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ORIGINAL ARTICLE

Causes of Hypertensive Anterior Uveitis in Thailand

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ABSTRACT

Purpose: To determine the prevalence of viral infections in patients with hypertensive anterior uveitis in Thailand from polymerase chain reaction (PCR) of aqueous humor.

Methods: Thirty-one patients with anterior uveitis with intraocular pressure (IOP) above 25 mmHg were included for PCR analysis for cytomegalovirus (CMV), herpes simplex (HSV), varicella-zoster (VZV), rubella, chikungunya and Zika virus.

Results: The prevalence of PCR-positive results was 32%, including 19% for CMV, 10% for HSV, and 3% for VZV; PCR for other tested viruses demonstrated negative results. PCR-positive patients exhibited satisfactory IOP control with antiviral and anti-glaucomatous treatment compared to PCR-negative patients, and more than half of PCR-negative patients required glaucoma surgery within 12 months (P = .01).

Conclusion: PCR evidence of infection with herpes group viruses was found in one-third of patients with hypertensive anterior uveitis; CMV being the most common pathogen. The PCR-positive group generally responded well to a combination of antiviral and anti-glaucoma treatment.

Keywords: Cytomegalovirus, herpes simplex virus, hypertensive anterior uveitis, polymerase chain reaction, varicella-zoster virus

Anterior uveitis (AU) represents the most common type of uveitis worldwide.[1] Causes of AU vary widely, from noninfectious entities (such as HLA B27-associated AU or sarcoidosis) to numerous infections.[2] Viral agents were repeatedly detected in the intraocular fluid of patients with AU, especially in patients with unilateral hypertensive anterior uveitis (HAU), who were resistant to standard topical treatment with corticosteroids.[3,4] Multiple viral causes of AU were reported, the most common being members of the herpes virus group. Rubella virus (RV) was demonstrated in Europe and other countries and emerging viral agents as chikungunya, Zika, and Ebola viruses were also implicated.[5] Viral AU manifests predominantly as unilateral HAU often associated with some form of iris atrophy.[6]

We performed a retrospective study of 31 consecutive HLA B27-negative patients with HAU in Thailand and examined the clinical manifestations of patients positive for PCR outcomes and compared their features to patients with negative results.

METHODS

In this study, 31 patients with HAU were included, seen between October 2016 and January 2019 in the ophthalmology department of Chiang Mai University Hospital, Thailand. HAU patients were selected from a cohort of 110 uveitis patients who underwent aqueous polymerase chain reaction (PCR) examinations in the same period.

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All patients with uveitis underwent a diagnostic workup, which included erythrocyte sedimentation rate, complete blood counts, serology for syphilis, toxoplasma and HIV, chest X-ray and tuberculin skin test. Also, HLA-B27 testing was performed in AU and panuveitis cases. Classification of uveitis was performed according to SUN criteria.[7] AU patients with inconclusive results of initial workup and with clinical suspicion of a viral infection (such as active or recurrent unilateral AU not responding to topical corticosteroids) underwent the aqueous tap for PCR examinations.

HAU was defined as AU with IOP equal to or more than 25 mmHg in the affected eye. HAU patients with a prior diagnosis of glaucoma or steroid-induced ocular hypertension were excluded. Data on clinical manifestations were selected from patients' files. We registered the results of complete ocular examinations, including best-corrected visual acuity (BCVA), IOP, as well as the results of slit lamp examination of both anterior and posterior segments and indirect fundoscopy. In addition, we registered BCVA changes and all complications during one-year follow-up after the aqueous examination has been performed. **None of the patients with HAU had retinal inflammatory lesions**. In cases with bilateral involvement, only the eye with the highest IOP was evaluated. Diagnosis of Posner-Schlossman Syndrome (PSS) was made in cases with unilateral mild iritis with fine keratic precipitates, diffuse corneal epithelial edema, and highly elevated IOP (>40 mmHg). Fuchs Uveitis Syndrome (FUS) was diagnosed as in the presence of at least four of the following five signs: (1) unilateral low-grade AU without acute redness, (2) typical scattered keratic precipitates, (3) absence of synechiae, (4) diffuse iris atrophy, and (5) cataract.[6]

