Herpes Simplex Virus Type 1

A Cause of the Acute Retinal Necrosis Syndrome

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Abstract: The authors have isolated herpes simplex virus type 1 (HSV-1) from the vitreous of two patients with acute retinal necrosis. Clinical and laboratory data suggest that one case represented a primary HSV-1 infection, whereas the other case appeared to be a recurrent HSV-1 infection. In the primary case, changes on magnetic resonance imaging (MRI) suggest spread of the virus posteriorly to both optic tracts and the lateral geniculate ganglia. This case shares many features with the "von Szily" experimental model for HSV retinitis in the mouse. Ophthalmology 96:875–878, 1989

Acute retinal necrosis syndrome characteristically occurs in otherwise healthy patients, with the onset of diffuse uveitis, retinal vasculitis, necrotizing retinitis, vitreitis, and frequent retinal detachment (RD).[1–13] Varicella zoster virus is a proven cause of this disease.[14] Indirect evidence has suggested that herpes simplex virus (HSV) may also cause acute retinal necrosis.[15–21] Although acute retinal necrosis has been thought to represent a recurrence of latent varicella zoster virus[22–24] or HSV,[15,25] the possibility of a primary virus infection should also be considered. In this report, we describe for the first time two cases of acute retinal necrosis in which HSV type 1 (HSV-1) was isolated from the vitreous. One case appeared to represent a primary HSV-1 infection with associated subclinical encephalitis (case 1), and the other appeared to be a recurrent HSV-1 infection (case 2).

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CASE REPORTS

Case 1. A 27-year-old otherwise healthy white man noted the acute onset of painless blurring of vision in his right eye. Results of examination showed papillitis and a few scattered hemorrhages in the periphery of the right eye. Within 4 days, the visual acuity in the right eye deteriorated to no light perception. There was a right afferent pupillary defect, a hazy cornea, cells and flare in the anterior chamber, necrosis of the retina in the posterior pole, and hemorrhages along the superior and inferior temporal arcades. The visual acuity in the left eye was 20/30 and results of the fundus examination were completely normal. Increasing malaise and intermittent temperature elevations had developed; the patient was admitted to the hospital 3 days after the initial examination.

He had no previous history of oral or genital vesicular lesions. General physical examination results, blood count, and chest x-ray were normal. Blood cultures were negative. Interpretation of plain and contrast-enhanced computed tomography (CT) showed very small areas of hemorrhage in the right insular cortex and adjacent to the anterior third ventricle.

A diagnosis of acute retinal necrosis was made, and intravenous acyclovir was initiated (700–1000 mg every 8 hours). Six days after onset, fluorescein angiography showed filling of only the major vessels of the right eye, with nonprofusion of the capillaries and peripheral circulation. The superior nasal quadrant of the optic disc of the left eye showed mild edema and stained on fluorescein angiography. Automated static threshold perimetry in the left eye showed generalized constriction of the visual field (Fig 1, left). A lumbar puncture showed 163 erythrocytes, 67 leukocytes (100% monocytes), glucose level of 60 mg/dl, protein level of 70 mg/dl, nonreactive VDRL, and negative cultures

