Necrotizing and Nonnecrotizing Variants of Herpetic Uveitis With Posterior Segment Involvement

Barbara Wensing, MD, PhD; Jolanda D. F. de Groot-Mijnes, PhD; Aniki Rothova, MD, PhD

Objective: To describe the clinical characteristics and prognosis of diverse variants of herpetic uveitis with posterior segment involvement.

Methods/Design: Retrospective observational study of clinical, imaging, and laboratory data.

Results: Twenty-five patients were classified as having typical acute retinal necrosis (ARN) and 13 patients as not having ARN (non-ARN). Age at symptom onset, sex, bilateral involvement, and prevalence of viral species were not significantly different between patients in the ARN and non-ARN groups. All patients in the ARN group had necrotic retinal lesions that progressed quickly, whereas only 4 of 13 patients (31%) in the non-ARN group (P < .001) had necrotic retinal lesions that progressed slowly. Necrotizing variants were noted in 29 of 38 patients (76%), including 4 patients with slowly progressing lesions. Nine remaining patients in the non-ARN group had nonnecrotizing posterior uveitis without retinal lesions; their cases were characterized by vitritis, vasculitis, and/or papillitis, or as panuveitis without any distinct features (5 patients [38.5%]). At 6 months' follow-up, visual acuity of less than 0.1 developed in 13 of 25 patients (52%) in the ARN group and in 4 of 13 patients (31%) in the non-ARN group (P = .30).

Conclusions: Herpes simplex and varicella zoster viruses can cause a wide spectrum of clinical manifestations ranging from severe ARN to slow-progressing necrotizing and nonnecrotizing types of inflammation. The non-ARN variants are currently underdiagnosed. Patients with these variants could potentially benefit from earlier recognition and treatment.


Herpetic posterior uveitis predominantly has been linked to the ocular syndromes acute retinal necrosis (ARN) and progressive outer retinal necrosis. The latter is mainly found in patients with compromised immune systems, whereas the former typically affects patients with presumably competent immune systems. Acute retinal necrosis is characterized by typical clinical features and poor visual prognosis, with approximately half the affected eyes having a visual acuity (VA) of 0.1 or less at 6 months' follow-up. This syndrome is most often caused by varicella zoster virus (VZV) or herpes simplex virus (HSV)–1 and less frequently by HSV-2 and cytomegalovirus. Rapid diagnosis and prompt initiation of treatment are important to control the extent of necrotic lesions, minimize complications such as retinal detachment (RD), and protect vision.

Atypical manifestations of ARN and nonnecrotizing types of herpetic posterior uveitis have been reported sporadically but a systematic analysis has not been published yet, to our knowledge. In this article we describe the clinical features of 38 patients with herpetic uveitis with posterior involvement.

METHODS

PATIENT POPULATION

We included all 38 patients with a human immunodeficiency virus–negative diagnosis who had inflammation in the posterior segment of the eye and intraocular fluid analysis results that were positive for VZV or HSV and negative for cytomegalovirus or Toxoplasma gondii, who sought treatment in our department between October 1, 2001, and December 31, 2009. Patients were classified as having ARN or not having ARN (non-ARN) based on clinical criteria formulated by the Executive Committee of the American Uveitis Society. These criteria include: (1) focal, well-demarcated areas of retinal necrosis; (2) location of necrosis in the peripheral retina; (3) rapid, circumferential progression of necrosis; (4) occlusive vasculitis; and (5) prominent inflammatory reac-
determination of serum angiotensin-converting enzyme levels, serologic tests for syphilis, and chest radiography. Ocular fluid samples were obtained through diagnostic anterior chamber paracentesis or through pars plana vitrectomy. Polymerase chain reaction and Goldmann-Witmer coefficient analysis for HSV and VZV were performed, as described previously.7

DATA ANALYSIS

Medical records of the patients were analyzed retrospectively and assessed for patient demographics, viral species, clinical manifestations and complications, treatments used, and visual outcomes. Categorical variables were analyzed using the Fisher exact test. P<.05 was considered significant. Nonnormally distributed continuous variables of 2 groups were compared using the Mann-Whitney test via SPSS statistical software, version 15.0.1 (SPSS Inc, Chicago, Illinois). We analyzed clinical data based on number of affected patients; in patients with bilateral involvement, we included only data from the right eye.

PATIENT DEMOGRAPHICS AND CLINICAL FEATURES

Of 38 patients with herpetic uveitis and posterior segment involvement, 25 (66%) were classified as having typical ARN and 13 (34%) were assigned to the non-ARN group (including 4 with slowly progressive retinal lesions and 9 without any retinal lesions [a nonnecrotizing variant]). Therefore, the entire series included 29 patients with a necrotizing variant of herpetic uveitis (including 4 patients with atypically slow development). Patient demographics are shown in Table 1. Sex, age, and virus species did not differ widely between the ARN and non-ARN groups. Ocular findings in the anterior segment did not differ between patients in the ARN group and those in the non-ARN group, whereas the posterior segment findings differed for various features (Table 2). Immunosuppressive treatment for nonocular conditions before the onset of herpetic posterior uveitis symptoms was administered to 8 patients (4 in the ARN and 4 in the non-ARN groups).

