Poor prognosis of elderly individuals >80 years of age with acute retinal necrosis

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Abstract

Purpose: To report the clinical features and prognosis of acute retinal necrosis (ARN) in elderly (>80 years of age) individuals.

Methods: Six consecutive patients with unilateral ARN who attended the Department of Ophthalmology at Yamaguchi University Hospital between 2014 and 2015 were retrospectively reviewed. Clinical characteristics, causative virus, time from symptom onset to physician visit, visual acuity at presentation and final visit, and treatment were evaluated and compared between the three elderly and three middle-aged (<80 years) patients.

Results: Varicella zoster virus (VZV) DNA was detected in aqueous humor by the polymerase chain reaction in all six cases. The mean ± SD time between symptom onset and medical attention was 18.0 ± 8.7 and 8.3 ± 1.5 days in the elderly and middle-aged groups, respectively. All patients were treated with intravenous aciclovir, oral prednisolone, and a nonsteroidal anti-inflammatory drug, and five of the six patients also received oral valaciclovir and underwent vitrectomy. The final best corrected visual acuity of the affected eye was worse for the elderly patients (20/400, hand motion, and light perception negative) than for the middle-aged patients (20/15, 20/50, and 20/25).

Conclusions and importance: ARN in the elderly individuals of the present study was caused by VZV infection and associated with a poorer visual prognosis compared with that of middle-aged patients. A delay in the onset of antiviral treatment might contribute to the poor prognosis of elderly patients with ARN.

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1. Introduction

Acute retinal necrosis (ARN) is a rare and aggressive form of retinal infection that was first described in 1971 and is characterized by confluent peripheral necrotizing retinitis, peripheral occlusive retinal arteritis, and moderate-to-severe vitritis.1 ARN is diagnosed predominantly on the basis of clinical findings,2–4 with the success rate for isolation of DNA of the causative virus from aqueous or vitreous humor samples being variable.1 Both varicella zoster virus (VZV) and herpes simplex virus (HSV) have been implicated as causes of ARN.5–7

The prognosis of individuals with ARN is dependent on the disease course but is usually poor as a result of irreversible loss of vision, with best corrected visual acuity (BCVA) often deteriorating to between 6/60 and 6/98–9 and sometimes to no light perception.10–12 The aims of treatment for ARN are to prevent further damage and to target the causative virus by either systemic or intravitreal antiviral therapy.13 Furthermore, treatment with an argon laser or vitrectomy might be applied prophylactically to prevent retinal detachment.14 ARN usually develops in non-immunocompromised adults between 20 and 60 years of age, although it sometimes affects individuals with various degrees of humoral immune deficiency,15,16 and it often occurs as the result of reactivation of HSV-1 or HSV-2 or of VZV after chickenpox.17 Factors that contribute to visual prognosis of ARN include age, initial visual acuity, and retinal detachment.18

During a recent 2-year period, we detected indications of a possible outbreak of ARN in elderly individuals (>80 years of age). The prognosis of ARN specifically in such individuals has not been...
characterized, although such knowledge will become increasingly important as the aged population of developed countries increases. We now describe three cases of ARN in elderly patients and compare their prognosis, including visual acuity and treatment efficacy, with that of three cases in middle-aged individuals. The elderly patients had a poor visual outcome associated with periarteritis, dense vitreous opacity, peripheral retinal exudates, and retinal detachment despite administration of antiviral, corticosteroid, and antithrombotic therapy. We also investigated the possible causal factors for such poor prognosis in the elderly by analysis of clinical characteristics of the three cases.

2. Subjects and methods

Six consecutive patients (six affected eyes) with ARN who attended the Department of Ophthalmology at Yamaguchi University Hospital between 2014 and 2015 were identified and retrospectively reviewed. Clinical features, causative virus, time from symptom onset to initial physician visit, visual acuity at both presentation and final visit, and treatment were evaluated. All six patients were immunocompetent. VZV, HSV, and cytomegalovirus were examined as potential causative viruses on the basis of a Goldmann-Witmer coefficient of ≥6 for immunoglobulin analysis or of a positive polymerase chain reaction (PCR) test of aqueous humor or vitreous fluid, with all assays being performed by SRL (Tokyo, Japan).

3. Results

The patients were classified into an elderly group (>80 years of age, one man and two women) or a middle-aged group (<80 years of age, three women), and their clinical characteristics were compared (Table 1). The mean ± SD age of the two groups was 83.0 ± 1.7 and 53.7 ± 12.3 years, respectively. Two of the three patients in the middle-aged group had a documented history of herpetic infection, whereas none of those in the elderly group had such a history. In all six cases, the disease was unilateral and VZV was detected by PCR analysis of aqueous humor. The mean ± SD time from the onset of subjective symptoms to the first visit to a physician was 18.0 ± 8.7 and 8.3 ± 1.5 days for the elderly and middle-aged groups, respectively. The final BCVA of the elderly group was worse than that of the middle-aged group.

