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Review Article

Herpes Virus Associated Anterior Uveitis

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ABSTRACT

The treatment and prognosis of infectious etiologies differ from non-infectious; hence identification of an infectious cause is of crucial importance. Viral anterior uveitis is mainly caused by Herpes simplex and varicella-zoster viruses. Due to their variable and overlapping ocular manifestations, viral anterior uveitis can pose a diagnostic dilemma. Hence, for confirmation of etiology, analysis of quantitative polymerase chain reaction or Goldmann-Witmer coefficient from aqueous humour samples are preferred which also determine the disease severity thus impact the treatment. A clear differential between alpha and beta-type herpes viruses is essential due to their fulminant clinical course and persistence in ocular tissues which help in guiding acute and long-term treatment.

Keywords: Unilateral Anterior uveitis; Aqueous humor analysis; Herpes virus; Varicella-zoster virus; Acyclovir.

INTRODUCTION

Uveitis is characterized by wide-ranging variations in prevalence, etiology, clinical presentations and treatment outcomes which are influenced by geographical location, racial and genetic factors, socio-economic conditions and availability of diagnosis and treatment resources [1]. Viral Anterior Uveitis (VAU) is the most common form of infectious disease accounting for more than 10% of all cases of anterior uveitis. Herpes Simplex Virus (HSV), Varicella-Zoster Virus (VZV), Cytomegalovirus (CMV) and Rubella Virus (RV) are most common among viral etiologies [2,3] of which herpetic anterior uveitis most common accounting for 5–10% of all uveitis cases in the western world and 0.9–8.3% of all infectious uveitis in India [4,5]. Factors responsible for ocular damage include cytopathology induced by virus and subsequent inflammatory response. Glaucoma can develop in approximately 10%–40% of VAU patients [6]. Due to their variable and overlapping ocular manifestations, VAU can pose a diagnostic dilemma. The severity and outcome of VAU depend on type of virus, clinical characteristics of the disease, immune status, and genetic constitution of individual. There is risk of reactivation due to common sharing of persistent viral genome in infected tissues. Asymptomatic virus shedding occurs with variable frequencies depending on specific virus and host factors in immunocompetent individuals. Clear differentiation should be done between distinct genotypes of each of these viruses as these may have clinical implications and reinfection with different strains may lead to resistance to commonly used antivirals [7,8].

LITERATURE SURVEY

Clinical features

Herpes simplex: Herpetic Anterior Uveitis (HAU) is most common cause of infectious uveitis, accounting for 5-10% of all uveitis cases. HSV anterior uveitis and keratouveitis is commonly caused by type1 HSV and typically affects both genders in their 4th-5th decades of life. It lies latent within sensory ganglion of fifth cranial nerve and is transported down the axon after reactivation, manifesting in periocular skin, cornea or as intraocular inflammation causing recurrence. History of blisters or recurrent fever may be present. The incidence of corneal involvement in HSV varies from 33–41% and can present as active epithelial, stromal, interstitial, disciform keratitis, old corneal scar, endothelitis. HSV dendritic ulcers are branching with terminal bulbs. The fluorescein and rose Bengal stain ulcer base and borders respectively [9-11]. Anterior uveitis caused by HSV has typically an acute unilateral course, accompanied by increased ocular pressure. It commonly occurs with active or prior keratitis and the severity of the uveitis generally correlates with severity of the keratitis of which chronic stromal or

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endothelial disease have more profound association. However, absence of keratitis does not exclude HSV AU as dendrites may present less frequently during recurrence [12]. Moderate anterior chamber activity is generally seen with either non-granulomatous or granulomatous Keratic Precipitates (KPs)(Figure 1). During acute inflammation, sectoral iridoplegia and localized flattening of the affected pupil border leads to poor reaction to light. Once acute attack subsides, destruction of the pigment epithelium results in patchy or sectoral iris atrophy that trans illuminates in up to 50% of cases [13,14]. Severe inflammation may lead to transient hyphema, hypopyon, posterior synechiae (38%), and vitritis (43%). Although the diagnosis of anterior herpetic uveitis is usually straightforward in the setting of dermatitis or dendritic keratitis, it may be quite challenging in the absence of these lesions.

