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Ophthalmic Technology Assessment

Diagnosis and Treatment of Acute Retinal Necrosis

A Report by the American Academy of Ophthalmology

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Purpose: To evaluate the available evidence in peer-reviewed publications about the diagnosis and treatment of acute retinal necrosis (ARN).

Methods: Literature searches of the PubMed and Cochrane Library databases were last conducted on July 27, 2016. The searches identified 216 unique citations, and 49 articles of possible clinical relevance were reviewed in full text. Of these 49 articles, 27 were deemed sufficiently relevant or of interest, and they were rated according to strength of evidence. An additional 6 articles were identified from the reference lists of these articles and included. All 33 studies were retrospective.

Results: Polymerase chain reaction (PCR) testing of aqueous or vitreous humor was positive for herpes simplex virus (HSV) or varicella zoster virus (VZV) in 79% to 100% of cases of suspected ARN. Aqueous and vitreous specimens are both sensitive and specific. There is level II and III evidence supporting the use of intravenous and oral antiviral therapy for the treatment of ARN. Data suggest that equivalent plasma drug levels of acyclovir can be achieved after administration of oral valacyclovir or intravenous acyclovir. There is level II and III evidence suggesting that the combination of intravitreal foscarnet and systemic antiviral therapy may have greater therapeutic efficacy than systemic therapy alone. The effectiveness of prophylactic laser or early pars plana vitrectomy (PPV) in preventing retinal detachment (RD) remains unclear.

Conclusions: Polymerase chain reaction testing of ocular fluid is useful in supporting a clinical diagnosis of ARN, but treatment should not be delayed while awaiting PCR results. Initial oral or intravenous antiviral therapy is effective in treating ARN. The adjunctive use of intravitreal foscarnet may be more effective than systemic therapy alone. The role of prophylactic laser retinopexy or early PPV is unknown at this time. *Ophthalmology 2016;■:1–11 © 2016 by the American Academy of Ophthalmology*

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Retina/Vitreous Panel is to evaluate the diagnosis and treatment of acute retinal necrosis (ARN).

Background

Acute retinal necrosis was first described in 1971 by Urayama and colleagues[1] as a syndrome of acute panuveitis with retinal periarteritis progressing to diffuse necrotizing retinitis and retinal detachment (RD) (Figs 1 and 2). It is an uncommon syndrome caused by human herpes viruses that can affect immunocompetent or immunosuppressed patients of either gender at any age. On the basis of 2 nationwide UK surveys, the annual incidence of ARN is estimated to be 0.5 to 0.63 new cases per million population.[2,3]

In 1994, the Executive Committee of the American Uveitis Society[4] defined ARN on the basis of the following clinical characteristics: (1) 1 or more foci of retinal necrosis with discrete borders located in the peripheral retina, (2) rapid progression in the absence of antiviral therapy, (3) circumferential spread, (4) evidence of occlusive vasculopathy with arterial involvement, and (5) a prominent inflammatory reaction in the vitreous and anterior chamber. Non-necrotizing and multifocal posterior necrotizing variants also have been described.[5,6] Patients presenting with anterior uveitis should undergo a dilated eye examination to assess for ARN and other causes of uveitis.

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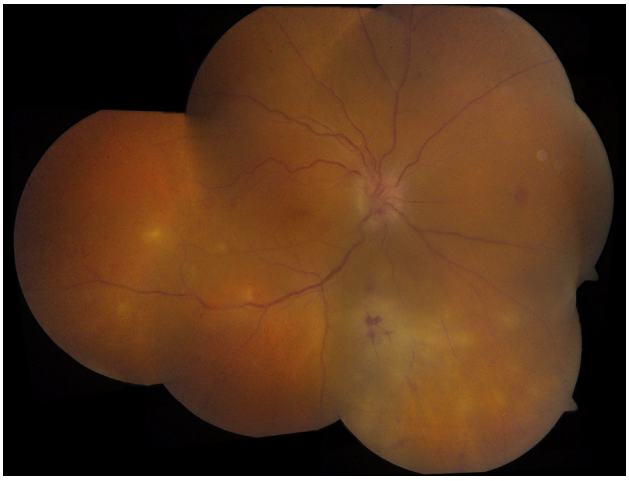

Figure 1. Montage fundus photograph of a patient with acute retinal necrosis (ARN) reveals vitritis, retinitis, retinal vasculitis, retinal hemorrhage, and optic nerve head edema. (Courtesy of Stephen J. Kim, MD.)

