Four cases of bilateral acute retinal necrosis with a long interval after the initial onset

Yoko Okunuki, Yoshihiko Usui, Takeshi Kezuka, Masaru Takeuchi, Hiroshi Goto

ABSTRACT

Aims To report the clinical features and causative virus of bilateral acute retinal necrosis (BARN) with a long interval after the initial onset.

Methods The causative virus and clinical features were retrospectively investigated in four patients with delayed-onset BARN with an interval of more than 3 years after the onset of the disease in the initially affected eye.

Results The intervals between the initially affected eye and the latter affected eye of the four cases were 8 years 7 months, 19 years 3 months, 9 years 7 months and 3 years 6 months. The fourth patient developed a second recurrence in the latter affected eye 17 years 6 months after the initial inflammation in the fellow eye. In all four cases, the same virus species, either varicella-zoster virus or herpes simplex virus, was detected in both eyes by PCR or antibody detection. In all cases, the final best-corrected visual acuity of the latter affected eye (20/20, 18/20, 20/20 and 12/20, respectively) was better than that of the initially affected eye (20 cm hand motion, light perception-negative, light perception-negative and light perception-positive, respectively).

Conclusion The present findings indicate that delayed-onset BARN in the fellow eye was caused by the same herpes virus species that induced the disease in the first affected eye.

Patients and Methods

Cases of BARN in which the disease developed in the fellow eye more than 3 years after the initial onset were chosen and retrospectively reviewed. All patients were diagnosed and treated at the Ophthalmology Clinic of Tokyo Medical University Hospital. Clinical features, causative virus and the interval between onset in the first eye and onset in the fellow eye were evaluated. All the patients were immunocompetent.

For detection of the causative virus, VZV, HSV and in some cases cytomegalovirus were examined. The causative virus was determined based on the results of immunoglobulin analysis with a Goldmann–Witmer coefficient of 6 or greater or positive PCR from the aqueous humour or vitreous fluid. Quantitative PCR was used after 2006. All the examinations were performed by SRL (Tokyo, Japan).

Results

All four patients who developed the disease in the fellow eye more than 3 years after onset in the first eye were male. Virus determination was performed in both the initially affected eye and the latter affected eye at the time of disease onset in each eye. In all four cases, the same virus species was detected in both eyes: VZV in two patients and HSV in two patients. In all cases, the final best-corrected visual acuity (BCVA) of the latter affected eye was better than that of the initially affected eye. The clinical course and patient characteristics are shown in the table 1.

Case 1

An 11-year-old boy first presented to an ophthalmologist on 19 December 1999, with complaints of redness in the right eye for 5 days. ARN was suspected by ophthalmologic examination. Treatment with intravenous acyclovir (1050 mg/day) and oral prednisolone (35 mg/day) was started. On 26 December, vitreous and cataract surgeries were performed due to the progression of retinal detachment. HSV-DNA was detected in the aqueous humour and vitreous fluid by PCR. Systemic administration of acyclovir and prednisolone was continued until 17 February. The final BCVA in the right eye was 20/200 at that time.

On 8 June 2008, he visited our department because of 5 days of blurred vision in the previously unaffected left eye. BCVA was 20-cm hand motion in the right eye and 20/20 in the left eye. Peripheral yellowish-white lesions in the temporal and inferior retina and mild retinal vasculitis in the peripheral fundus were observed (figure 1). ARN was suspected and treatment with intravenous...
acyclovir (2250 mg/day) and betamethasone (6 mg/day) was immediately started. He was diagnosed with HSV-ARN because 1.5×10^4 copies/ml HSV-DNA was detected in the aqueous humour by quantitative PCR. Additional PCR experiments revealed that the HSV type was HSV-2. The necrotic lesions were diminished by systemic administration of acyclovir and corticosteroid, which was continued until 15 July and 23 July, respectively. BCVA in the left eye was maintained at 20/20.

Case 2
A 47-year-old man presented to the ophthalmologist on 17 February 1989, with blurred vision and redness in the right eye. Iridocyclitis and disc oedema were observed. BCVA in the right eye was 20/20 until 25 February, when he experienced a sudden loss of vision. When he was referred to our hospital on 2 March, his BCVA was light perception-negative in the right eye and 20/20 in the left eye. Funduscopic examination revealed diffuse oedema and pallor in the retina, narrowed retinal arteries and an oedematous optic disc with haemorrhage along the retinal vessels. Treatment with intravenous acyclovir (1500 mg/day), interferon-β (5 000 000 IU/day) and oral prednisolone (30 mg/day) was initiated. On 23 March, laser photocoagulation was performed on the localised white lesions that had appeared in the peripheral temporal retina of the left eye. He was diagnosed with VZV-ARN because the Goldmann–Witmer coefficient, calculated using the aqueous humour of the right eye, which was negative at the first visit, was 34.8. On April 4, vitreous surgery was performed on the right eye due to progressive retinal detachment, but the visual acuity of the right eye did not recover. Interferon-β, acyclovir and prednisolone were continued until 6 April, 14 April and 3 May, respectively. BCVA in the left eye was maintained at 20/20.

