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REVIEW ARTICLE

Clinical Characteristics of Herpes Simplex Virus Associated Anterior Uveitis

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ABSTRACT

Purpose: The aim of this study is to describe the clinical characteristics of molecularly proven Herpes simplex virus (HSV) anterior uveitis.

Methods: The literature on HSV anterior uveitis whereby the diagnosis was confirmed by polymerase chain reaction (PCR) and or Goldmann–Witmer coefficient in aqueous humor was reviewed. Three studies from Europe and one from Japan could be included.

Results: It was observed that HSV anterior uveitis is mostly an acute unilateral disease mainly occurring in middle-aged people with a predominance in females. The incidence of keratitis in HSV is between 33 and 41%. High intraocular pressure is frequently observed and ranged from 46 to 90%. Sectorial iris atrophy may be absent, especially early in the disease.

Conclusion: The clinical characteristics of HSV anterior uveitis can mimic other viral and non-infectious anterior uveitis entities especially at onset. Aqueous humor analysis for PCR and GWC can be useful in case of suspected viral uveitis.

Keywords: Anterior uveitis, aqueous humor analysis, clinical characteristics, Europe, Herpes simplex virus, Japan

Herpetic anterior uveitis (HAU) is a common cause of infectious uveitis, accounting for 5–10% of all uveitis cases.[1] The diagnosis can be fairly easily confirmed by analyzing anterior chamber fluid applying polymerase chain reaction (PCR) or the Goldmann–Witmer coefficient (GWC). Sensitivity and specificity of PCR for genomic DNA for infectious uveitis were reported to be 91.3% and 98.8%, respectively.[2] However, this technique is not always available. Therefore, it is of value to be able to make a diagnosis based on clinical characteristics. Moreover, a clinical diagnosis allows for timely commencement of directed treatment before the results of the molecular diagnostic tests are known.

The clinical presentations of anterior uveitis caused by Herpes simplex virus (HSV), Herpes zoster virus (HZV), cytomegalovirus (CMV), and rubella virus (RV) are quite similar but some subtle differences may be observed.[3,4]

Anterior uveitis caused by HSV has typically an acute unilateral course, appears often in older patients, is accompanied by conjunctival redness, and may show endotheliitis, medium to large keratic precipitates (KPs) and may be accompanied by increased ocular pressure. Typically for HSV uveitis is focal or sectorial iris atrophy although the difference between segmental and diffuse iris atrophy seems to be correlated with disease duration and possibly different pathological mechanisms.[4,5]

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When present, keratitis can be a valuable sign. However, when keratitis is absent it does not exclude the presence of herpetic uveitis origin.[5]

Since typical signs as keratitis and iris atrophy are not always present at first presentation, we reviewed the clinical characteristics of HSV anterior uveitis in patients confirmed by aqueous humor analysis for PCR or GWC.

METHODS

Literature search was performed in Pubmed for HSV anterior uveitis using aqueous humor analysis for diagnosis. Three studies from Europe fulfilled the criteria.[3,5,6] The European studies included confirmation of diagnosis by PCR as well as the GWC, whereas the Japanese study applied only PCR on ocular fluid.[3,5–7] No studies from the US and South and Central America using aqueous humor analysis in HSV uveitis were found in the literature.

RESULTS

The data from three European studies, an observational study ($n = 39$; from The Netherlands, from Belgium and from Slovenia), another study from Netherlands ($n = 27$), and one study from Italy ($n = 189$), were compared.[3,5,6] Since these three studies included patients with other viral uveitis entities as well, and defined different outcome measures, the exact number of disease characteristics could not always be extrapolated from the data. For instance, keratitis was an exclusion criteria and iris atrophy an inclusion criteria in the study of van de Lelij et al.[5] Also aqueous humor analysis was not performed in all patients from the study of van der Lelij et al. (74%) and Miscchierocchi et al. (20%), whereas it was an inclusion criterion in the study of Wensing et al.[3,5,6] The GWC was slightly more frequently positive for HSV (65–83%) compared to PCR on ocular fluid (50–74%).[3,5] In these studies, sensitivity and specificity for HSV PCR and GWC in aqueous humor was not mentioned.

