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Acute Retinal Necrosis - Current Perspectives

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ABSTRACT

Acute retinal necrosis (ARN) is a rare infectious viral uveitis syndrome that may result in visually devastating consequences if not diagnosed and treated timely. The most common etiology involved is varicella zoster virus followed by herpes simplex virus. Over past several decades, initial treatment regimens have shifted from intravenous antivirals requiring hospital admission to oral antivirals with intravitreal antivirals for immediate local control. The true incidence of ARN is not known. Polymerase chain reaction testing from aqueous sample provides a rapid and sensitive method of identifying the viral etiology but one should not delay treatment while awaiting PCR results. Due to its rarity and lack of large-scale prospective research trials, still debate continues over recommended practice guidelines for an ideal treatment protocol. Further studies are needed to refine disease protocols and improve outcomes for this challenging infectious disease.

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Introduction

Acute retinal necrosis (ARN) is a rare infectious viral uveitis syndrome manifesting as acute panuveitis with retinal periarteritis which progress to diffuse necrotizing retinitis leading to substantial morbidity and poor visual outcome if not diagnosed and treated timely. It was first described by Urayama and colleague in 1971, but more than a decade later its herpetic aetiology was discovered and antiviral therapy became the mainstay of treatment [1-3]. There is no prediction for either gender or age. The most common viral etiology is Varicella zoster virus (VZV) followed by herpes simplex viruses (HSV-1 and HSV-2). Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) have also been implicated less frequently [4,5].

The surveys in the UK estimated an incidence of 1 case per 1.6 to 2.0 million population per year [6]. A genetic association has been seen with HLA-DQw7 antigen and HLA-Bw62 suggesting its possible immune predisposition [7]. Retinal detachment is the most common cause of vision loss which occurs in 20-73% of treated eyes according to most recent studies [8,9]. Other complications may include chronic vitritis, cystoid macular edema, epiretinal membrane, macular ischemia and optic neuropathy [10].

Additional morbidity and mortality may be associated with central nervous system or contralateral eye involvement. Bilateral ARN occurs in up to 70% of untreated patients [11]. Contralateral involvement usually varies from months to years later [12]. Long-term maintenance therapy is essential to prevent disease recurrence or contralateral eye involvement keeping multiple factors in mind like functional status of the affected eye, renal status of patient. Its rarity precludes the conduct of large randomized clinical trials. Hence, clinical management largely has been guided by case reports and retrospective studies.

Clinical features

Acute retinal necrosis is a rapidly progressive disease having potential for significant ocular morbidity if not diagnosed and treated accurately. It commonly presents as acute panuveitis syndrome involving multiple ocular tissues. During early course of disease, Anterior segment findings often predominate [13]. The disease may begin as unilateral disease and may affect both eyes in most cases. Most patients complain of pain, redness, photophobia, floaters and decreased vision. Examination will reveal unilateral anterior uveitis with or without granulomatous keratic precipitates in early phase.

The sclera and adjacent structures may involve secondary to inflammation [14,15]. With disease progression and viral cellular immunity stimulation, dense vitritis may develop. Patients may complain of worsening of floaters and visual acuity due to vitreous opacification. Fundus examination may reveal multiple focal, well-demarcated areas of peripheral retinal whitening corresponding to active retinal necrosis which progress circumferentially to involve the posterior pole if not treated timely [Figure1]. Acute vasculitis may be present in the form of perivascular hemorrhages, sheathing and obliteration of arterioles. 86% of patients develop retinal breaks in peripheral necrotic lesions. It is often complicated

by secondary retinal detachment leading to most common cause for visual loss.

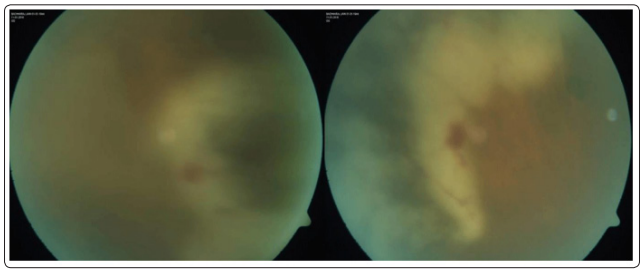

Figure 1: Fundus photograph showing multiple foci of confluent retinal necrosis with discrete borders in the peripheral retina with vitreous haze in both eyes

Other complications include cystoid macular edema, optic atrophy, macular hole and epiretinal membrane [16]. The morbidity of ARN increases with involvement of central nervous system, such as encephalitis or meningitis, and contralateral eye. Bilateral disease either simultaneous or sequential, occurs in up to 70% of untreated and 90% of immunocompromised patients [17-19]. Factors responsible for poor visual prognosis and higher incidence of retinal detachment include poor visual acuity at time of presentation, delay in diagnosis or treatment, increased retinitis area involvement and zone one retinal involvement [20-22].