On 6 June 2008, he visited our department because of 7 days of blurred vision in the left eye. BCVA was light perception-negative in the right eye and 12/20 in the left eye. Anterior chamber cells, disc oedema, patchy granular lesions in the posterior retina and yellowish necrotic lesions between the previous photocoagulation scars were observed (figure 2). ARN was suspected and treatment with intravenous acyclovir (2250 mg/day) and betamethasone (6 mg/day) was immediately started. VZV-DNA was detected by quantitative PCR with 2.7×10^6 copies/ml in the aqueous humour, and he was diagnosed with VZV-ARN. Despite initial enlargement, the necrotic lesions diminished 2 weeks after hospitalised treatment. Systemic administration of acyclovir and corticosteroid was continued until 3 September. The BCVA of the left eye improved to 18/20.

Case 3
In 1995, a 43-year-old man had severe uveitis in the right eye and VZV-DNA was detected by PCR in the aqueous humour. He was diagnosed with VZV-ARN and treated with acyclovir. A cataract operation was performed in 1999, but his visual acuity decreased to hand motion in 2002 because of proliferative vitreoretinopathy. On 30 April 2005, he was referred to our department

Table 1  Summary of four cases of delayed-onset bilateral acute retinal necrosis (BARN)

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>First affected eye</th>
<th>Fellow eye</th>
<th>Final visual acuity: first affected eye/fellow eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>11</td>
<td>19</td>
<td>HM: 20/20</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>47</td>
<td>67</td>
<td>LP(−): 18/20</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>43</td>
<td>52</td>
<td>LP(−): 20/20</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>39</td>
<td>60</td>
<td>LP(−): 12/20</td>
</tr>
</tbody>
</table>

GWC, Goldmann–Witmer coefficient; HM, hand motion; HSV, herpes simplex virus; LP, light perception; M, male; qPCR, quantitative PCR; VZV, varicella-zoster virus.

Figure 1  Fundus photograph of patient 1. Peripheral white necrotic lesions and mild vasculitis were observed in the temporal and inferior retina.

Figure 2  Fundus photograph of patient 2. Yellowish necrotic lesions between the previous photocoagulation scars were observed.
because of a 2-day history of blurred vision in his previously unaffected left eye. His BCVA was light perception-negative in the right eye and 20/20 in the left eye. Mild inflammation in the anterior chamber and two areas of retinal necrosis were observed in the left eye by ophthalmoscopy. ARN was suspected and treatment with intravenous acyclovir (2250 mg/day) and betamethasone (4 mg/day) was started immediately. Laser photocoagulation was also performed to prevent retinal detachment (figure 3). VZV-DNA was detected in the aqueous humour and he was diagnosed with VZV-ARN. Beta-methasone was administrated for 9 days and oral administration of acyclovir was continued until 1 June. The retinal lesions were diminished by the treatments and BCVA was maintained at 20/20.

Case 4
A 39-year-old man was referred to our department on 24 February 1988, due to ocular pain and blurred vision in the right eye starting 8 days earlier. BCVA was 20/50 in the right eye and 20/20 in the left eye. In the right eye, optic disc hyperaemia and dense white retinal lesion was observed in the temporal peripheral retina. ARN was suspected and treatment with acyclovir (1200 mg/day) and interferon-β (500 000 IU/day) was started and continued until 11 September and 23 August, respectively. Laser photocoagulation around the retinal lesion was also performed. HSV-DNA was detected by PCR in the aqueous humour and he was diagnosed with HSV-ARN in the right eye. Vitrectomy and scleral buckling were performed due to the development of retinal detachment. After cataract surgery performed the next year, BCVA was 8/200 in the right eye.

There was no remarkable change until August 1991. He visited our department on 16 August complaining of floaters and ocular pain for 5 days in the previously unaffected left eye. BCVA was 20/400 in the right eye and 20/20 in the left eye. A dense white retinal lesion was observed in the temporal peripheral retina. ARN was suspected and treatment with acyclovir (1200 mg/day) and interferon-β (3 000 000 IU/day) was started and continued until 11 September and 23 August, respectively. Laser photocoagulation around the retinal lesion was also performed. HSV-DNA was detected by PCR in the aqueous humour and he was diagnosed with HSV-ARN in the left eye. The retinal lesion diminished with the treatment and visual acuity was unchanged.