Demographics showed that HSV was observed in patients of middle age with slightly higher occurrence in females. It had a predominant unilateral presentation with an acute onset of the disease in more than half of the patients (Table 1). Although sectorial atrophy of the iris is considered as pathognomonic for the diagnosis of HAU, it is often not present at disease onset but will develop during the course of the disease. Raised intraocular pressure (IOP) (>30 mmHg) is seen in 46–90% of the patients and is considered to be caused by trabeculitis (Table 2). Patients may present with high pressure (>50 mmHg), which generally rapidly drops after treatment with steroids and anti-glaucoma medication. Keratitis is observed in more than one third of the patients (Table 2). Corneal edema can be due to interstitial keratitis but may also be due to attacks of elevated intra-ocular pressure.[4] Secondary glaucoma developed in 18–30% during the course of the disease.[3–5] Posterior synechiae are seen in half of the patients. Cataract might be seen at onset, may be related to the age of the patient, and the incidence increases during the course of the disease.[3] HAU shows medium to large KPs. Small KP's may be more typical of CMV or Rubella uveitis.[3]

COMPARISON OF CLINICAL CHARACTERISTICS OF JAPANESE PATIENTS WITH HSV-AU, VZV-AU, AND CMV-AU

Before PCR was introduced for the diagnosis of herpes virus-induced anterior uveitis, presence of HSV-anterior uveitis could not be confirmed and there were no case

TABLE 1. General characteristics of Herpes simplex anterior uveitis.

	Japanese patients	European patients		
Characteristics	Takase 2014[4]	Van der Lelij 2000[5]	Wensing 2011[3]	Mischerocchi[6] 2014
Number of patients	8	27**	39	189
Average age at presentation (st. dev., range)	50 (age at disease onset)	39	43	54
Male gender	12.5%	29%	49%	40%
PCR performed	100%	74%*	100%	20%
Positive PCR	100%	60%	74%	-
Positive GWC	ND	80%	65%	ND
Unilateral	100%	100%	97%	95%*
Acute course	62%	–	61%	–
Chronic course	13%	–	39%	–
Average follow-up time (years)	0.21: disease duration from onset to diagnosis	14	2,7	–

HSV: Herpes simplex virus, VZV: Varicela zoster virus, PCR: polymerase chain reaction, NA: not Applicable. *Bonferroni analysis.
*exact number of HAU not provided in study.
**patients with accompanied keratitis were excluded.

TABLE 2. Clinical presentation Herpes simplex virus anterior uveitis.

Clinical presentation	Takase 2014[4]	Lelij 2000[5]	Wensing 2011[3]	Mischerocchi 2014[6]
Conjunctival redness	43%	ND	62%	ND
Corneal edema	25%	often	54%	ND
(previous) keratitis	ND	***	33%	41
KPs* present	100%	ND	76%	ND
Cells ≥2+	Average flare counts:33 photons/msec	ND	54%	ND
Posterior synechiae	25%	58%*	38%	ND
Eye pressure > 30 mmHg	63%	90%*	46%	ND
Glaucoma	ND	ND	18%	31%
Iris atrophy	25%	100%**	ND	ND
Distorted pupil	ND	90%	ND	ND
Cataract (at presentation)	ND	ND	32%	27
Inflammatory cells in vitreous	13%	ND	43%	10/23 (43%)

ND: not done.
*exact number HAU not provided in study.
** inclusion criteria.
*** exclusion criteria.