All patients received intravenous aciclovir treatment (600, 750, 1250, or 1850 mg/day) for 7 or 14 days after clinical diagnosis, and five of the six patients also received oral valaciclovir (500 or 1000 mg/day) for 7 or 14 days (according to clinician preference) (Table 2). All patients were treated with an oral steroid to control persistent intraocular inflammation and with a nonsteroidal anti-inflammatory drug (NSAID) to prevent coagulation (Table 2).

Table 1
Clinical features of unilateral acute retinal necrosis in elderly and middle-aged patients.

| Case | Age (years) | Sex | Virus [AC] | Days from symptom onset to first visit | Presenting BCVA | Final BCVA | Follow-up (months) |
|------|-------------|-----|------------|---------------------------------------|----------------|-----------|-------------------|
| Elderly |             |     |            |                                       |                |           |                   |
| 1    | 81          | F   | VZV/none   | 12                                    | 20/40          | 20/400    | 23                |
| 2    | 84          | F   | VZV/none   | 28                                    | CF             | HM        | 26                |
| 3    | 84          | M   | VZV/none   | 14                                    | 20/200         | LP (−)    | 20                |
|      | 83.0 ± 1.7  |     |            | 18.0 ± 8.7 days                       |                |           |                   |
| Middle-aged |         |     |            |                                       |                |           |                   |
| 4    | 40          | F   | VZV/herpetic stomatitis | 7                          | 20/15          | 20/15    | 27                |
| 5    | 57          | F   | VZV/none   | 10                                    | 20/100         | 20/50    | 16                |
| 6    | 64          | F   | VZV/herpes zoster | 8                            | 20/25          | 20/25    | 10                |
|      | 53.7 ± 12.3 |     |            | 8.3 ± 1.5                              |                |           |                   |

Abbreviations: AC, anterior chamber tap; BCVA, best corrected visual acuity; CF, counting fingers; HM, hand motion; LP (−), light perception negative; VZV, varicella zoster virus.

Five patients with posterior involvement or severe vitritis that prevented observation of the retina underwent prophylactic vitrectomy to avoid the development of retinal detachment vitrectomy to treat or prevent the development of retinal detachment (Table 2). All three eyes in the elderly group developed ischemic neuropathy, with onset times of 3 days, 5 weeks, or 8 months after the diagnosis of ARN. There was no recurrence in either the affected or healthy eye of any patient during follow-up.

3.1. Case 1

An 81-year-old woman first presented to an ophthalmologist with complaints of ocular pain and a strange feeling in her left eye that had begun 12 days previously. Treatment with betamethasone eyedrops and oral prednisolone (30 mg/day) was started. She was referred to our department 7 days later, when her BCVA in the affected eye was 20/40 and mild inflammation, including cells, keratic precipitates (KPs) with mutton fat–type appearance, and corneal edema, was detected in the anterior chamber of the left eye. Ophthalmoscopy revealed retinal hemorrhage along her whitish vessels as well as yellowish lesions in the peripheral retina involving the supraposterior pole (Fig. 1A), whereas spectral domain–ocular coherence tomography (SD-OCT) showed a largely normal anatomy with mild vitreous opacity (Fig. 1B).

ARN was suspected and treatment with intravenous aciclovir (1250 mg/day; 15 mg/kg per day), oral prednisolone (30 mg/day), and oral bayaspirin (100 mg/day) was immediately started. Two days after her first visit to our hospital, vitreous surgery was performed on the left eye because of progressive periarteritis including retinal hemorrhage, dense vitreous opacity, peripheral retinal exudates, and retinal detachment. VZV DNA was detected in aqueous humor by quantitative PCR analysis, and the patient was therefore diagnosed with ARN due to VZV infection. Periarteritis including retinal hemorrhage, dense vitreous opacity, and peripheral retinal exudates were attenuated somewhat after vitrectomy (Fig. 1C and D), and systemic administration of aciclovir and corticosteroid was continued for a total of 14 days and 3 months, respectively. However, the necrotic lesions did not diminish, macular edema and retinal atrophy remained apparent in the posterior pole, and BCVA of the left eye had dropped to 20/400 at the patient's final visit (Fig. 1E and F).

3.2. Case 2

An 84-year-old woman first presented to an ophthalmologist with complaints of visual disturbance in her left eye that had started 4 weeks previously. One month later, she visited our department because of worsening of the visual disturbance. Her BCVA was counting fingers in the left eye. Mild inflammation in the
anterior chamber, including cells, KPs with mutton fat–type appearance, and corneal edema, as well as vitreous opacity, widely distributed peripheral-to-posterior areas of retinal necrosis, and optic disc ischemia were observed in the left eye by ophthalmoscopy (Fig. 2A).