He was referred to our department again on 10 February 2009. His BCVA was light perception-positive in the right eye and 20/20 in the left eye. Mild anterior chamber cells, keratic precipitates and mild vitreous opacity were observed in the left eye. Because there was no retinal lesion, non-specific ocular inflammation was first suspected. By 3 March, however, small retinal lesions appeared and his BCVA decreased to 20/200 and HSV-DNA was detected by quantitative PCR in the aqueous humour at 4.7×10^6 copies/ml. Additional PCR experiments revealed that the HSV type was HSV-2. He was diagnosed again with HSV-ARN in the left eye. He was treated with intravenous acyclovir (2250 mg/day) and betamethasone (2 mg/day), which were administrated until 8 April and 11 March, respectively. Vitrectomy and scleral buckling were necessary due to the development of retinal detachment. On June 2009, his BCVA was 12/20 in the left eye.

**DISCUSSION**
In the present study, we report four cases of delayed-onset BARN in which the causative virus was diagnosed in both eyes. In our records of ARN between 1985 and 2009, nine patients developed BARN in addition to the four patients in the present report among 108 consecutive cases. All nine of these patients developed the disease in the fellow eye within 2 months after the initial onset. Consequently, we selected BARN patients who developed the disease in the fellow eye more than 3 years after the initial onset of delayed-onset BARN. In several previous reports of BARN, the disease developed in the fellow eye either within a few months or more than 3 years after disease onset in the initially affected eye, and very few patients developed the disease in the fellow eye between a few months and 3 years. Consequently, it is reasonable that these four patients were considered to have delayed-onset BARN separately from so-called BARN in which the fellow eye disease develops within a few months.

Pathways of viral spread in BARN and the immune response in ARN are not fully understood. Based on studies of animal
models with ARN induced by HSV-1, several routes, such as the optic nerve and optic chiasm, parasympathetic pathways and the suprachiasmatic nucleus,18–20 were suggested for viral spread to the contralateral eye. In experimental ARN, T cells, natural killer cells and neutrophils are thought to be important in the prevention of viral spread.21–24 Although animal studies using HSV-1 do not fully apply to human ARN in which HSV-2 or VZV is also associated with the development, a similar mechanism of viral spread is suggested for human ARN.25 After the initial active infection, the virus establishes latency in the sensory neurons. Although the part of the nervous system in which the virus causing delayed-onset BARN maintains latency is not clear, HSV-1 is reported to be latent not only in the trigeminal ganglion but also in dorsal root ganglia, sympathetic sensory neurons. Although the part of the nervous system in which the virus establishing latency in the contralateral eye was unknown.

In the present report, the causative virus was detected in both the eye with the first onset and the eye with later onset, and the same virus species was detected in both eyes of each patient. Although a couple of previous reports of delayed-onset BARN describe the causative virus for the fellow eye, few reports describe the causative virus of the onset in the first affected eye.10 11 15 16 Our findings that the same causative virus species was detected in both eyes in delayed-onset BARN suggest that the reactivated latent virus that affected the first eye is the causative virus of the disease in the fellow eye, rather than the fellow eye being affected by a different virus. Subtyping or genotyping of the virus, however, is needed to determine if the same virus induced the fellow eye disease, especially in cases 1 and 4, whose causative virus in the fellow eye was HSV-2, but the HSV subtype in the initially affected eye was unknown.

In general, inflammation and retinal necrosis in the fellow eye in BARN is less severe compared with that in the first affected eye. In the present report of delayed-onset BARN, the severity of the disease in the fellow eye was lower than that in the first affected eye in all four cases and none of the patients required surgical treatment for the fellow eye except case 4, who developed the disease twice in the fellow eye. In BARN, in which the fellow eye disease develops within a few months, one reason for the mildness of the fellow eye disease might be that antiviral treatment of the first affected eye effectively reduces the severity of the disease in the fellow eye. There might also be some mechanisms that reduce inflammation and retinal necrosis of the fellow eye in delayed-onset BARN, or earlier diagnosis and better treatment in the second affected eye may partly contribute to better prognosis. Although not investigated in retinal infection, vaccination is reportedly effective for reducing the severity of recurrent HSV-1 induced keratitis in mice and herpes zoster in humans.28 29 In a murine model of HSV-1 reactivation in the trigeminal ganglion, the immune cells observed earliest in the trigeminal ganglion were T cells, which are suggested to be virus-specific memory cells,30 and in vitro-activated virus-specific T lymphocytes have a protective effect on contralateral retinitis.31 Consequently, in delayed-onset BARN, immune reactions occurring at the time of the initial inflammation might prime immune cells, working like a vaccinination, which then functions to suppress the second infection.

In conclusion, the same virus species is suggested to be the causative virus of the disease in the fellow eye in delayed-onset BARN. Although delayed-onset BARN is very rare, physicians must consider the possibility of the development of ARN in the fellow eye, even many years after the initial onset.

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