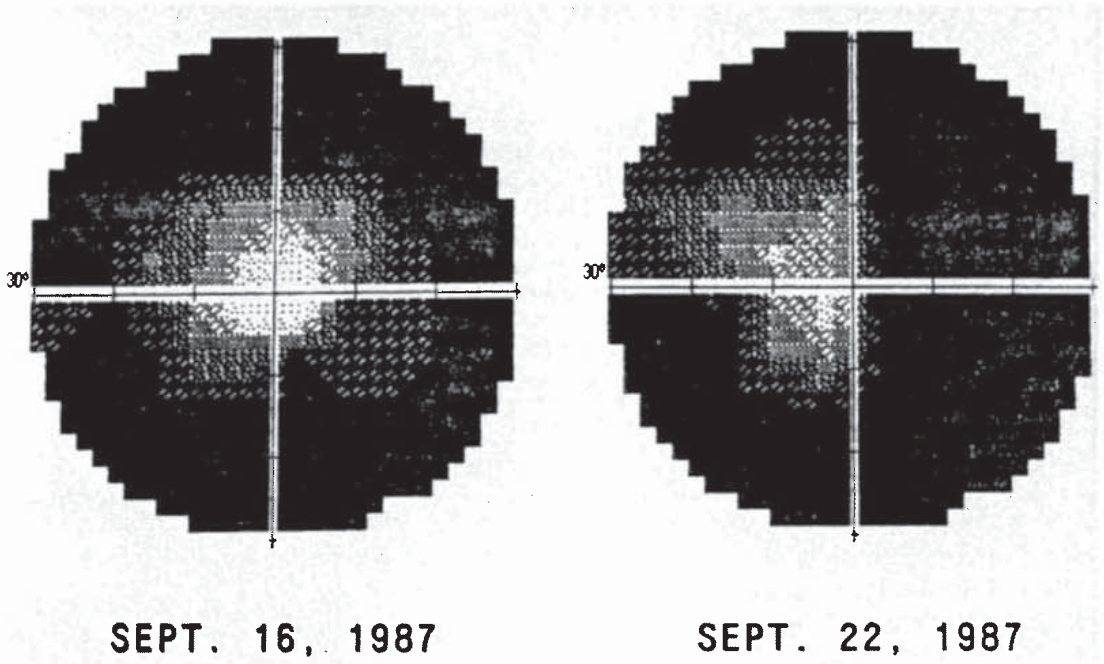

Fig 1. Case 1. *Left,* automatic static perimetry of the left eye on September 16, 1987, showing severe peripheral constriction. *Right,* repeat perimetry of the left eye on September 22, 1988, showing loss of the entire nasal field.

for bacteria, virus, and fungi. After the lumbar puncture, headaches developed which were made worse by sitting up, but results of neurologic examination were otherwise unremarkable.

On the seventh day from the onset of symptoms, a diagnostic vitrectomy was performed on the right eye. Cultures of vitreous specimens yielded HSV-1; bacterial and fungal cultures were negative. A repeat visual field of the left eye showed complete loss of the nasal field, and constriction of the temporal field (Fig 1, right). An electroretinogram (ERG) of the left eye showed a normal a wave but the b wave amplitude was moderately reduced for both rods and cones, suggestive of inner retinal dysfunction. Results of echographic examination showed the nerve and nerve sheath to be markedly enlarged on the right and normal on the left. The left eye continued to be free of vitreitis, retinitis, and vasculitis.

Intravenous methylprednisolone (250 mg every 6 hours) was initiated because of the progressive involvement of the visual field in the left eye. Magnetic resonance imaging (MRI) of the brain showed bilateral high-intensity signal abnormalities in the region of both optic tracts (greater on the left), the lateral geniculate ganglia, overlying temporal lobes, and the left midbrain (Fig 2). Even with these central findings, no signs or symptoms usually associated with herpes simplex encephalitis developed.[26]

The intraocular inflammatory reaction began to clear in the right eye on the third day of steroid therapy. Steroids were gradually tapered over 1 week to 60 mg of oral prednisone daily. Intravenous acyclovir was continued throughout the 3-week hospitalization and then the patient was placed on oral acyclovir (800 mg 5 times daily). A total RD developed with large retinal holes in the right eye. Repeat echography, ERG, visual fields of the left eye and optic nerve, and MRI all showed improvement. Retinitis never developed in the left eye, and visual acuity remained 20/20. Initially, there was no detectable IgG antibody to HSV-1 (IgG antibody titer = 0.17 by enzyme-linked immunoassay [ELISA]), whereas 2 weeks later, high levels of antibody were found (IgG antibody titer = 1.31 by ELISA). Serologic testing was negative for varicella zoster virus, human immunodeficiency virus, toxoplasma, and syphilis.