Polymerase chain reaction for CMV, HSV-1, HSV-2, VZV, RV, chikungunya, and Zika viruses was performed in all aqueous fluid samples from included patients. Real-time PCR for CMV, HSV-1, HSV-2, and VZV was performed as described previously.[8,9] Briefly, nucleic acid was extracted from 25 µl of aqueous fluid using a commercially available kit, QIAamp® DNA Blood Mini Kit (QIAGEN, Inc., Valencia, CA, USA) according to the manufacturer's instruction and stored until use in aliquots at −80□C. For assurance and monitor the quality of extraction and the amplification procedures, 2,500 to 5,000 copies/mL of Phocid herpes virus type 1 (PhHV-1) were added to each sample before extraction.[10] The detection of each investigated pathogenic DNA was performed at the Division of Clinical Microbiology, Department of Medical Technology, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand, as described previously.[9,11] The forward primers, reward primers and probes specific for CMV, HSV-1, HSV-2 and VZV as following, F-GCCGATCGTAAAGAGATGAAGAC, R-CT CGTGCGTGTGCTACGA GA, *P*-(5HEX)AGTGCAG CCCCGACCATCGTTC(BHQ1a~5HEX), F-TCCACC AGG ACCACGTAG, R-CTGTCGCCTTACGTGAAC AAGAC, *P*-(6~ FAM)CCCGTCTCCAT GTCCAG GATGGG(TAMRA~6~ FAM), F-TCCACGAGGACC ACGTAGG, R-CTG GCGCCTTACGTGAACAAGAC, *P*-(6~ FAM)CCCGTCTCCATGTCCAGGACGGG (TA MRA~6~ FAM), F-AAGTTCCCCCCGTTCGC, R-TGG ACTTGAAGATGAACT TAATGAAGC and *P*-(6~ FAM)CCGCAACAACTGCAGTATATATCGTC (TA MRA~6~ FAM), respectively. Briefly, 10 µl of the extracted nucleic acid was added to 15 µl of the real-time PCR reaction mixture (DyNAmo Probe qPCR; New England Biolabs, Inc), which contains specific primers and probes. Then, real-time PCR was performed in a real-time PCR machine (CFX96™ Real-time System; Bio-Rad). The PCR analysis for RV, chikungunya and Zika viruses was performed in Erasmus Medical Center as reported previously.[12–14]

Treatment regimens for CMV-positive HAU included 2% topical ganciclovir (4 to 6 times/day during the first month, followed by 4 times/day for 2 to 3 months and 3 times/day for additional 3 months). Treatment duration was at least 6 months; no systemic or intravitreal treatments were given. Treatment for HSV and VZV HAU included a 3% acyclovir ointment (5 times/day for 6 weeks and tapered to 2 to 3 times/day for up to 4 months) together with systemic acyclovir (800 mg twice a day for 6 to 8 weeks, followed by 400 to 800 mg daily for 4 months). Topical corticosteroids and IOP lowering drugs were added according to the severity of inflammation and IOP values.

This study was done in accordance with the tenets of the Declaration of Helsinki, and the study protocol was approved by the ethics board of Maharaj Nakorn Chiang Mai Hospital, the Chiang Mai University.

Statistical Analysis

Quantitative data were reported as mean (±SD) while categorical variables are analyzed using the Chi-square test, and quantitative difference between groups analysis using the Paired t-test. A *P*-value <0.05 was considered to be statistically significant.

RESULTS

Demographic data and clinical characteristics of included patients are illustrated in Table 1. The most frequent complaint consisted of blurred vision, less prevalent were redness and pain.

TABLE 1. Characteristics of patients with hypertensive anterior uveitis according to polymerase chain reaction results.