reports of HSV-anterior uveitis except for cases with keratouveitis, i.e., anterior uveitis associated with keratitis causes by HSV where keratitis is the major inflammatory lesion and anterior uveitis is a secondary lesion. However, investigations of aqueous humor by PCR opened a new era of uveitis and revealed the presence of a group of patients who have anterior uveitis without keratitis and are positive for the genomic DNA of HSV, but not other human herpes viruses.[7] In fact, there were no case reports of HSV-anterior uveitis before the era of PCR-guided diagnosis of anterior uveitis in Japan. Takase et al. reported eight cases of HSV-AU and compared clinical presentations of patients with HSV-AU (n = 8), VZV-AU (n = 20), and CMV-AU (n = 18) at Tokyo Medical and Dental University and Miyata Eye Hospital. The diagnosis was made based on the detection of genomic DNA of HSV, VZV, or CMV in the aqueous humor by multiplex qualitative PCR and by real-time quantitative PCR.[4]

The following clinical characteristics of Japanese patients with HSV-AU as compared with VZV-AU and CMV-AU are based on a study reported by Takase et al.[4]

Demography of Japanese Patients with Herpetic Anterior Uveitis

Male/female ratio (% of men) was 1/7 (12.5%) in patients with HSV-AU, 11/9 (55.0%) in VZV-AU, and 14/4 (77.8%) in CMV-AU. The mean age at disease onset was 50 years in patients with HSV-AU, 61 years in VZV-AU, and 54 years in CMV-AU. All patients had unilateral anterior uveitis (Table 1).

Systemic Condition

Essentially all patients were immunocompetent. Immunodeficiency was not seen in patients with HSV-AU and CMV-AU and in one patient (5%) with VZV-AU who had been treated with long-term corticosteroids and cyclophosphamide due to ANCA-associated nephritis.

Chief Complaints at Initial Presentation

Nearly half of patients with HSV-AU had conjunctival redness (43%), ocular pain (57%), and blurring of vision (57%), whereas none of patients with CMV-AU had conjunctival redness or ocular pain. Patients with VZV-AU have less ocular pain (28%) and blurring vision (22%). None of patients with HSV-AU and CMV-AU had dermal manifestations (blisters or dermal pain without blisters) at uveitis onset, while one quarter of patients with VZV-AU had dermal manifestations (Table 2).

Ocular Findings

There are no significant differences in the mean visual acuity at presentation among the three herpetic AU: −0.315 logMAR in HSV-AU, −0.412 logMAR in VZV-AU, and −0.189 logMAR in CMV-AU. As for corneal manifestations at uveitis onset, dendritic or pseudodendritic keratitis was seen in only one patient with VZV-AU (1/20, 5%), but not in patients with HSV-AU (0/8) and CMV-AU (0/18). Coin-shaped lesions were seen in patients with CMV-AU (2/18, 11%), but not in patients with HSV-AU (0%) and VZV-AU (0%). Corneal endotheliitis was seen in three types of herpetic AU (25% in HSV-AU, 20% in VZV-AU, 6% in CMV-AU). The mean corneal endothelial cell density (CECD) was 2743 cells/mm^2 in eyes with HSV-AU and 2362 cells/mm^2 in eyes with VZV-AU, but 1599 cells/mm^2 in eyes with CMV-AU, and the density was significantly lower

in CMV-AU. As for the intraocular inflammation, medium size KPs were seen in 100% of HSV-AU and 85% of VZV-AU, but only in 39% of CMV-AU, whereas fine to small size KPs were seen in 44% of CMV-AU and 10% in VZV-AU and none in HSV-AU. Intensity of inflammation in the anterior chamber measured by a laser flare meter was highest in VZV-AU (97 photons/msec) and lowest in CMV-AU (17 photons/msec) and intermediate in HSV-AU (33 photons/msec). Fibrin formation in the anterior chamber was seen in 13% of HSV-AU, 5% of VZV-AU, but none of CMV-AU. Posterior iris synechiae were seen in 25% of HSV-AU, 30% of VZV-AU but only 5% of CMV-AU. Nodule formation at trabecular meshwork by gonioscopic examination was detected in 13% of HSV-AU, 15% of VZV-AU and 6% of CMV-AU, while peripheral anterior synechiae were seen in 13% of HSV-AU, 15% of VZV-AU and 39% of CMV-AU. Iris atrophy was equally seen in eyes with the three herpetic AU: 25% of HSV-AU, 45% of VZV-AU and 33% of CMV-AU.