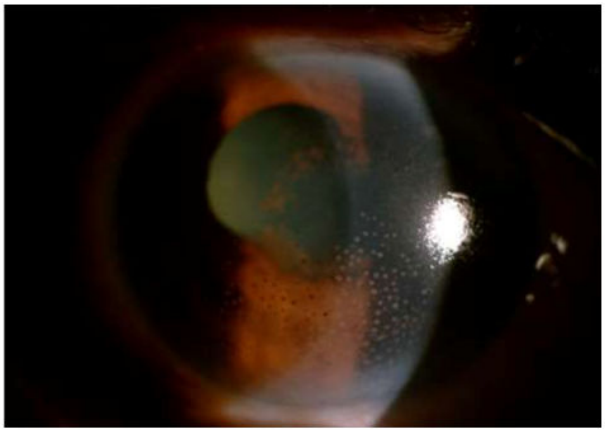

Figure 1: Fundus Slit lamp photograph showing active granulomatous kps in Herpes AU.

Varicella zoster virus: VZV lies in neural sensory ganglia as dormant state usually in childhood following primary infection and reactivation seen during 6th or 7th decade of life when VZV specific immunity wanes [15,16]. VZV AU occurs in 40–60% of Herpes Zoster Ophthalmicus (HZO) patients. After 2 weeks following the eruption of vesicles along distribution of ophthalmic branch of trigeminal nerve, acute hypertensive anterior uveitis with either non-granulomatous or granulomatous KPs may be seen. The inflammation due to VZV is generally more severe than in HSV AU because it invades the root of iris epithelium leading to occlusive vasculitis. In 25% of cases corneal involvement has been reported in the form of profound reduced corneal sensation, limbal keratitis, nummular keratitis, ring infiltrates and pseudo dendrites. Posterior synechiae (40%), secondary glaucoma (15–43%) and vitritis (83%) may be associated in VZV AU [17,18]. The severity of iris atrophy and pupil distortion is closely associated with aqueous viral load. Differentiation of HSV from VZV keratitis can be done by pattern of dendritic keratitis. While HSV dendrites are usually branching with terminal end bulbs staining with fluorescein at base and rose Bengal at border. VZV pseudo-dendrites are usually broader, polymorphous with less regular branching that stain centrally with rose Bengal and fluorescein pooling along edge. However, in Fuchs' uveitis syndrome, the iris atrophy tends to be stromal and concentrated over the iris sphincter rather than full thickness, the trans-illumination defects tend to be radial rather than sectoral, and the elevated intraocular pressure due to cumulative damage to the trabecular meshwork rather than a transient trabeculitis and thus, unresponsive to topic corticosteroid and antiviral therapy. While ocular inflammation follows a uniphasic course in most patients, chronic or recurrent course may also be seen [19,20]. Diagnosis of VZV associated uveitis is often clinical based upon either history or presence of HZO on affected side or in the absence of dermatitis, presence of unilateral inflammation with suggestive clinical feature like corneal involvement; large, often pigmented kps or iris nodules; patchy or sectoral iris atrophy; and/or inflammatory ocular hypertension [21].

Cytomegalovirus: CMV is the most common congenital viral infection seen in neonates and immunocompromised patients. Anterior segment involvement is less frequent and usually mild in immunocompromised patients. However, in immunocompetent patients, CMV has been associated with corneal endothelitis as well as anterior uveitis with ocular hypertension [22,23]. CMV may remain latent in ocular tissues like iris and ciliary body. An intraocular immunocompromised state leading to impaired immunity especially the virus specific T cell response may trigger CMV reactivation. CMV AU may present as 'Acute Recurrent AU' [CMV associated PSS (Posner Schlossman Syndrome)] associated with ocular hypertension and typically presents in middle-aged patients. It is characterized by recurrent episodes of mild iritis, diffuse corneal edema, few fine kps and elevated IOP. The IOP is normal between attacks and open anterior chamber angle. Iris atrophy is present in 15% of cases [24]. Chronic AU [CMV associated FUS (Fuchs Uveitic Syndrome)] is seen at older ages in contrast to rubella-associated FUS, The minimal inflammation with diffuse, fine and stellate keratic precipitates fairly evenly distributed over endothelium may be noted. Mild anterior chamber activity with diffuse iris atrophy (60%) is present [25]. Nodular endothelial lesions which are white medium sized with a surrounding translucent halo and may become pigmented over time are more common in chronic CMV AU. It is unilateral mostly and bilateral in 7% cases [26]. A linear pattern KPs also may be noted just above the limbus inferiorly. Coin shaped lesions with small sized KPs in ring pattern distribution are pathognomonic of CMV and seen in both acute and chronic infection [27].The pupil is usually round and posterior synechiae are notably absent. Glaucomatous optic neuropathy in 36% and posterior sub-capsular cataract in 75% of cases are noted. Patches of focal endotheliitis and vitritis may be also observed. The different clinical manifestations between HSV, VZV and CMV have been summarized in Table 1.