Characteristic	Total HAU N = 31	CMV-DNA positive N = 6	HSV/VZV-DNA positive N = 4	PCR-negative N = 21	*P-v*alue**
Mean age of onset	50.54 ± 11.85	51 ± 11.04	51.25 ± 15.06	50.28 ± 12.13	0.985
Male	18 (58%)	4 (67%)	1 (25%)	13 (72%)	0.349
Redness/pain	9 (29%)	4 (67%)	1 (25%)	4 (19%)	0.075
Corneal involvement	11 (35.5%)	2 (33%)	3 (75%)	6 (28.5%)	0.204
Scars	2 (6.5%)	0	0	2 (9.5%)	
Edema	6 (19%)	1 (17%)	2 (50%)	3(14.%)	
Endotheliitis	3 (10%)	1 (17%)	1 (25%)	1(5%)	
Small to medium-sized keratic precipitates	20 (65%)	4 (67%)	2 (50%)	14 (67%)	0.809
Anterior chamber cells					0.866
2+	26 (84%)	5 (83%)	3 (75%)	18 (86%)	
2+	5 (16%)	1 (17%)	1 (25%)	3 (14%)	
Iris involvement					
Posterior synechiae	3 (10%)	1 (17%)	0	2 (9.5%)	0.682
Iris atrophy	9 (29%)	4 (67%)	1 (25%)	4 (19%)	0.075
Cataract at first presentation	16 (52%)	1 (17%)	2 (50%)	13 (62%)	0.147
Average highest IOP (Range)	33 mmHg (25–46)	30 mmHg (23–33)	28.5 mmHg (26–31)	34 mmHg (25–46)	0.098

CMV: Cytomegalovirus, HSV: Herpes simplex virus, VZV: Varicella zoster virus, HAU: Hypertensive anterior uveitis, PCR: Polymerase chain reaction, IOP: Intraocular pressure

*There were 8 patients who underwent cataract surgery before their first presentation in our center

**PCR positive versus PCR negative patients

Most patients suffered from unilateral HAU. No differences were found in gender or age. **The most common anterior segment findings included small to medium-sized white/gray keratic precipitates (KPs)** and a mild anterior chamber inflammation. The only case of HAU with hypopyon was later diagnosed with Behçet's disease. Despite the high IOP at the onset, only five eyes had at that time a cup-to-disc ratio ≥ 0.7. At the first presentation in our department, eight patients already underwent cataract surgery. Out of 23 phakic eyes, 16 (52%) had cataract at initial presentation. **Cystoid macular edema was not present**.

Positive PCR results were found in 10/31 (32%) patients (CMV = 6, HSV = 3, and VZV = 1). None of the patients was positive in PCR for RV, chikungunya, and Zika virus. **No complications of anterior chamber tap were encountered, such as endophthalmitis, lens injury, and hemorrhage**. Out of the remaining PCR negative patients, only one patient received a definitive diagnosis (Behçet's disease), and the others remained of unknown origin.

Patients with CMV-positive HAU had all mild AC reaction and small to medium-sized KPs. Clinical features were not distinct from HAU associated with HSV, VZV, or PCR negative AU group. In CMV-positive HAU, IOP was commonly well controlled with medication. None of our CMV-positive HAU patients needed glaucoma surgery during the first year of follow-up (Table 2).

All affected eyes in HSV/VZV group exhibited corneal involvement, out of which two eyes required corneal transplantation during the follow-up. IOP range was similar to CMV-positive HAU, and none of the patients needed filtering surgery for glaucoma within one year of follow-up. Interestingly, one 28-year-old female with unilateral HAU was found positive for HSV-2. She reported no associated general symptoms and was not known with any comorbidity. This patient demonstrated a low-grade unilateral anterior chamber inflammation, fine KPs, and presenting IOP of 28 mmHg, but responded well to

TABLE 2. Development of new complications and intraocular surgeries in patients with hypertensive anterior uveitis during a follow-up of 12 months after initial presentation.