Case 2. Over a 3-week period, a 37-year-old man experienced decreasing vision and periocular pain in the left eye which was associated with granulomatous iridocyclitis, confluent peripheral necrotizing retinitis, retinal arterial sheathing, papillitis, and a constricted visual field, consistent with acute retinal necrosis syndrome (Fig 3). The right eye was initially normal, with 20/20 visual acuity, a normal visual field, and no retinal abnormalities. He had been otherwise healthy, with the exception of a history of recurrent vesicles and "fever blisters" of the lips. He was initially treated with oral, intramuscular, and periocular corticosteroids, followed by the addition of intravenous acyclovir (500 mg every 8 hours) and aspirin (300 mg daily). Results of CT scan of the brain were negative. On this therapy, the retinitis progressed in the left eye and peripheral necrotizing retinitis and arteritis developed in the superotemporal quadrant of the right eye. A diagnostic vitrectomy was performed on the left eye at this time, resulting in the isolation of HSV-1 from the vitrectomy specimen. The intravenous acyclovir dose was increased to 1000 mg every 8 hours, and methylprednisolone (125 mg intravenously every 8 hours) was added. The retinitis gradually resolved in both eyes. A total RD developed in the left eye 6 weeks after the onset of symptoms and was surgically reattached; final visual acuity was light perception. Prophylactic argon laser photocoagulation was applied posterior to the previous retinitis in the right eye, which retained 20/20 visual acuity and a full visual field throughout the course of observation. Acute and convalescent serologic studies showed stable antibody levels to HSV-1 (specific acute and convalescent serum titer = 1:128) and HSV-2 (specific acute and convalescent serum titer = <1:8), and varicella zoster (acute serum titer = 1:64, convalescent serum titer = 1:128). Serologic testing was negative for toxoplasma, syphilis, and human immunodeficiency virus.

The vitreous samples from both cases were cultured on monolayers of human fibroblasts and monkey kidney cells. Cytopathologic effect consistent with HSV was observed. Confirmation of isolates as HSV-1 was obtained by direct immunofluorescent testing using monoclonal antibodies to HSV-1 (Syva Co, Palo Alto, CA).

DISCUSSION

These two cases demonstrated characteristic features of acute retinal necrosis syndrome with rapid progression of necrotizing retinitis, retinal vasculitis, papillitis, vitreitis, and rhegmatogenous RD. Herpes simplex virus has been suspected as a cause of acute retinal necrosis by other investigators who have demonstrated high antibody titers to HSV or HSV antigen in the vitreous.[16-19] Furthermore, virus particles morphologically compatible with the herpesvirus family (varicella zoster virus, HSV-1, HSV-2, cytomegalovirus, Epstein-Barr virus) have been identified electron micrographically in retinal specimens.[27-30] We have previously shown that varicella zoster virus is a cause of some cases of acute retinal necrosis by isolation of the virus from the vitreous and by immunocytologic techniques.[14] Similarly, in this article, we report for the first time the isolation of HSV-1 from the vitreous and conclusively demonstrate that HSV-1 is also a cause of acute retinal necrosis. Grutzmacher et al[31] have reported the isolation of HSV-1 from a chorioretinal biopsy obtained from a patient with a chronic chorioretinitis distinctive from acute retinal necrosis.

Case 2 presented with a retinitis for the first time which was suggestive of a recurrent HSV-1 infection as evidenced by the patient's previous history of labial vesicles and stable HSV-1 titers. In contrast, case 1 presumably represented a primary HSV-1 infection as evidenced by the initial absence of detectable HSV-1 antibody followed by rapidly rising titers to HSV-1, as well as a negative history of prior herpetic infections. IgM titers were not measured early in the illness so direct immunologic evidence for primary infection was not available. Although the clinical course in case 2 was typical of previously reported cases of acute retinal necrosis syndrome, the more fulminant ocular course and intracranial involvement observed in case 1 possibly were features of a primary infection and the absence of preexisting immunity to HSV-1.

Previous reports have documented occasional cases of HSV encephalitis associated with retinitis in adults.[17,32-36] In these cases, it has been generally assumed that the virus spreads from the brain down the optic nerve(s) to secondarily involve the retina(s). It is possible in our case 1 that the virus spread from the right retina posteriorly along the right optic nerve to both optic tracts and both lateral geniculate ganglia, sparing the left optic nerve and retina. If this hypothesis is true, the route of initial viral inoculation of the retina is unclear. The more severe involvement of the left optic tract and geniculate ganglion was compatible with the right hemianopic field loss in the left eye. Sergott et al[37] demonstrated intraorbital enlargement of the optic nerve in two cases by CT similar to our echographic and MRI findings. If MRI studies of the optic radiations posterior to the orbit are obtained in future acute retinal necrosis patients, it is possible that similar unsuspected involvement of the visual pathways may be demonstrated.