Variables	Herpes simplex	Varicella zoster	Acute CMV	Chronic CMV
Age	40-50 year	50-70 year	30-50 year	41-70 year
Sex	Equal	Equal	Males (65%)	Males (80%)
Race	All	All	Predominantly Asian	Predominantly Asian
Laterality	Mostly unilateral	Unilateral	Unilateral	Mostly unilateral

Course	Acute, Recurrent	Acute, Recurrent	Acute, Recurrent	Chronic
Dermal involvement	Crop of vesicles	Dermatome blister along CN V1	None	None
Conjunctival injection	Moderate to severe	Moderate to severe	Mild	Mild
Corneal sensation	Reduced	Reduced	Intact	Intact
Corneal scar	Present (33%)	Present (25%)	Rare	
Endothelitis	May be present	May be present	May be present	May be present, nodular endothelial lesion
KPs	Small to medium, white may be pigmented	Small to medium, white may be pigmented	Medium to large, white or grey	Fine and stellate, white or grey ,may be pigmented
Endothelial cell count	Normal	Normal	Reduced	Reduced
Anterior chamber inflammation	Moderate to severe	Severe	Mild	Mild
Iris atrophy	Sectoral or patchy	Sectoral, rarely massive iris atrophy	Mostly absent, rarely diffuse stromal	Diffuse stromal
Posterior synechia	May be present	May be present	Absent	Absent
Pupil shape	May be irregular	May be irregular	Round	Round
Intraocular pressure	Elevated (38%-90%)	Elevated (40%-75%)	Elevated (100%)	Elevated (69%)
Cataract	Present (28%-35%)	Present (27%-30%)	23%	75%
Glaucoma	Present (18%-54%)	Present (30%-40%)	23%	36%
Vitritis	43%	83%	0%	9%
Recurrence	15%-65%	13%-51%	100%	NA

Table 1: Clinical manifestations of HSV, VZV and CMV.

Investigation and diagnosis

Although viral serology may be helpful in excluding viral etiology in case of negative, the presence of Immunoglobulin G (IgG) does not help in confirming the diagnosis due to prior exposure to these viruses. Concurrent active systemic infection is indicated by positive IgM but it does not prove ocular infection. Viral cultures of aqueous humour samples are difficult, time-consuming, and not sensitive and are therefore not commonly done.

Anterior chamber tap: As clinical features may not always be sufficient to differentiate between the various viral AU, aqueous humour analysis is a useful to determine etiology and disease severity and sample sent for Polymerase Chain Reaction (PCR), Goldmann–Witmer coefficient (GWC) analysis, metagenome sequencing [28,29].

Polymerase chain reaction: PCR based analysis of aqueous humour samples can detect even minimal amount of viral DNA thus enabling rapid confirmation of diagnosis (Figure 2). PCR tends to be positive during early reactivation with high viral DNA. The aqueous tap should be done ideally during IOP spike prior to initiating therapy especially while suspecting CMV [30]. A negative PCR can result from low intraocular viral load, limited sample volume; presence of inhibitory compounds in sample or microorganism polymorphism, hence does not exclude a viral etiology. PCR may give false positive result by detecting DNA from latent viruses in leukocytes which may be present in the anterior chamber during inflammation. A qualitative multiplex PCR can be done for screening viruses. Subsequent real-time PCR identify the causative virus, quantify the viral load as a marker of severity of the infection and monitor response to therapy and drug resistance [31].