	CMV-positive N = 6	HSV/VZV-positive N = 4	PCR-negative N = 21	*P*-value*
New complications				
• Cataract	1 (17%)	0	1 (5%)	0.49
• Glaucoma	1 (17%)	0	12 (57%)	0.03
• Corneal decompensation	1 (17%)	2 (50%)	5 (24%)	0.46
Intraocular surgeries				
•Cataract surgery	1 (17%)	0	1 (5%)	0.49
•Glaucoma filtering surgery	0	0	11 (52%)	0.01
•Corneal transplantation	1 (17%)	1 (25%)	3 (14%)	0.86

CMV: Cytomegalovirus, HSV: Herpes simplex virus, VZV: Varicella zoster virus, PCR: Polymerase chain reaction

*PCR positive versus PCR negative patients

treatment and did not develop any complications during the 12 months.

Out of 21 HAU patients negative for tested viruses, two (9%) exhibited large mutton fat KPs. Though the clinical manifestations of PCR-negative patients did not differ from the PCR positive group, IOP of PCR-negative HAU patients was often not adequately controlled with medication and required surgical intervention in 11/21 (52%) during the first follow-up year (Table 2).

Iris atrophy was documented in 9/31 (29%) patients (4 positive for CMV, 1 for HSV, and 4 were PCR negative). Diffuse iris atrophy was more frequently seen (n = 6), and a sector iris atrophy was observed in 3 CMV-positive cases, of whom 2 already underwent cataract extraction. Posterior synechiae developed in 3/31 (10%) eyes (1 CMV-positive and 2 PCR-negative cases) and ranged up to 90 degrees.

TABLE 3. Comparison of specific viral infections in patients with hypertensive anterior uveitis in recent studies from Asia.

Author	Year	Number of patients	CMV %	HSV %	VZV %	Other viral agents (%)
Our study	2019	31	19	10	3	N/a
Keorochana N et al.[15]	2019	64	34	6.3	11	1.6 (EBV)
Hsiao Y-T et al.[16]	2019	102	27	8.8	5	1 (EBV)
Miyazaki D et al.[17]	2018	197	18 (AU)	N/a	N/a	N/a
Choi JA et al.[18]	2016	42	29	N/a	N/a	N/a
Chee S-P et al.[19]	2008	105	23	N/a	N/a	N/a

CMV: Cytomegalovirus, HSV: Herpes simplex virus, VZV: Varicella zoster virus, EBV: Epstein Barr virus, AU: Anterior uveitis, N/a: not applicable

Visual Prognosis and Complications

At baseline, 7/31 (22%) patients had visual acuity of less than 0.1. At six months follow-up, 2/31 patients had VA < 0.1 (both due to corneal opacities) and at 12 months, one additional patient developed VA less than 0.1 due to bullous keratopathy. In our series, glaucoma did not cause central vision loss. During the first year of follow-up, 18/31(35%) HAU patients needed at least one surgical intervention (2 cataract extractions, five corneal transplantations, and 11 filtering surgery for glaucoma; Table 2). Eight patients underwent cataract extraction before the referral. Development of cystoid macular edema was not observed.

DISCUSSION

Our study of HAU patients from Thailand shows that one-third of patients were positive in PCR analysis for herpes viruses, most commonly for CMV, but none were found positive for RV, chikungunya, and Zika viruses.

Our results are analogous to previous studies from Asia, which all showed that CMV was the most common agent found by PCR in intraocular fluid samples of HAU patients. The prevalence of CMV in HAU in our series was 19%, which is consistent with previous results from Asia, which varied between 23-34% (Table 3).[15–19] Miyazaki et al. used different inclusion criteria and reported a prevalence of 18% of CMV in anterior uveitis and 35% in patients with endotheliitis [ref].[17] The differences in PCR detection levels might have influenced our somewhat lower prevalence of CMV. We used only 25µl of aqueous humor for DNA extraction and might have had more positive results with a larger volume.

