ACUTE RETINAL NECROSIS IN CHILDREN CAUSED BY HERPES SIMPLEX VIRUS

JAMES C.H. TAN, FRCPHTH,* DANIEL BYLES, FRCPHTH,†
MILES R. STANFORD, FRCPHTH,* PEGGY A. FRITH, FRCP,†
ELIZABETH M. GRAHAM, FRCP, FRCPHTH†

Purpose: To report the diagnosis, management, and outcome of acute retinal necrosis syndrome in children.

Method: Case series of three consecutive children aged 11 years and younger who were diagnosed with acute retinal necrosis. In addition to full ocular and systemic examinations, the children underwent vitreous biopsy (Patients 1 and 2) or aqueous tap (Patient 3) for polymerase chain reaction analysis.

Results: All patients had unilateral retinitis that was associated with preexisting chorioretinal scars, and two patients (Patients 1 and 3) had concurrent extraocular central nervous system abnormalities. Intraocular herpes simplex virus was detected in all three children: Type 1 in Patient 1 and Type 2 in Patients 2 and 3. In addition, all three children had a history of extraocular herpes simplex virus infection.

Conclusions: Retinitis associated with preexisting chorioretinal scars and detectable intraocular herpes simplex virus on polymerase chain reaction was common to all three children with acute retinal necrosis.


Acute retinal necrosis (ARN) is a necrotizing retinitis that is usually progressive and typically affects adults. Because it is less commonly reported in children, a high index of suspicion is particularly crucial to achieving a prompt diagnosis. We describe three children with ARN who had intraocular herpes simplex virus (HSV) identified by polymerase chain reaction (PCR), one of whom was found to have HSV Type 1 (HSV-1).

Case Reports

Patient 1

An 11-year-old boy with no significant ocular history had pain, injection, photophobia, and blurred vision in his left eye for 6 days. His left upper lid had been swollen and erythematous for 6 days.

He had a history of cortical vein thrombosis at 1 month of age, which was presumed to have been caused by a bacterial scalp infection. This had been complicated by focal seizures in his left arm that were attributed to right internal capsule and focal parietal lobe abnormalities on electroencephalography and computed tomography neuroimaging. He has since remained seizure-free, although he retains residual weakness in his left arm. At the age of 9 years, he was presumptively diagnosed with viral meningitis after a febrile illness associated with bilateral leg weakness that was self-limited. Cerebrospinal fluid analysis had been unremarkable.

At presentation, his left visual acuity (VA) was 20/30 with normal Ishihara color vision and no relative afferent pupillary defect. An erythematous vesicular rash was present on his left upper lid (Figure 1). He had 2+ cells and 1+ flare in the anterior chamber, fine keratic precipitates, and a vitritis consisting of 2+
cells. An area of confluent superotemporal retinal opacification adjacent to a pigmented chorioretinal scar was visible in the periphery (Figure 2), as was prominent retinal arteriolar vasculitis and optic disk swelling. An absolute inferonasal scotoma extended to 15° from fixation on Goldmann perimetry. A provisional diagnosis of ARN was made, and the patient was administered intravenous acyclovir. A left diagnostic vitreous biopsy was also performed with a skin scrape of his left upper lid.

Two days later, the patient awoke with reduced vision in his left eye and could see only hand movements in that eye. His retina had a necrotic appearance with widespread patchy opacification and hemorrhages that now involved the posterior pole (Figure 3). A total exudative retinal detachment (RD) with shifting fluid was present, and many retinal arterioles appeared nonperfused. The RD was not considered amenable to successful surgical treatment.

Herpes simplex virus Type 1 DNA was identified on PCR from the vitreous and skin rash. Electroencephalography was performed and proved to be unremarkable. The patient completed a 10-day course of intravenous acyclovir followed by an additional 3 months of oral acyclovir. To date, he has a VA of light perception in his left eye but has a healthy right eye with a VA of 20/17.

Patient 2

A 9-year-old girl had redness and blurring in her right eye for 1 week with 3 preceding days of photophobia and a flulike febrile illness. Her only remarkable history consisted of annual recurrences of painful right earlobe blistering since the age of 5 years, although it had not recurred in the last year. These blisters characteristically crusted and resolved spontaneously in 1 week.