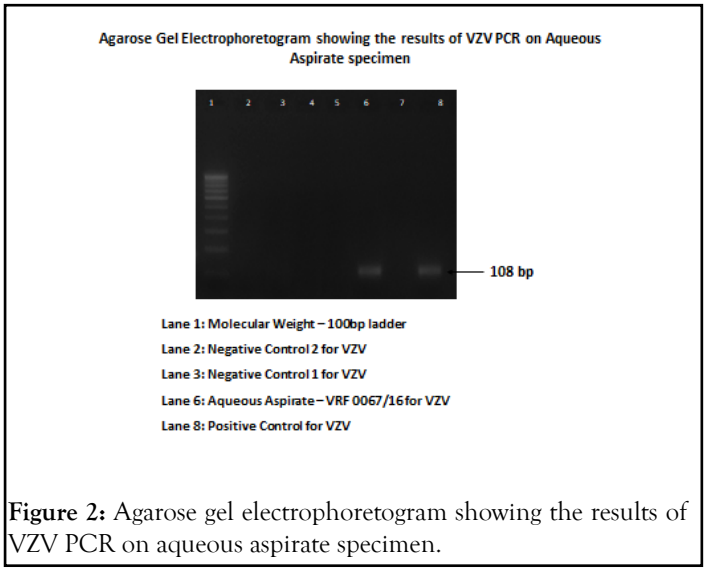

Figure 2: Agarose gel electrophoretogram showing the results of VZV PCR on aqueous aspirate specimen.

Goldmann-Witmer coefficient analysis: The GWC calculation helps to determine pathogen-specific intraocular antibody production and may take up to 2 weeks to become positive in the acute phase but remains positive for longer period. Although, it is less specific than PCR due to possible cross-reactivity of antibodies, but more useful especially when patients present later during the acute episode when DNA levels are low.

As the diagnostic utility depends on time of aqueous sampling, patient's immune status, chronicity of infection, performing both the PCR and GWC analysis in parallel increases the diagnostic accuracy.

Others: Anterior segment imaging specular microscopy demonstrate lowered Endothelial Cell Counts (ECC) in CMV AU. The extent of endothelial cell loss also correlates with viral disease burden. Anterior segment optical coherence tomography can demonstrate nodular endothelial lesions and coin-shaped lesions seen as an irregularly thickened, highly reflective endothelial cell layer [32]. Confocal microscopy is non-invasive and demonstrate presence of "owl eye cells" (large endothelial cells containing nuclei with a high reflection area surrounded by a halo of low reflection within the cornea) and allows the monitoring of treatment response [33]. Newer investigations like metagenomic deep sequencing can detect fungi, parasites, and DNA and RNA viruses in as little as 20 μL of intraocular fluid samples in a single assay and are promising in their potential to improve the diagnostic utility of infectious uveitis [34].

Management

Herpes simplex: Prompt use of therapeutic doses of antiviral therapy may shorten duration of anterior uveitis and maintenance therapy is effective in decreasing recurrence. Oral acyclovir 400 mg five times daily for 4 weeks with topical corticosteroids, cycloplegics is preferred. The Herpetic Eye Disease Study (HEDS), a multicenter, prospective, randomized trial demonstrated that oral acyclovir decreases the recurrence rate of herpetic stromal disease and this beneficial prophylactic effect depends on continued use of suppressive doses of an oral antiviral agent [35]. The HEDS collaborators also examined the effect of oral acyclovir on the duration and number of recurrences of anterior uveitis in patients with prior or concurrent herpetic keratitis [36]. Oral acyclovir has been shown to reach therapeutic levels in both tears and aqueous humour, virtually eliminating the need for a topical antiviral agent, even in patients with active corneal disease. Valacyclovir (a prodrug with better bioavailability) 500 mg three times a day for 4 weeks followed by 500 mg twice a day for maintenance may also be used [37]. Valacyclovir has been reported to cause the thrombocytopenic purpura/hemolytic uremic syndrome in HIV patients and should be avoided in this. Most topical antiviral agents fail to reach therapeutic levels in the aqueous humour and also can be toxic to both corneal and conjunctival epithelium with prolonged use. However, topical therapy including acyclovir ointment does not prevent viral reactivation in sensory ganglia. For these reasons, most specialists recommend using oral antivirals in patients with active anterior chamber inflammation and consider long-term oral therapy in patients with HSV or VZV-associated eye disease that is either recurrent or difficult to control. Some patients may even require a very low dose of topical corticosteroid indefinitely to maintain long-term control of their inflammation. In eyes with raised IOP, anti-glaucoma medications are given topically. Severe IOP elevation may require oral carbonic anhydrase inhibitors and filtration surgery. Prophylactic oral antiviral therapy is found to be useful in viral uveitic eye while preparing for cataract surgery.