Our findings suggest that chikungunya and Zika viruses do not frequently cause HAU in Thailand. The chronic character of RV-associated uveitis might explain the absence of positive PCR results for RV virus. The previous study from Thailand showed that 24% of intraocular fluid samples of AU patients tested by GWC for RV were found positive, but none exhibited positive PCR result.[11] The low prevalence of positive PCR results for RV was also documented in other areas of the world.[14]

Clinical features in our HAU population are consistent with earlier reports; specifically, HAU was predominantly unilateral and had no gender predilection. The clinical manifestations of PCR positive patients were not distinct for the HAU with negative PCR results. It has been previously suggested that differentiation between specific herpes viruses cannot be based solely on the clinical features. However, corneal involvement was reported to be common in AU associated with HSV and VZV, which was also observed in the present series.[19–21] While most studies do not distinguish between HSV-1 and HSV-2 infection, one remarkable finding in this study was a positive HSV-2 PCR. Although both HSV-1 and HSV-2 can cause ocular infections, HSV-2 is more commonly associated with acute retinal necrosis and congenital infections. Therefore, to find the HSV-2 in a young female with HAU was surprising and indicated that HSV2 might also cause anterior uveitis only.

In our series, none of the PCR-positive patients required glaucoma surgery during the first year of

follow-up. In contrast, more than half of patients with negative PCR results developed uncontrolled IOP despite the maximal medication and required glaucoma surgery during the first year after the presentation. It is feasible that the identified viral causes of uveitis and the subsequent antiviral treatment might have positively influenced the low need for glaucoma surgery. This observation is supported by a study from Hwang et al.,[22] who reported on well-controlled IOP in CMV positive HAU patients treated with intravitreal ganciclovir. However, Su et al. reported that 37% of their CMV-positive HAU developed uncontrolled IOP in the late stages and implied that the need for glaucoma surgery in CMV HAU develops after more than five years.[23]

Our study has the limitations typical for all retrospective studies. The investigations were not performed at the previously determined intervals, and the detailed clinical observations of iris atrophy and subtle corneal changes might have been unnoticed or underreported. Besides, our follow-up period was limited. **Like most studies, we included only PCR examinations and did not determine Goldmann-Witmer coefficient (GWC). Since GWC is typically positive in the chronic phase of the disease, it is conceivable that without the GWC determination**, the diagnosis in some patients, especially those presenting in our hospital during the late phase of their uveitis, could be missed. **Lastly, the limited number of PCR-positive cases and the lack of exact data on viral loads precluded meaningful analyses of relationships between the viral loads and specific clinical manifestations such as the development of glaucoma.**

The clinical findings suggesting the viral cause of HAU included mostly unilateral involvement, mild anterior chamber inflammation, small to medium non-granulomatous KPs, some form of iris atrophy (Figures 1 and 2). **The absence of macular edema was also well established. Patients presenting with these clinical features, especially those with ongoing uveitis activity despite the standard treatment with corticosteroid drops, might profit from PCR analysis of aqueous fluid. Ideally, PCR should be combined with GWC determinations.[8] However, GWC determination requires also a serum sample, and the laboratory procedure is complicated and requires additional laboratory investments. One should realize that with PCR examination only, some chronic viral infections could be missed as previously documented for RV.[11]**

In conclusion, we show that PCR examinations for HSV, VZV, and CMV revealed positive results in one-third of patients with HAU while the negative PCR outcomes for RV, chikungunya, and Zika were typical. The initial high IOP in patients with positive PCR results was well controlled, possibly also due to the adequate and early antiviral treatment in addition to IOP lowering medications. A prospective study with more patients and more