Treatment with intravenous aciclovir (600 mg/day; 7.5 mg/kg per day, limited by the complication of renal dysfunction), oral prednisolone (25 mg/day), and oral bayaspirin (100 mg/day) was initiated. Vitrectomy was performed because of the development of periarteritis, dense vitreous opacity, peripheral retinal exudates, and retinal detachment. Quantitative PCR analysis detected VZV DNA in aqueous humor, and the patient was therefore diagnosed with ARN due to VZV infection. Two weeks after surgery, a wide area of retinal necrosis with vascular occlusion and optic nerve atrophy was observed. At 2 months after surgery, widely distributed yellowish necrotic lesions and proliferative fibrosis were apparent (Fig. 2B), and BCVA in the left eye was hand motion.

Table 2

| Case | Acyclovir (i.v.) | Valacyclovir (oral) | PSL (oral) | NSAID | History of affected eye | General conditions | Surgery |
|------|-----------------|--------------------|-----------|-------|------------------------|-------------------|---------|
| Elderly |                 |                    |           |       |                        |                   |         |
| 1    | 1250 mg, 14 days| 1000 mg, 14 days   | 30 mg     | 100 mg| Cataract                | Hyperlipidemia, RF| PPV + PEA + IOL + SO |
| 2    | 600 mg, 14 days | 1000 mg, 14 days   | 25 mg     | 100 mg| RRD postexplant         | HT, Pyelonephritis| PPV + PEA + IOL + SO |
| 3    | 1850 mg, 14 days| 1000 mg, 14 days   | 25 mg     | 100 mg| Cataract                | HT, RF, Prostatic enlargement| PPV + PEA + IOL + SO |
| Middle-aged |            |                    |           |       |                        |                   |         |
| 4    | 750 mg, 7 days  | 500 mg, 7 days     | 30 mg     | 100 mg| None                   | None              | PPV + PEA + IOL + SO |
| 5    | 1850 mg, 7 days | 500 mg, 7 days     | 30 mg     | 100 mg| None                   | Rheumatoid arthritis| PPV + PEA + IOL + SO |
| 6    | 750 mg, 14 days | 1000 mg, 14 days   | 10 mg*    | 100 mg| None                   | Rheumatoid arthritis| PPV + PEA + IOL + SO |

Abbreviations: HT, hypertension; IOL, intraocular lens implantation; NSAID, nonsteroidal anti-inflammatory drug; PEA, phacoemulsification; PPV, pars plana vitrectomy; PSL, prednisolone; RF, reflux esophagitis; RRD, rhegmatogenous retinal detachment; SF6, sulfur hexafluoride injection; SO, silicone oil injection. *The physician prescribed 10 mg of prednisolone and 6 mg/week of methotrexate for rheumatoid arthritis at the onset.

Fig. 1. Fundus photographs and spectral domain–ocular coherence tomography (SD-OCT) findings for case 1. (A and B) At presentation, funduscopy (A) revealed extensive retinal whitening, arteritis, and retinal hemorrhage in the nasal-to-superior aspect, whereas SD-OCT (B) revealed a healthy anatomic structure with mild vitreous opacity. (C and D) At 1 week after treatment onset, funduscopy (C) through silicone oil revealed retinal whitening, arteritis, and retinal hemorrhage, whereas SD-OCT (D) revealed retinal thickening at the macula, although the ellipsoid zone was detectable. (E and F) At 7 months after treatment onset, funduscopy (E) revealed severe vitritis resulting in vitreoretinal traction at the superior retina as well as proliferative vitreoretinopathy and fractional retinal detachment in the periphery, whereas SD-OCT (F) revealed disorganization of the outer retina in the macular region as well as a wavy retinal pigment epithelial layer. Arrows in fundus photographs indicate directions, whereas N and T in the SD-OCT images denote nasal and temporal, respectively.
3.3. Case 3

An 84-year-old man presented to an ophthalmologist with blurred vision and redness in his left eye that had started 2 weeks previously. He was treated for the redness with fluoroquinolone eyedrops. After 1 week, his conjunctivitis had improved, but retinal infiltration involving the posterior pole and including the macula had become apparent. He visited our department the same day because of his disease progression. BCVA was 20/200 in the left eye and 20/32 in the right eye. Given that cells in the anterior chamber, KPs with mutton fat—type appearance, optic disc edema, as well as patchy granular lesions and yellowish necrotic lesions distributed widely in peripheral-to-posterior areas were observed (Fig. 3A), the patient was diagnosed with ARN. Vitreous surgery on the left eye was performed the same day because of severe dense vitreous opacity that prevented observation of posterior regions. The detection of VZV DNA in aqueous humor by PCR analysis led to the diagnosis of ARN due to VZV infection. Treatment with intravenous aciclovir (1850 mg/day; 15 mg/kg per day), oral prednisolone (25 mg/day), and oral bayaspirin (100 mg/day) was also started immediately. The retinal lesions were diminished by the treatment (Fig. 3B), but 3 months later BCVA in the left eye was zero (light perception negative) as a result of optic nerve atrophy.

