Acute Retinal Necrosis Syndrome: Clinical Manifestations and Visual Outcomes

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Background: In this paper we attempt to describe the clinical features, visual outcomes, and surgical results of patients with acute retinal necrosis (ARN) syndrome and elucidate the risk factors for a poor prognosis. We also review the methods of treatment.

Methods: This was a retrospective, noncomparative, observational study of patients diagnosed with ARN syndrome. Nine patients (11 eyes) in Chang Gung Memorial Hospital, Kaohsiung from January 1990 to December of 2002 were enrolled. Blood sera and vitreous specimens were analyzed. Necrosis locations and surgical results are described.

Results: Bilateral involvement occurred in 2 of our 9 patients (2/9, 22.2%). There was no specific relationship between age and level of the serum virus antibody. All of our polymerase chain reaction data for herpes simplex virus were negative. All 6 eyes of 6 patients who underwent surgery for retinal detachment had partial retinal reattachment postoperatively. Overall, anatomic success was achieved in 8 eyes (8/11, 72.7%). The percentage of eyes with ambulatory visual acuity was 36.3% (4/11), and visual acuity was preserved in 27.3% (3/11) at the last visit.

Conclusions: We found that retinal necrosis which extended rapidly to the posterior pole was associated with a poor visual outcome. Eyes with less than grade II necrosis extension are good candidates for prophylactic peripheral retinal photocoagulation. Early detection and prompt treatment with acyclovir seems to improve the final visual outcome.

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Key words: acute retinal necrosis syndrome, retinal detachment, peripheral retinal photocoagulation.

Acute retinal necrosis (ARN) is a distinct ocular inflammatory syndrome with the classically described triad of (1) arteritis and phlebitis of the retinal and choroidal vasculature, (2) confluent, necrotizing retinitis preferentially affecting the peripheral retina, and (3) moderate to severe vitritis. Herpes virus has been implicated as the causative agent. In recent years, vitreous or aqueous specimens have been analyzed by polymerase chain reaction (PCR) for both a diagnosis of ARN syn-
drome and determination of the specific virus causing the syndrome.\(^{(2)}\)

Retinal detachment is a frequent complication of the syndrome. The incidence has been reported to be as high as 85%, despite the efficacy of acyclovir in hastening resolution of the retinitis.\(^{(3)}\) Measures for the prevention and treatment of retinal detachment have included prophylactic photocoagulation,\(^{(4)}\) a prophylactic vitrectomy and scleral buckling with acyclovir infusion during the acute phase of retinitis,\(^{(5)}\) scleral buckling alone,\(^{(6)}\) a pars plana vitrectomy, endolaser photocoagulation, and long-acting retinal tamponade.\(^{(4,6)}\)

We herein report on our case series in a recent 12-year period and attempt to evaluate the risk factors for a poor visual outcome.

**METHODS**

We reviewed data of 9 patients (11 eyes) at Chang Gung Medical Hospital, Kaohsiung, between 1990 and 2002 (Table 1). These patients were diagnosed with ARN syndrome according to the characteristic clinical criteria described by the Executive Committee of the American Uveitis Society, which include findings of 1 or more focal, well-demarcated areas of retinal necrosis located in the peripheral retina; rapid, circumferential progression of necrosis; evidence of occlusive vasculopathy with arteriolar involvement; and a prominent inflammatory reaction in the vitreous and anterior chambers.\(^{(7)}\) Charts were retrospectively reviewed for the following items: age, gender, year and month of onset, place of onset, initial signs, examinations on initial visit, and clinical course. Information on initial signs checked included aqueous and vitreous cells, mutton fat keratic precipitates, intraocular pressure, the extent of retinal arteritis and phlebitis, and retinal areas of involvement with exudates. No systemic diseases were noted in our patients during the follow-up period.