Diagnosis

The diagnosis of ARN is mainly based on clinical examination, but under diagnosis or misdiagnosis is major concern, because delay in diagnosis often leads to poor visual outcomes. The use of serum and intraocular fluid antibody testing, viral culture, retinal biopsy and immunocytochemistry have been limited by their poor sensitivity or specificity [23]. Polymerase chain reaction is a method used to identify viral DNA from aqueous or vitreous samples through enzymatic amplification of nucleic acids using DNA polymerase and specific primers [Figure 2].

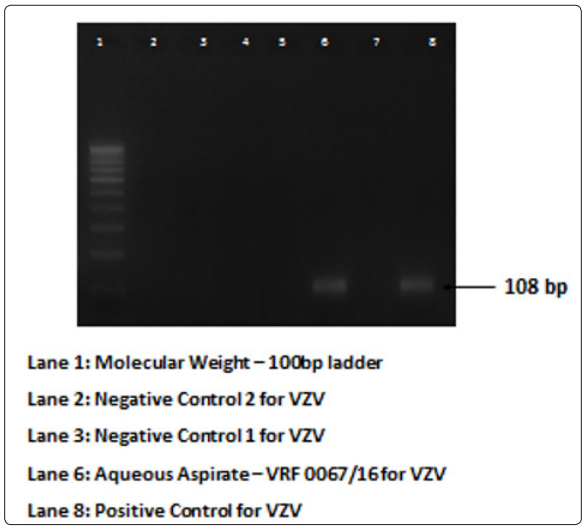

Figure 2: Agarose Gel Electrophoretogram showing the results of VZV PCR on Aqueous Aspirate specimen

PCR of ocular samples for HSV and VZV has reported sensitivity between 79% and 100% in clinically defined ARN cases [24,25]. One should not wait for results while starting treatment. A negative PCR test should alert the clinician to consider for other diagnosis or retesting sample in case of false negative suspicion. Quantitative PCR testing helps in identifying specific virus, assist in treatment and to follow intraocular DNA levels during treatment or recalcitrant therapy, prognosis. High number of DNA copies have been shown association with worse visual acuity, more extensive retinitis and development of retinal detachment [26].

Other Investigations

Although not diagnostic, fluorescein angiography provide details not appreciated on funduscopy. however, is often limited due to overlying vitritis. It may demonstrate signs of occlusive arteritis and areas of capillary nonperfusion. Choroidal vasculature may demonstrate areas of early hypofluorescence and late staining due to ischemia induced inflammatory changes. Diffuse leakage from retinal vessels and hyperfluorescence of the optic nerve may indicate active vasculitis and optic nerve involvement respectively. B-scan ultrasonography may be a useful modality for assessing onset of retinal detachment, especially when visibility is limited by vitritis. Viral meningoencephalitis has been also reported. Patients presenting with signs of neurological disease may require further investigation as appropriate. Laboratory test should include complete blood count, liver and renal function panel prior to initiation of antiviral therapy, drug toxicity monitoring and subsequent dosing considerations particularly in renal failure patient. Other infectious etiologies need to be ruled out like tuberculosis, syphilis and HIV test.

Management

The main goal of therapy are to inhibit viral replication and halt disease progression in the affected eye and prevent contralateral involvement. Advances in technology have allowed for the rapid identification of responsible viruses. Treatment response is determined by various parameters including visual outcomes, time to regression of retinitis, fellow eye involvement and incidence of retinal detachment.

Systemic Therapy

The most frequently reported initial treatment of ARN includes intravenous acyclovir or oral valacyclovir. Other treatments include oral famciclovir, valganciclovir and intravenous foscarnet or ganciclovir. Acyclovir is a purine nucleoside analog that inhibits viral DNA synthesis. Due to this, acyclovir is highly specific for herpes infected cells. Valacyclovir is an oral prodrug that is converted to acyclovir having higher bioavailability of 54–60%. Famciclovir is also oral prodrug that is converted to penciclovir in the liver having bioavailability of 77%. Foscarnet selectively inhibits pyrophosphate binding sites on viral DNA polymerases not affecting human DNA polymerases. Foscarnet is an effective alternative treatment in acyclovir-resistant HSV strains.

Ganciclovir is an inhibitor of viral DNA polymerase that acts against both CMV and HSV. It can be administered by intravenous, oral or intravitreal route. Immunocompromised patients taking valacyclovir are at higher risk for nephrotoxicity and thrombocytopenia and need to be monitored carefully [Table1]. showed that paraenteral acyclovir followed by oral acyclovir significantly decreased fellow eye involvement and was more likely to occur in the first 14 weeks after the initial infection [11].