Culbertson et al[7] first described histologic evidence of herpetic involvement in ARN in 1982. Several laboratory studies have confirmed a herpetic cause, including polymerase chain reaction (PCR)-based techniques, serum or intraocular fluid antibody testing, viral culture, retinal biopsy, and immunocytochemistry.[8] Varicella zoster virus (VZV) is the most common cause, followed by herpes simplex virus (HSV) types 1 and 2.[3,9,10] Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) also have been reported as causative agents.[8,10]

Visual outcomes are generally poor, and 48% of affected eyes have a visual acuity (VA) worse than 20/200 6 months after onset of ARN.[2] Retinal detachment is the most common cause of decreased vision; it occurs in 20% to 73% of treated eyes in more recent studies,[9,11] but rates up to 85% have also been reported.[12] Vision loss also may occur as a result of chronic vitritis, epiretinal membrane, macular ischemia, macular edema, and optic neuropathy.[9,13] Additional morbidity and mortality may occur with central nervous system or contralateral eye involvement. Bilateral ARN occurs in up to 70% of untreated patients.[14] Contralateral involvement usually occurs within a few months but may occur years later.[14,15]

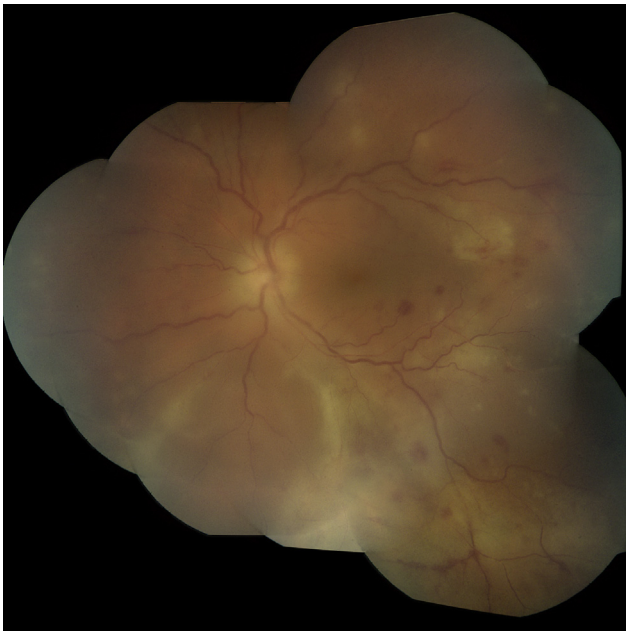

Figure 2. Montage fundus photograph of a patient with ARN reveals vitritis, multifocal and confluent areas of retinitis, retinal vasculitis, retinal hemorrhage, optic nerve head edema, and retinal detachment. (Courtesy of Stephen J. Kim, MD.)

In 1986, Blumenkranz et al[12] reported the regression of retinal lesions with intravenous acyclovir. In 1991, Palay et al[14] found a reduction in contralateral eye involvement from 70% to 13% with intravenous acyclovir. Treatment at a dose of 10 mg/kg every 8 hours or 1500 mg/m^2 per day divided into 3 doses for 7 to 10 days followed by an oral antiviral is the most established treatment regimen.[9,10,12,15] However, since the advent of newer oral antivirals (e.g., valacyclovir, famciclovir) that have greater bioavailability and the increasing adoption of intravitreal injection, multiple studies have reported successful outcomes using initial oral with or without intravitreal therapy without concomitant intravenous treatment.[15–17]

Adjunctive treatment modalities have been described, including early pars plana vitrectomy (PPV) with or without silicone oil before RD, laser retinopexy around areas of necrosis to prevent RD, systemic or local corticosteroids, and systemic antiplatelet agents.[9,15]

Acute retinal necrosis is a rapidly destructive disease that has substantial morbidity and the predilection to involve the fellow eye, but its rarity precludes the conduct of large randomized clinical trials. Consequently, clinical management largely has been guided by retrospective studies and case reports. Given recent advances in the diagnosis and the introduction of new treatments, this subject merits further review.

Description of the Intervention

Early accurate diagnosis of ARN is critical to initiate timely antiviral therapy. Multiple diagnostic methods have been reported, and many recent studies have used PCR-based techniques for rapid diagnosis. The advent of newer oral antivirals with greater bioavailability has resulted in a greater use of first-line oral therapy, which has the distinct advantage of outpatient administration at substantial cost savings. In addition, the adjunctive use of intravitreal antiviral therapy has been increasingly reported and provides immediate intravitreal drug levels that greatly exceed what can be initially achieved by systemic administration. Because of the high risk of RD with ARN, some ophthalmologists have advocated using prophylactic laser retinopexy (posterior to or surrounding the areas of the necrotic retina) and early PPV to reduce the risk of RD.[10,11]

Resource Requirements

Most treatment regimens for ARN consist of initial intravenous acyclovir therapy for 7 to 10 days.[9,10,12,15] Patients are then treated with oral therapy at the discretion of the