Locations in which retinal necrosis was found to have reached were expressed as follows: (1) grade I, necrosis was restricted to the area between the ora serrata and vortex veins; (2) grade II, necrosis extended into the area between the vortex vein and vascular arcades; (grade IIp, partial degrees, and grade IIt, entire 360° of area) (Fig. 1); and (3) grade III, necrosis extended further beyond the vascular arcades (Fig. 2).\(^{(8)}\)

Blood serum was obtained from all patients for the detection of viral antibodies of herpes simplex virus and herpes zoster virus. Vitreous specimens were collected from 7 patients (2-5 and 7-9) for PCR analysis for detecting the herpes simplex virus. PCR analysis for varicella-zoster virus was not performed because the test was not available in our hospital.

All patients were treated with intravenous 5-10 mg/kg acyclovir q8h for 7-10 days followed by 400 mg oral acyclovir (p.o.) 5 times/day for 1-3 months.

**Table 1. Clinical Profile of the 11 Eyes**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Eye</th>
<th>Age/Gender</th>
<th>Symptoms</th>
<th>Initial vision (corrected vision)</th>
<th>Follow-up period (months)</th>
<th>Extent of necrosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L</td>
<td>60/M</td>
<td>Blurred vision for 1 wk</td>
<td>0.05</td>
<td>33</td>
<td>IIt</td>
</tr>
<tr>
<td>2</td>
<td>L</td>
<td>30/M</td>
<td>Blurred vision for 1 wk with pain</td>
<td>HM 1m</td>
<td>30</td>
<td>III</td>
</tr>
<tr>
<td>R</td>
<td>No specific symptoms</td>
<td>1.0</td>
<td>30</td>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>32/F</td>
<td>Blurred vision with floaters for 1 wk</td>
<td>0.5</td>
<td>41</td>
<td>IIp</td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>26/F</td>
<td>Blurred vision with pain for 1 wk</td>
<td>CF/20 cm</td>
<td>48</td>
<td>IIp</td>
</tr>
<tr>
<td>5</td>
<td>L</td>
<td>28/M</td>
<td>Blurred vision with pain for 1 wk</td>
<td>0.05</td>
<td>24</td>
<td>IIt</td>
</tr>
<tr>
<td>6</td>
<td>R</td>
<td>55/M</td>
<td>Blurred vision for 1 wk</td>
<td>CF/30 cm</td>
<td>61</td>
<td>III</td>
</tr>
<tr>
<td>L</td>
<td>No specific symptoms</td>
<td>0.9</td>
<td>61</td>
<td>IIp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>R</td>
<td>57/M</td>
<td>Blurred vision for 1 wk</td>
<td>HM &gt; 1 m</td>
<td>44</td>
<td>IIp</td>
</tr>
<tr>
<td>8</td>
<td>R</td>
<td>29/M</td>
<td>Blurred vision with pain for 1 wk</td>
<td>0.05 (0.2)</td>
<td>24</td>
<td>IIp</td>
</tr>
<tr>
<td>9</td>
<td>R</td>
<td>38/M</td>
<td>Blurred vision with pain for 1 wk</td>
<td>0.01 (0.02)</td>
<td>9</td>
<td>IIt</td>
</tr>
</tbody>
</table>

**Abbreviations:** F: female; M: male; wk: week; HM: hand motion; CF: counting fingers; R: right; L: left.

* Necrosis location: grade I, necrosis was restricted to the area between the ora serrata and vortex veins; grade II, necrosis extended into the area between the vortex vein and vascular arcades (grade IIp, partial degrees, and grade IIt, the entire 360° of area); grade III, necrosis extended further beyond the vascular arcades.
before or concurrently with the development of retinal detachment (RD). Patients were also treated with prednisolone and aspirin. For patients in whom acyclovir was to be used, a complete blood count was obtained, creatinine and blood urea nitrogen (BUN) levels were determined, and liver function tests were carried out prior to initiating therapy and periodically thereafter.