Table 1

Drug	Route of administration	Adverse effects
Acyclovir	15 mg/kg/day divided every 8 h IV for 7-14 days, followed by 800 mg five times daily po for 3–4 months	Common: GI symptoms, rash, headache Uncommon: renal/CNS toxicity
Valacyclovir	1000–2000 mg po q8 h	Nephrotoxicity and thrombocytopenia in immunocompromised patients
Famciclovir	500 mg po q8 h	Common: headache, GI symptoms, rash
Ganciclovir	5mg/kg IV q12 h for 2-3 week followed by 5mg/kg od for maintenance	Common: anaemia, granul ocytopenia,thrombocytope nia,renal toxicity
	2–5 mg/0.1 ml Intravitreal injection, three times per week	Uncommon: retinal detachment, vitreous haemorrhage, endophthalmitis
	Vitrasert surgical implant	Uncommon: retinal detachment, hypotony, haemorrhage, endophthalmitis
Valganciclovir	900 mg twice daily po for 3 weeks induction, then 450 mg twice daily po for maintenance	Common: headache, GI symptoms Serious: bone marrow suppression, renal dysfunction
Foscarnet	For CMV: 60 mg/kg every 8 h IV for 2–3 weeks, For HSV: 40 mg/kg every 8 h IV for 2–3 weeks	Common: headache, GI symptoms Uncommon: renal/CNS toxicity
	2.4 mg/0.1 ml Intravitreal injection, weekly	Uncommon: retinal detachment, vitreous haemorrhage, endophthalmitis

Intravitreal Therapy

Various intravitreal therapy options include intravitreal foscarnet and ganciclovir. This provides direct and immediate therapy to the area of active infection. The intravitreal foscarnet and ganciclovir is mainly indicated in patients resistant to initial systemic therapy or in patients not tolerating antivirals. Comparative studies assessing the role of intravitreal foscarnet showed that combination systemic and intravitreal therapy is more beneficial as compared to systemic therapy alone. Intravitreal therapy cannot be used alone due to the risk of contralateral involvement without systemic therapy [1,10]. A report by showed reduced vison loss and incidence of RD and by decrease in risk of RD by 67% in patients with systemic antiviral and intravitreal foscarnet [27,28]. Escalation of therapy should be considered in patients with refractory disease despite standard first-line therapy. Intravitreal injections additionally cause risk of endophthalmitis, vitreous hemorrhage, and retinal detachment.

Adjunctive Therapy

Due to severe inflammatory response caused by ARN, immunomodulatory agents are taken into consideration concurrent or after with antiviral therapy. Topical and systemic corticosteroids can be used in patients having severe inflammation; however, corticosteroid should be used cautiously as early initiation of corticosteroid may potentiate viral replication leading to rapid progression of retinitis and can be added 24–48 hours after the start of antiviral therapy in certain cases to minimize vitritis and the risk of retinal detachment [29].

Sudden drop in vision due to ischemic optic neuropathy have led to trials looking into the effect of anticoagulants such as aspirin, along with high-dose oral steroids after initiation of antiviral therapy. The pathogenesis of ARN also involves vascular occlusion manifesting as retinal ischemia and hyperaggregation of platelets treated successfully with corticosteroids and aspirin [29]. Other therapies for anticoagulation include heparin and warfarin. However, strong evidence does not currently exist for the use of anticoagulant. Additionally, important consideration should be taken regarding safety of these drugs in the context of other systemic diseases in each patient.

Surgical Consideration

Most common complications in ARN is the development of atrophic retinal holes and rhegmatogenous retinal detachments (RRD) leading to retinal atrophy and vitreoretinal traction. Prophylactic laser photocoagulation has been used to prevent RD by creating strong chorioretinal adhesions posterior to the area of the involved retina [29]. Factors that prevent laser photocoagulation in ARN patients are vitreous inflammation and the view of the posterior pole. Surgical therapy consists of pars plana vitrectomy, endolaser and silicone oil tamponade and is generally favored to long-acting gas therapy due to high risk of proliferative vitreoretinopathy and recurrent RD. PPV allows for the removal of inflammatory mediators and vitreous traction and silicone oil permits consistent, long-term tamponade after retinal detachment. However, no direct comparative studies have been conducted assessing silicone oil versus other tamponade techniques.

Conclusion

Although it is an uncommon disease, ARN can be associated with substantial ocular morbidity if not accurately diagnosed and treated. Aqueous PCR testing should be considered in cases of suspected ARN or unclear presentation to confirm the diagnosis or rule out other masquerade diseases but one should not wait for PCR results while starting treatment. Prospective, randomized, double masked controlled studies should be gold standard for determining treatment effect however, due of its rarity these studies are difficult to conduct. Further studies should focus on standardized definitions of outcomes to better assess responses which is lacking in most of retrospective studies. While choosing a specific therapeutic regimen, factors including the precise herpetic viral etiology, the immune status of the patient, concomitant medical morbidities, and response to therapy should be kept in mind to guide the management of each patient. However, significant advances have been made, further studies are needed to refine disease protocols and improve outcomes for this challenging infectious uveitis syndrome.

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