Varicella zoster virus: Acyclovir 800 mg five times daily for 10 days given within 72 hours of onset of skin lesions reduces incidence and severity of episcleritis, keratitis, and anterior uveitis in acute condition. However, for chronic VZV anterior uveitis treatment duration should be for at least 4 weeks or longer, especially in immunocompromised patient [38]. Valacyclovir 1 gm thrice daily or famciclovir 500 mg three times daily may be used as alternatives. Topical steroids must be tapered very slowly to avoid rebound inflammation [39]. VZV uveitis should be treated without delay and the therapy should be continued as long as the condition remains active. Thereafter, prophylactic course of thrice weekly dose of 500 mg or 500 mg daily should be continued for 3-12 months. These drugs may cause acute renal failure and should be monitored carefully.

Cytomegalovirus: The acute recurrent phenotype of CMV AU frequently exhibits quiescence without antiviral therapy. CMV AU responds to oral valganciclovir, ganciclovir, and foscarnet and may require long term antiviral therapy to reduce recurrence risk. The induction regimen of oral valganciclovir is 900 mg twice daily for 3 weeks followed by maintenance regimen of 450 mg twice daily for a minimum of 4 weeks [40]. Regular laboratory monitoring for renal and hepatic toxicity and the cost of treatment makes it less feasible as long term therapy in developing countries. Intravitreal ganciclovir has less systemic toxicity but high recurrence rate. Topical ganciclovir 0.15% five times daily is an alternative form. Topical corticosteroids may be useful in reducing ocular inflammation. Ganciclovir in eye drop and gel form have shown good results in CMV corneal endothelitis and AU. These are well tolerated with minimal toxicity, less expensive and do not require laboratory monitoring, hence may be more viable option for long term antiviral therapy. Patients with uncontrolled intraocular pressure may require filtration surgery. The Systemic and Topical Control of CMV Anterior Uveitis Treatment Outcomes (STACCATO) is an ongoing randomized trial for comparing efficacy of oral valganciclovir and 2% topical ganciclovir which may provide effective routes of antiviral therapy further in CMV AU [41]. In chronic CMV anterior uveitis with a moderately high viral aqueous load, treatment may be initiated with topical ganciclovir with anti-inflammatory ± antiglaucoma treatment. In case of poor response, especially if persistently elevated IOP, switchover from topical to systemic antiviral therapy should be considered. Some author may prefer intravitreal ganciclovir 2 mg/0.05–0.1 ml weekly for 3 months with or without adjunctive oral valganciclovir.

CONCLUSION

Viral etiology should be highly suspected in any case of hypertensive AU or iris atrophy. Herpes virus families are frequent, underdiagnosed cause of acute and chronic intraocular inflammation. AU caused by various herpes viruses' shares common clinical features with distinct characteristic findings. However, due to variable and overlapping clinical manifestations, quantitative PCR or GWC assay of aqueous humour samples are preferred for confirming the etiology as this is important for planning therapy. Varying disease characteristics

depending upon viral type and their persistence in ocular tissues lead to prompt, specific, and often long term treatment. Reactivation of the disease may ultimately lead to loss of vision, hence prophylactic treatment against recurrences should be considered as a matter of course in all cases. Glaucoma is most common sight threatening complication of Viral AU. Newer diagnostic techniques will offer opportunities to identify more viruses that were previously idiopathic.

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