The VA in her right eye was 20/60. Ishihara color vision was normal, and she did not have a relative afferent pupillary defect. She had 2+ cells and 1+ flare in the right anterior chamber, fine keratic precipitates, and a vitritis with 2+ cells. There were several distinctly bordered confluent areas of whitened retina in the inferior periphery with associated retinal hemorrhages and vascular sheathing. Adjacent to this and just inferior to the swollen, hyperemic optic disc was a pigmented chorioretinal scar. Her right Goldmann visual field showed a mild generalized depression. The examination of her left eye and right ear and the systemic examination were unremarkable.

Sampling of the right vitreous and PCR analysis detected HSV Type 2 (HSV-2) DNA, whereas the findings from magnetic resonance neuroimaging and electroencephalography were within normal limits. Meanwhile, the patient was given intravenous acyclovir for 10 days followed by oral acyclovir for 3 months for presumed ARN. After 2 weeks of treatment, the VA in her right eye was 20/40, and the signs of intraocular inflammation were less marked. Previous areas of retinitis showed atrophy and increased pigmentation. Currently, her right retina remains flat and the left eye is healthy.

Patient 3

A 10-year-old boy had painless left ocular injection, mildly blurred vision, a lower lip cold sore, and flulike illness for 6 days. His only significant history was recurrent cold sores in the past year.

The VA was 20/30 in his left eye. He had 1+ flare and 3+ cells in the anterior chamber, fine keratic precipitates, and a vitritis with 1+ cells. Fundus examination showed pale confluent inferior retinitis with fluffy borders and satellite lesions, but no associated hemorrhages (Figure 4). A superonasal hyperpigmented chorioretinal scar, 2 disk diameters in size, was located adjacent to the vascular arcade, and there was marked optic disk swelling (Figure 5). Examination of the right eye was unremarkable.
The next day, an exudative RD had developed inferiorly. A presumptive diagnosis of ARN was made and the patient was given 10 mg/kg intravenous acyclovir every 8 hours. Deterioration continued for the following 3 days and included a reduction in VA of the left eye to counting fingers and increased optic disk swelling. Impaired color perception and a relative afferent pupillary defect were present for the first time. The Goldman visual field was grossly constricted. Magnetic resonance neuroimaging showed left optic nerve head swelling with contrast enhancement that extended posteriorly to the optic chiasm. There was also an area of high signal intensity in the right temporal lobe. An aqueous tap was performed for PCR analysis and showed the presence of HSV-2 DNA.

Gradual resolution of the retinitis and exudative RD ensued, but the optic disk swelling remained unchanged. One week after treatment began, a decision was made to switch from intravenous acyclovir to oral valacyclovir. Six days later, however, the patient experienced a headache with accompanying drowsiness and vomiting. In light of the temporal lobe finding on magnetic resonance imaging, this new presentation was interpreted to be consistent with HSV encephalitis, so intravenous acyclovir was administered for an additional 16 days. Cerebrospinal fluid analysis showed oligoclonal bands, although PCR findings were negative. This course of management was followed by a rapid improvement in his systemic condition.

The left retinitis was inactive after 4 weeks and left a sharply demarcated area of inferior chorioretinal scarring. Ten months after presentation, his VA remained at counting fingers in the left eye with a pale optic disk and grossly constricted visual field. His right eye remained unaffected.

Discussion

Substantial evidence confirms that ARN has a viral cause, with varicella zoster virus being the most commonly implicated inciting agent.1–3 Herpes simplex virus, especially HSV-2, has been less commonly described in this condition, but there is growing evidence that disease in younger patients with ARN is more likely to be caused by this virus.4–8 Reports that directly substantiate this hypothesis have relied on PCR and viral culture of affected vitreous from patients younger than 45 years of age.4–8

It is postulated that ARN caused by HSV may be the result of a recurrence of previous retinitis caused by the virus. Thompson et al7 identified HSV-2 by PCR as the potential cause of ARN in a 30-year-old man and two children using immunologic studies. Because these patients had chorioretinal scars, histories of maternal or congenital herpes infection, or both, it was suggested that their disease had occurred as recrudescence of congenital herpetic retinitis. The authors thought this to have been triggered by preceding physical trauma in each case. Another report details ARN presumptively caused by HSV in two patients who had preexisting inactive chorioretinal scars, one of whom experienced two recurrences separated by 9 months.8 All our described patients with ARN had stigmata of previous chorioretinal disease accompanying their retinitis and provide further speculative support for the concept of recurrence with intraocular HSV infection. Because of the paucity of previous ophthalmic documentation with our patients, however, it is difficult to conclusively rule out the possibility that their preexisting chorioretinal scars may have had alternative and unrelated causes.