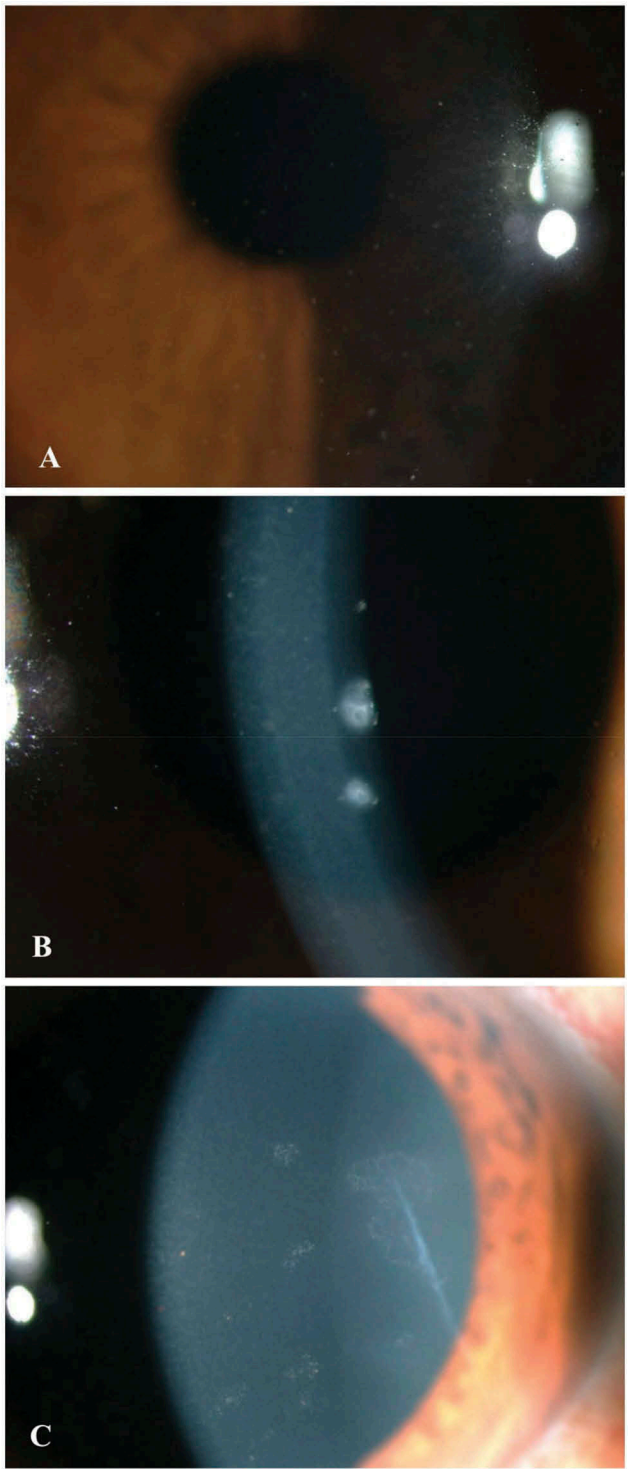

FIGURE 1. Keratic precipitates in viral hypertensive anterior uveitis.(A). Fine keratic precipitates located at Arlt's triangle. (B). Coin-shaped endothelial lesions in cytomegalovirus-associated anterior uveitis. (C). Linear keratic precipitates in cytomegalovirus-associated anterior uveitis

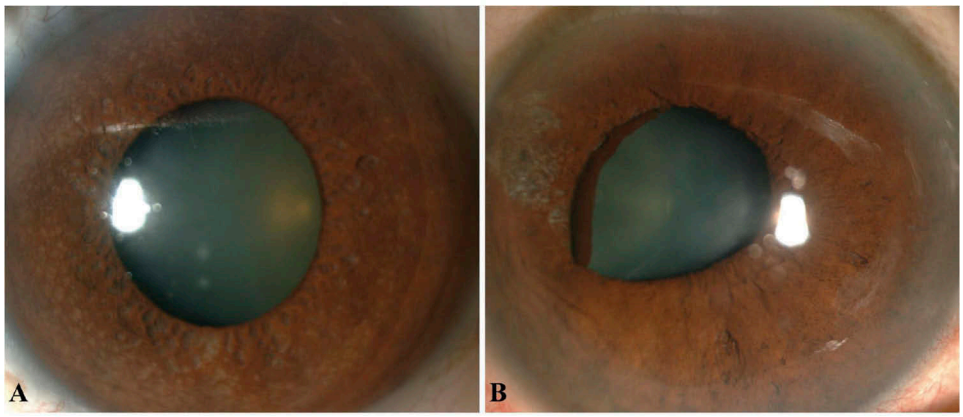

FIGURE 2. Iris atrophy in viral hypertensive anterior uveitis.A). Diffuse iris atrophy in cytomegalovirus-associated hypertensive anterior uveitis. (B). Sector iris atrophy in herpes simplex virus-associated hypertensive anterior uveitis(

extensive intraocular fluid examinations might reveal so far unknown causes of HAU and open new avenues for its treatment.

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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