4. Discussion

We here describe three cases of ARN in elderly (>80 years of age) individuals, with the clinical diagnosis being confirmed by detection of VZV DNA in aqueous humor. The prognosis of these elderly patients with regard to visual acuity was poor compared with that of middle-aged patients, even though the treatment regimens were similar in the two groups. For the middle-aged patients, visual acuity improved or did not deteriorate between presentation and after treatment, whereas it worsened markedly in all three elderly patients. All cases in both groups were unilateral and were treated with a combination of antiviral, anti-inflammatory, and anticoagulant agents, with five of the six eyes also undergoing vitrectomy as necessary.

We were not able to identify the reason for the poor prognosis of ARN in the elderly patients of the present study. However, we suspect that the time from subjective symptom onset to the first visit to a clinician may have been a contributing factor. Posterior pole involvement is very rare and typically occurs at late or advanced stages in the disease course. An advanced stage of the disease at the time of initiation of antiviral therapy has been associated with a poor outcome. The mean interval between symptom onset and the seeking of medical attention in the present study was twice as long for the elderly patients as for the middle-aged subjects. In addition, elderly patients tend to have a history of cataract and some preexisting visual disturbance that can lead to a delay in the detection of ARN or other diseases because of the masking of subjective symptoms.

Aging of ocular structures also might affect the prognosis of ARN. In addition to the barrier function of the blood-retinal barrier, vitreous status appears to influence susceptibility to infectious pathogens. The gel volume decreases substantially after 40 years of age, and more than half of the vitreous is liquid by age 80–90 years. This age-related vitreous liquefaction in elderly (>80 years of age) individuals might thus contribute to dissemination of viral pathogens to the retina through the vitreous liquid. An age-related
decrease in choroidal circulation may also affect the delivery of systemic antiviral drugs to the posterior segment of the eye. Laser speckle flowgraphy has revealed a negative correlation between chorioretinal hemodynamics and age.\textsuperscript{20,27}

Most cases of ARN are thought to occur in individuals between 20 and 60 years of age, with the bimodal age distribution showing peaks at around 20 and 50 years that reflect the peak incidence of HSV and VZV infection, respectively.\textsuperscript{8,11,12,28} A prospective surveillance study in the United Kingdom reported five cases of ARN in patients aged >80 years out of a total of 45 cases encountered between 2007 and 2008, although the details of these cases including their prognosis were not described.\textsuperscript{29} The records of our hospital from 1991 to 2015 revealed no cases of ARN in patients of >80 years of age other than the three presented here out of 28 consecutive cases. Of these 28 cases, VZV was the causative agent in 26 patients and HSV-1 in two patients. The fact that the three cases of VZV-associated ARN in the elderly reported in the present study all occurred during a recent 2-year period is suggestive of a possible outbreak. The estimated incidence of ARN in individuals of >80 years of age was 5/45 = 0.11 for the U.K. surveillance study.\textsuperscript{22} We experienced 1.5 cases per year in a hospital that serves a community of about a million people. In advanced countries such as Japan, the rapid aging of the population resulting from a decline in birth rate might account for an increase in the incidence of ARN.

Although the mechanism underlying the development of ARN in the elderly was not determined in the present study, the level of T cell–mediated immunity to VZV is an important factor for the pathophysiology of ARN. Reexposure to VZV via contact with children protects latently infected adults against zoster.\textsuperscript{30} A decline in childhood varicella incidence as a result of vaccination might therefore lead to an increased incidence of adult zoster. The level of T cell–mediated immunity to VZV declines with time after varicella infection\textsuperscript{31} and, unlike the level of virus-specific antibodies, correlates with protection against herpes zoster.\textsuperscript{32} Such a decline in immunity might thus contribute to the development of ARN in the elderly.

Limitations of the present study include the small number of cases and its retrospective nature, both of which are inherent in studies of rare diseases such as ARN or uveitis. Prospective and multicenter surveillance studies on a national or global scale are thus warranted to address these limitations.

In conclusion, we here report three cases of ARN in individuals >80 years of age. Although the incidence of ARN in the elderly is not high, it may be increasing. The stage of the disease at the time of initiation of antiviral therapy affects prognosis including visual acuity. However, advanced age may be associated with a delay in the diagnosis of ARN as a result of the masking of subjective symptoms by other conditions.

Patient consent

The patients consented to publication of their cases in writing. This study was approved by the Ethics Committee of Yamaguchi University Hospital.

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Conflicts of interest

None.

Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

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