Seven eyes were treated with prophylactic peripheral retinal photocoagulation (P-RP) in an attempt to prevent posterior pole detachment for patients with less than grade II necrosis location. Six patients underwent a vitrectomy, including 3 eyes for rhegmatogenous retinal detachment (R-RD), 2 eyes for tractional-RD and R-RD, and 1 eye for exudative-RD. A meticulous anterior vitreous base vitrectomy, with 360° scleral decompression, was part of each vitrectomy. Epiretinal membranes were dissected from the retinal surface and removed from each of these eyes. Encircling prophylactic scleral buckles were put in place in all patients who had vitreous surgery, not to support specific retinal breaks, but to relieve any peripheral anterior vitreous base contractions that might occur during the postoperative period. Five eyes did not receive an operation, because 2 of them were grade III, 2 eyes (second eye of 2 patients) received early acyclovir treatment with good medical response, and 1 patient refused the operation.

Efficacy was measured both by anatomic success, defined as complete retinal attachment or macular attachment, and by visual acuity success, defined as preservation of visual acuity or ambulatory vision (visual acuity of 0.02 or greater, Snellen equivalent 4/200).

RESULTS

The clinical data of these 9 patients (11 eyes) are summarized in Table 1. Seven of the 9 patients were males and 2 were females; their ages ranged from 26 to 60 years, with a mean of 39.4 years. Follow-up ranged from 9 to 61 months, with a mean of 34.8 months. Bilateral involvement occurred in 2 of 9 patients (22.2%). All of our PCR data were negative for HSV (Table 2).

Of the 11 eyes, 10 were initially phakic with clear lenses and 1 senile cataract with nuclear sclerotic. Five of 6 eyes undergoing vitreoretinal surgery initially demonstrated clear lenses, but ultimately became cataractous. Postoperative partial retinal reattachment occurred in all 6 eyes of the 6 patients who underwent surgery for retinal detachment associated with ARN syndrome. Overall, anatomic success was found in 8 eyes (72.7%). The percentage of
eyes with ambulatory visual acuity was 36.3% (4/11), and visual acuity was preserved in 27.3% (3/11) at the last visit. Two eyes with grade III necrosis extension had a poor visual outcome (LS(-)) despite treatment with acyclovir. A final visual acuity of 1.0 was noted in 2 second eyes of 2 patients who had bilateral involvement and received acyclovir treatment as soon as ARN was diagnosed in the first eye (Table 3).

**DISCUSSION**

The ARN syndrome is a well-known clinical entity that was first described in the Japanese literature by Urayama et al. in 1971 and later became known in Japan as Kirisawa type uveitis. ARN has been reported in patients ranging in age from 9 to 89 years. No predilection for gender, race, or age has been identified. The cases typically affect the
patients between 20 and 60 years old with a bimodal distribution of peaks at about 20 and 50 years.

Bilateral involvement occurs in approximately 1/3 of patients. It occurred in 2 of our 9 patients (22.2%). There was no specific relationship between age and serum virus antibody in our patients, but serum Ig G(+) and Ig M(-) suggested latent infection.

Rhegmatogenous retinal detachment occurs in 50% to 75% of cases not treated by prophylactic laser photocoagulation. Retinal detachment usually lags behind the onset of inflammation by several weeks to several months. Rhegmatogenous retinal detachment may occur as soon as 1 week after the onset of symptoms, however. One of our cases developed retinal detachment during the acute phase of retinitis. With severe cases of ARN, exudative retinal detachment can develop early in the disease course, in conjunction with active inflammation. It has been suggested, but not proven, that this finding indicates an underlying herpes simplex virus infection.

