table 1)

DISCUSSION

CMV has been implicated in the etiology of AU after the recent advances in the identification of the viral genome by PCR and the GWc calculation on aqueous humor. PCR analysis of intraocular fluids may detect minimal amounts of viral DNA, making it a powerful and rapid diagnostic method. Classically used on vitreous samples, PCR is presently performed also on aqueous samples. Quantitative PCR-based tests may provide additional information on viral load, disease activity and response to therapy.[2,11,12]

On the other hand, the GWc calculation is based on antibody detection in peripheral blood and intraocular fluids, in order to identify a causative agent. Antibodies found in the eye during an uveitis attack can derive from the blood due to either disruption of the blood-aqueous barrier or intraocular synthesis by plasma cells.[6] In particular, GWc is helpful in establishing whether pathogen-specific intraocular antibody production, and thus infection, has occurred.[2] The combination of the two tests gives a higher probability of CMV AU diagnosis.[2,4]

Both antibody detection and PCR assays on intraocular fluids have their limitations.[13–15] On the one hand, antibody detection demonstrates only indirectly the presence of an infectious agent and is less efficient in immunocompromised states and sometimes in treated patients.[6,16] On the other hand, PCR may lack sufficient sensitivity because of the small amount of ocular fluid, the presence of inhibitory compounds in the sample or microorganism polymorphism.[17] In addition, test positivity depends on the stage of disease. In viral infections, PCR is usually positive in the early stages of the disease, whereas at later stages, GWc values are positive when PCR might be negative. Presumably, in later stages of the infection, the pathogen is cleared or the microbial load is reduced to below the detection limit, whereas intraocular IgG production is sustained for a longer period of time.[6,17]

PCR led to the diagnosis in 15/21 patients (71.4%), and GWc in 8 of the 9 tested patients (88,9%) patients and was the only positive test in 6/9 tested patients (66,6%). In Utrecht, where PCR and GWc could be performed initially simultaneously, the diagnosis was obtained in all the 6 patients from the first tap. In Brussels, the diagnosis was obtained after 1 tap in nine patients, after 2 taps in five patients and after 3 taps in one patient (Figure 2). Our study confirms that PCR is a good test for the early detection, especially when a cellular inflammation in the anterior chamber is present, while the GWc allows a later diagnosis, when a low inflammation is observed in the anterior chamber. In our study, PCR was negative in all 6 taps where no cell were present in the AC at the time of the anterior chamber tap, though KPs and/or active endotheliitis were still present. The initial PCR negative results could be attributed to the small volume of aqueous submitted for testing and/or the absence of cells. CMV anterior uveitis can be recurrent or chronic, in recurrent cases CMV AU may also present with intermitting episodes of activity, where PCR may become negative during remission, but GWc remains positive for a longer period of time. Indeed, the rapid rise in IOP and self-limiting tendency of the ocular inflammation observed in PSS suggest that the resolution of intraocular infection and elimination of viral DNA may be fairly rapid, leading to a false-negative tap. Because of the retrospective nature of our data, we could not determine if the interval between the onset of the symptoms and the tap was a possible confounding factor, but the use of both laboratory tests improved the diagnosis of CMV AU.

CMV AU in immunocompetent patients has a wide spectrum of clinical presentation.[18] It may present either as a characteristic PSS[19,20], or as a chronic AU resembling FUS.[21] Furthermore, it might be associated with an acute relapsing or chronic raise in intraocular pressure (IOP). Endotheliitis is another possible manifestation linked to a CMV infection of the anterior segment of the eye.[22] These features are consistent with the finding of CMV in the smooth muscle cells of the iris, the ciliary body, and the endothelial cells of the Schlemm canal.[23]

Differently from the Asian series reported in Singapore by Chee et al.[8], most of the patients in our European study presented with clinical

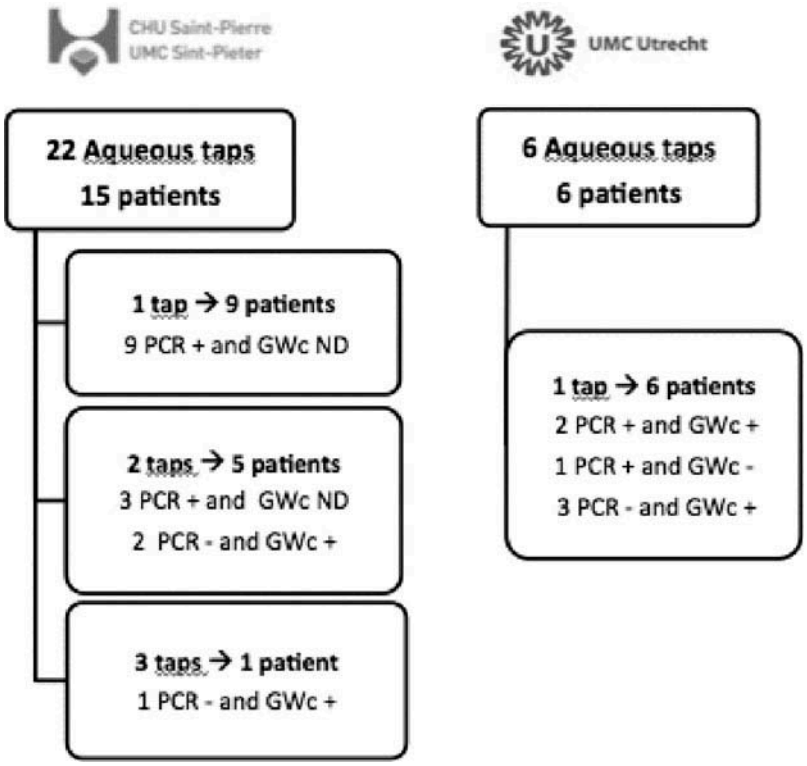

FIGURE 2. Number of taps performed to obtain biological confirmation of CMV anterior uveitis. Abbreviations: PCR, polymerase chain reaction; GWc, Goldmann-Witmer coefficient; ND, Not done.

characteristics of PSS, while the only Asian patient of our study presented with features of FUS. This patient had only few cells in the vitreous (vitreous haze grade 0.5 according to SUN)[9], which may help us to clinically differentiate CMV AU from rubella virus AU/intermediate uveitis. Four patients (19,0%) had associated endotheliitis, which is slightly lower than the findings published in previous series, where 30% of Asian or European patients with CMV uveitis presented with concomitant corneal endotheliitis.[24,25] This might result from the retrospective collection of data. Some slight endotheliitis might not have been described in the chart of patients. In these patients the contribution of GWc, in order to establish the CMV AU diagnosis was higher than PCR (60%), which might suggest that in these cases, with associated endotheliitis, a chronic inflammation or a post infectious immune reaction might be present.

Current management of CMV AU emphasizes the importance of early diagnosis and prompt treatment in order to avoid serious ocular complications[26] characterized by severe glaucomatous damage, cataract and corneal decompensation.[27] In our series, five patients (23.8%) had cataract surgery consisting of a phacoemulsification and IOL insertion without any complication, and eight patients (38.1%) had glaucoma. None of the patients with corneal endotheliitis had severe corneal decompensation.

In conclusion, the confirmation of CMV AU remains difficult and can be improved by the combination of PCR and GWc and by repeating aqueous taps in patients with clinical characteristics of PSS or FUS. A prompt diagnosis allows for a more accurate treatment and a better prognosis in patients with CMV AU.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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