The average IOP at the inflammatory phase was 30 (range 18–42) mmHg in eyes with HSV-AU, 35 (range 17–60) mmHg in eyes with VZV-AU, and 41 (range 14–70) mmHg in eyes with CMV-AU. The average of maximum IOP was highest in CMV-AU and lowest in HSV-AU among the three types of herpetic AU. The incidence of an IOP>25 mmHg was 63% in eyes with HSV-AU, 85% in eyes with VZV-AU and 78% in eyes with CMV-AU.

Viral Loads by Real-Time Quantitative PCR

Viral loads in the aqueous humor measured by real-time PCR were highest in VZV-AU and lowest in CMV-AU: 1.0 x 10^6 copies/mL in HSV-AU, 1.0 x 10^8 copies/mL in VZV-AU, and 1.1 x 10^5 copies/mL in CMV-AU. The viral loads were significantly correlated with the aqueous flare counts in the eyes with VZV-AU, but the correlation was not significant in eyes with HSV-AU or CMV-AU.

Treatment

As for the therapies, after PCR-guided definite diagnosis was made, oral valacyclovir, or intravenous acyclovir was given to all patients with HSV-AU and 95% of VZV-AU whereas oral valgancyclovir was given to 83% of patients with CMV-AU.

DISCUSSION

In this review, the clinical presentation of HAU was compared using studies from Europe and Japan. We focused on clinical characteristics of HSV uveitis, confirmed by aqueous humor analysis with PCR and/or GWC. Due to the recent availability of confirmation test for HSV PCR in aqueous humor, the number of proven HSV uveitis in Japan was small.[6] In the study from Italy, aqueous humor analysis was only performed in the minority of the patients.[6]

However, based on these studies, we observed that HAU is an acute unilateral disease mainly occurring in middle-aged people with predominance in females. However, several cases of bilateral HAU have been reported.[8] HAU can occur in the absence of keratitis.[5,6] The incidence of keratitis in HSV seems to be between 33–41%.[3,6] Corneal involvement can include active keratitis, endotheliitis, old scarring or corneal edema due to inflammation or high IOP. High IOP is frequently observed and ranged from 46 to 90%.[3,5,6] This rise in pressure seems to be transient since only a minority of these patients progressed to secondary glaucoma (18–31%). Since IOP can rise to high levels, the eye pressure should be carefully monitored in patients with HSV uveitis. For future studies, it would be interesting to include corneal anesthesia in the outcome measures which was not mentioned in the studies reviewed in this paper.

Sectorial iris atrophy is considered to be pathognomonic for viral anterior uveitis, especially for HSV and VZV. However, early in the disease, iris atrophy can be absent and therefore, it is only a useful diagnostic criteria in recurrent or chronic disease. Van der Lelij et al. described that a distorted pupil can be a sign of spiraling of the iris or iris atrophy.[5] Only a minority of the patients with a very wide pupil had severe photophobia in quiescent episodes.[3,5]

Other characteristics are conjunctival redness, moderate anterior chamber inflammation (>2+ cells in anterior chamber), posterior synechiae and vitreous cells.[3,6,7]

Many of the above mentioned clinical symptoms occur in non-infectious anterior uveitis as well. Therefore it is important that patients are carefully questioned for the onset of disease, general health and previous diseases. Additionally, patients should be screened for non-infectious anterior uveitis as well, such as HLA-B27 and sarcoidosis. We conclude that HSV anterior uveitis is mostly an acute unilateral disease mainly occurring in middle- aged people that may resemble other viral uveitis entities. Additionally, aqueous humor analysis for PCR and GWC is useful in case of suspected viral uveitis or undetermined cases, especially when refractory to conventional 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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