ARN is a clinical syndrome, so diagnosis depends on the history and associated physical findings. However, it is believed that most cases of ARN are due to secondary reactivation of a latent herpes virus infection. The possible involvement of a herpes group virus as the causative agent of the ARN syndrome was first suggested by Culbertson and associates in 1982, after histopathologic and electron microscopy evaluation of an enucleated eye. Since then, pathologic examination of retinal biopsy specimens, viral culture from intraocular specimens, immunocytochemical studies, serologic analysis of serum and/or intraocular fluid, and a temporal relationship between ARN syndrome and herpetic dermatitis have further implicated varicella-zoster virus, herpes simplex virus types 1 and 2, and occasionally cytomegalovirus (CMV) as causative agents of ARN syndrome.

In a large case series report, vitreous or aqueous specimens from 28 patients (30 eyes) were analyzed by PCR-based assays. The data suggested that VZV or HSV 1 caused ARN in patients older than 25 years, whereas it was caused by HSV 2 in patients younger than 25 years. The high specificity of the assay for herpes simplex virus DNA in aqueous specimens is promising for the use of PCR-based assays in the clinical management of viral retinitis. PCR for VZV was not checked due to non-availability of the test in our hospital. All of our PCR data for HSV were negative. This may have been due to the small amount and low virus titer of specimens or to the pathogen not being HSV. We suggest that vitreous specimens be considered for the PCR assay.

Management is geared toward medically treating the viral etiology and surgically treating its complications. ARN may occasionally follow a mild self-limiting course, but in general, it requires aggressive treatment with high-dosage intravenous acyclovir or famciclovir, which may reduce the incidence of the development of bilateral disease. High-dosage oral prednisolone may be required, particularly if optic disc swelling is present. To reduce the risk of retinal detachment, prophylactic laser demarcation can be performed around the necrotic foci.

Given the evidence that most cases of ARN are due to varicella zoster or herpes simplex, acyclovir therapy is recommended. All our patients were treated with intravenous 5-10 mg/kg acyclovir q8h for 7-10 days, followed by oral 400 mg acyclovir (p.o.) 5 times/day for 1-3 months. This time period was used because most occurrence in the second eye began within 6 weeks of the initial symptoms. Treatment with acyclovir reduced the risk of fellow-eye involvement at 2 years from 64.9% to 24.7%, and the protective effect was greatest during the first 14 weeks. Untreated eyes tend to show spontaneous regression of the necrotic lesions over a period of 6 to 12 weeks. Most clinicians have observed that acyclovir speeds this regression and prevents new lesion formation. Unfortunately, it does not decrease the incidence of subsequent retinal detachment.

Our patients were also treated with prednisolone and aspirin. Antithrombotic agents were given in an attempt to prevent vascular obstructive complications. There have been no clinical trials proving the efficacy of this, although aspirin (125 to 650 mg once or twice a day) has been advocated in the treatment of patients with ARN. High-dose systemic corticosteroid treatment appears to suppress intraocular inflammation. Treatment with periocular or systemic corticosteroids has been recommended within the first 24 hours of beginning acyclovir treatment. Systemic corticosteroid treatment is tapered down as the oral acyclovir is also reduced.

Regarding surgical results, partial retinal reattachment postoperatively occurred in all 6 eyes of
our 6 patients who underwent surgery for retinal detachment. Overall, anatomical success was found in 8 eyes (72.7%). Proper surgical management is necessary for preservation of sight. Most lenses either became cataractous after successful reattachment or were removed primarily during the retinal reoperation to facilitate vitreous base removal.

Sternberg et al. described a 75% decrease (17% vs. 67%) in the rate of RD using prophylactic photocoagulation in 12 eyes with ARN. In our study, eyes with less than grade II necrosis extension were good candidates for prophylactic peripheral retinal photocoagulation. Since clear media are required to successfully perform prophylactic laser photocoagulation, eyes manifesting the greatest vitreous reaction, as eyes 2, 3, 6, and 7 of our series, which probably had the poorest prognoses, are most likely to be unsuitable for laser photocoagulation. In fact, that type of laser treatment does not stop the progression of retinitis, and repeated treatments may be necessary.