It has been suggested that ARN, which is fulminant, especially when complicated by exudative RD, should raise the suspicion of HSV infection.4 Our first patient, who had previously documented central nervous system disease, developed fulminant retinitis that culminated in widespread retinal necrosis and total exudative RD. Herpes simplex virus Type 1 was established as the cause in this patient as a result of viral
DNA isolation from the vitreous and eyelid exanthem. The relentless progression of the disease, despite early maximal treatment with intravenous acyclovir and intravitreal ganciclovir, may reflect that it represents a more severe spectrum of the syndrome. Similarly, our third patient experienced rapid, irreversible visual deterioration to counting fingers in 9 days, despite treatment. This occurred on the background of retinitis, exudative RD, optic neuropathy, a temporal lobe lesion, and PCR-substantiated intraocular HSV-2. Duker et al\(^4\) cultured HSV-1 from the vitreous of a 22-year-old man who showed aggressive disease with exudative RD and had a history of temporal lobe astrocytoma. Another report describes a patient with ARN secondary to HSV-1 with severe posterior pole retinal necrosis, whose vision rapidly deteriorated to no light perception in 4 days. Neuroimaging in this patient showed focal abnormalities involving the central visual pathways and midbrain, but there was no clinical evidence of herpes simplex encephalitis.\(^5\) A retrospective study further documents three immunocompetent patients with rapidly progressive ARN who had PCR-proven HSV-1 and histories of encephalitis or neurosurgery. This suggests that the presence of HSV should be considered in patients with severe ARN who have a history of central nervous system disease.

Many direct methods for virus isolation from the eyes of patients with ARN have been used with mixed success. Polymerase chain reaction analysis of the vitreous in ARN is a direct and potentially more sensitive means of viral detection than other techniques, such as vitreous viral cultures and endoretinal biopsy. The sensitivity of these techniques variably depends on the nature of the acquired sample. Although PCR theoretically requires only a minute quantity of viral DNA to yield a positive result, the success of endoretinal biopsy, for example, relies heavily on accurate sampling at the interface between viable and necrotic retina. The location of this interface can be ambiguous. This is shown in a report of acute ARN in which an apparently judicious retinal biopsy was not diagnostic, whereas PCR successfully detected HSV-2 from the vitreous.\(^6\) Likewise, negative viral cultures are known to occur despite the presence of countless virions being seen on electron microscopy.\(^3,9\) Another report failed to generate positive viral cultures from vitreous washings despite HSV-2 being detected on PCR.\(^7\) In our patients, the diagnostic usefulness of PCR was apparent in its ability to detect HSV-1 in aqueous, vitreous, and eyelid skin samples. In a separate report, PCR detection of HSV-2 in a vitreous specimen was found to be reproducible in two separate laboratories.\(^8\) Retrospective studies have also found the technique to be sensitive for detecting herpesviruses from the vitreous in viral retinitis,\(^10\) further indicating its diagnostic potential in ARN.

In summary, ARN is known to have a wide age distribution, and our report directly confirms that this disease occurs in children and may be caused by HSV-1 or HSV-2. All the children we described had intraocular HSV detected on PCR with retinitis that was associated with chorioretinal scars. Furthermore, in our patients, this was associated with the presence or history of other nonocular stigmata of HSV infection. This correlates with the thought that the disease in younger patients is more commonly caused by HSV than by varicella zoster virus. In these patients, PCR appears to be useful for directly identifying a causative virus. The presence of rapidly progressive disease, especially with exudative RD, should alert the clinician to the possibility that HSV may be present, a pattern manifested in our first and third patients. This pattern was seen in two of our patients. Recognition of these features will further facilitate prompt diagnosis, which is important in maximizing visual preservation in this disease.

Key words: acute retinal necrosis, acyclovir, herpes simplex virus, necrotizing retinitis, polymerase chain reaction, vitreous aspirate.

References