Features of case 1, including unilateral retinitis, subclinical encephalitis, with optic nerve, optic tract, and lateral geniculate ganglia involvement, parallel the extensively studied "von Szily" model for primary HSV-1 retinitis in rabbits[38,39] and mice.[40] In the mouse model, mice with no previous exposure to HSV-1, when injected

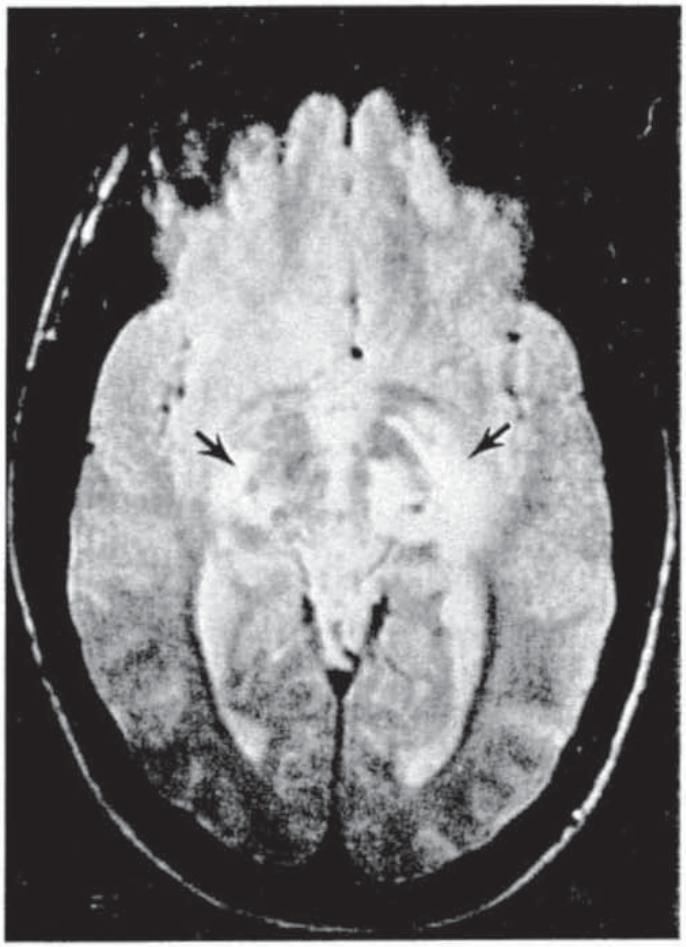

Fig 2. Magnetic resonance imaging (axial) of case 1, showing high-intensity signal abnormalities (arrows) in the region of the optic tracts and lateral geniculate ganglia which were greater on the left side. These changes were thought to represent acute inflammation in this patient.

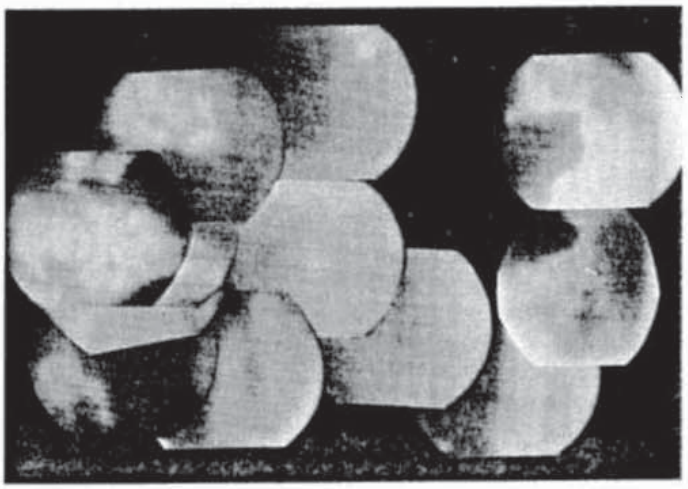

Fig 3. Fundus appearance of the left eye in case 2. After the media was cleared by vitrectomy, the areas of necrotizing retinitis could be seen.

with HSV-1 in the vitreous develop necrotizing retinitis in the contralateral eye within 7 to 10 days, whereas the injected eye appears to be protected from the retinitis.[41,42] The virus appears to spread to the brain via the optic nerve and then from the brain to the opposite eye via the contralateral optic nerve. Although necrotizing retinitis does not develop in the injected eye, Hamasaki et al[43] have demonstrated that the ERGs are extinguished in both eyes of these mice. Our case had an abnormal ERG in his apparently uninvolved left eye and Bando et al[4] also noted an abnormal ERG in the uninvolved eye in one of their cases. This finding may indicate that retinal tissues of the uninvolved eye were indeed impaired directly or indirectly by virus infection.

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