Good anatomical success rates and visual results for vitrectomy without the use of scleral buckling have been reported. Peyman and coworkers employed a prophylactic pars plana vitrectomy, scleral buckling, and intravitreal infusion of acyclovir in 7 cases of active ARN that had not yet developed retinal detachment. Visual acuity improved in 5 cases. In our series, a vitrectomy was performed on 6 eyes in combination with various adjunctive procedures (Table 3). No eyes underwent a vitrectomy without placement of a scleral buckle. Partial retinal reattachment was seen postoperatively in all 6 eyes of our 6 patients who underwent surgery.

One recent report showed that final visual acuity might partially depend on the number of virus copies in ocular fluids. The extent of retinal arteritis, the amplitude of the electroretinogram, and levels of circulating immune complex at an early stage of acute retinal necrosis can be used as prognostic factors to predict the clinical course and visual outcome. The manifestation of diffuse retinal arteritis on initial examination was accompanied by reduced amplitude of the electroretinographic a and b waves and elevated levels of the circulating immune complex.

The long-term visual prognosis for patients with ARN syndrome is generally poor. It has been reported that 2/3 of all patients with ARN prior to the use of systemic antiviral therapy, prophylactic photocoagulation, and advanced microsurgical vitrectomy techniques are left with vision of 20/200 (6/60) or worse. In our series, final visual acuity of 1.0 was noted in 2 fellow eyes of 2 patients who had bilateral involvement and received acyclovir treatment as soon as ARN was diagnosed in the first eye. Early detection and prompt treatment with acyclovir seem to be key to improving the final visual outcome.

The percentage of eyes with ambulatory visual acuity was 36.3% (4/11), and visual acuity was preserved in 27.3% (3/11) at the last visit in our review. It is clear that the prognosis was associated with the necrosis location. In patients with poor visual outcome and anatomical failure despite vitreoretinal surgery, retinal necrosis extended rapidly, involved large areas of the retina including the posterior pole, and developed vitreoretinal adhesion at a high rate, as opposed to those patients with a good visual outcome. Direct causes of poor visual acuity were traction and/or rhegmatogenous retinal detachment and macular involvement, with exudates resulting from the above characteristics. Recurrence has been documented but cases are rare, and second-eye involvement may occur several years later.

Frequent dilated retinal examination of both eyes must be performed during the convalescence period and for several years thereafter.

REFERENCES

Hui-Ping Chen, et al

Acute retinal necrosis syndrome

急性視網膜壊死之臨床表現及手術結果

陳惠萍  郭錫恭 郭明倫 陳勇仁 蔡世豪

背 景： 為了進一步描述急性視網膜壊死病患之臨床特徵，視力之預後，手術治療的效果及
後遺症的危險因子。我們也回顧了目前常見的治療方式。

方 法： 這是個回顧分析，非比較性觀察研究。包括1990年1月到2002年12月，在高雄長庚
醫院的急性視網膜壊死之病患，共有9位病患(11隻眼睛)。病人血清及玻璃體液體被
收集加以分析，另外針對這些病患視網膜壊死的位置及手術結果加以探討。

結 果： 9位病患中2位是雙眼病例(2/9, 22.2%)。病人年齡與血清病毒抗體並無特異關係，
所有玻璃體液體對单纯疱疹病毒的多元聚合鍵反應都沒有特別發現。因急性視網膜壊
死導致視網膜剝離而接受手術的6隻眼睛，術後都達到局部視網膜復位。綜合來說，
解剖構造的成功率估計了8/11(72.7%)。最後一次檢查可達行動視力的佔了4/11
(36.3%)，而保留住視力的佔了3/11(27.3%)。

結 論： 快速擴展到後極部的網膜壊死與較差的預後有關聯。網膜壊死在二級範圍以內的
是進行預防性周邊雷射治療的適當人選。早期正確診斷及即刻性的治療是保住視力
的重要關鍵。
(長庚醫誌 2004;27:193-200)

關鍵字： 急性視網膜壊死，網膜剝離，周邊雷射治療。