Table 1 shows the clinical characteristics of the patients in the non-ARN group. Necrotic retinal lesions were present in 4 of 13 patients (31%; 2 with HSV and 2 with VZV). All lesions spread circumferentially but none pro-

OCULAR FLUID EXAMINATION

In this study, we included patients with positive analysis results for HSV and VZV in intraocular fluids in polymerase chain reaction and/or with a Goldmann-Witmer coefficient of 10 or greater. In our institution, we test aqueous fluid for diagnostic purposes in patients with severe and/or progressive uveitis of unknown origin and who had a negative result on our screening analysis for uveitis, which includes erythrocyte sedimentation rate, red and white blood cell counts, HLA-B27 typing, determination of serum angiotensin-converting enzyme levels, serologic tests for syphilis, and chest radiography. Ocular fluid samples were obtained through diagnostic anterior chamber paracentesis or through pars plana vitrectomy. Polymerase chain reaction and Goldmann-Witmer coefficient analysis for HSV and VZV were performed, as described previously.7

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gressed rapidly. We refer to this variant as slow-type ARN. Two of these 4 patients (50%) were initially diagnosed as having intermediate uveitis with snowbanking (Figure 1). The 9 patients with a nonnecrotizing variant had vitritis, vasculitis, and/or papillitis (4 patients [31%]), or panuveitis without any distinct features (5 patients [38%]). None of them had necrotic or other retinal lesions and/or retinal scars (Figures 2, 3, and 4).

Retinal detachment occurred in 7 of 25 patients (28%) in the ARN group, of which 4 patients’ detachment occurred within 3 weeks of onset of symptoms, and in 1 of 13 patients (8%) in the non-ARN group (P = .22). Of the 7 patients in the ARN group with RD, 4 had undergone preventive barrier laser treatment. Cystoid macular edema developed in 5 of 25 patients (20%) in the ARN group and in 2 of 13 (15%) in the non-ARN group (P = .99; Figure 5). Hypotony developed in 4 of 25 patients (16%) in the ARN group and in none of those in the non-ARN group (P = .29).

**TREATMENT MODALITIES**

Antiviral medication was prescribed to 20 of 25 patients (80%) in the ARN group and to 2 of 13 (15%) in the non-

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**Table 3. Herpetic Posterior Uveitis: Clinical Characteristics of Patients From the Non-ARN Group**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Symptom Onset, y</th>
<th>Virus Species</th>
<th>Necrotic Retinal Lesions</th>
<th>Vasculitis</th>
<th>Papillitis</th>
<th>VA &lt; 0.1 at 6 mo</th>
<th>Type of Herpetic Posterior Uveitis</th>
<th>Assigned Type</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>VZV</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Necrotizing</td>
<td>Slow-type ARN</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>HSV</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Necrotizing</td>
<td>Slow-type ARN</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>VZV</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Necrotizing</td>
<td>Slow-type ARN</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>HSV</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Necrotizing</td>
<td>Slow-type ARN</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>VZV</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Nonnecrotizing</td>
<td>Vasculitis/papillitis</td>
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<tr>
<td>6</td>
<td>71</td>
<td>VZV</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Nonnecrotizing</td>
<td>Vasculitis/papillitis</td>
</tr>
<tr>
<td>7</td>
<td>19</td>
<td>HSV</td>
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<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Nonnecrotizing</td>
<td>Vasculitis/papillitis</td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>HSV</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Nonnecrotizing</td>
<td>Vasculitis/papillitis</td>
</tr>
<tr>
<td>9</td>
<td>72</td>
<td>VZV</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Nonnecrotizing</td>
<td>Panuveitis</td>
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<tr>
<td>10</td>
<td>81</td>
<td>VZV</td>
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<td>No</td>
<td>No</td>
<td>No</td>
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<td>Panuveitis</td>
</tr>
<tr>
<td>11</td>
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<td>VZV</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Nonnecrotizing</td>
<td>Panuveitis</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>VZV</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Nonnecrotizing</td>
<td>Panuveitis</td>
</tr>
<tr>
<td>13</td>
<td>68</td>
<td>VZV</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Nonnecrotizing</td>
<td>Panuveitis</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARN, acute retinal necrosis; HSV, herpes simplex virus; RD, retinal detachment; VA, visual acuity; VZV, varicella zoster virus.

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**Figure 1.** Peripheral retinal lesions of 2 patients with slow-type ARN; lesions were initially mistaken for snowbanking.

**Figure 2.** Retinal vasculitis without necrotic retinal lesions in a 21-year-old patient 3 weeks after finishing a 10-day course of valacyclovir hydrochloride treatment for herpetic encephalitis.
ARN group (\(P < .001\)) within 3 weeks of onset of symptoms. After this period, another 5 patients in the ARN group and 8 in the non-ARN group received antiviral treatment. After commencing antiviral therapy, systemic steroid drugs were also prescribed to 22 of 25 patients (88%) in the ARN group and 3 of 10 (33%) in the non-ARN group. Pars plana vitrectomy was carried out in the active phase in 7 of 25 patients (28%) in the ARN group and in 3 of 13 (23%) in the non-ARN group (\(P > .99\)) for RD or diagnostic purposes. Preventive laser therapy was performed in 15 of 25 patients (60%) in the ARN group and in 4 of 13 (31%) in the non-ARN group (\(P = .17\)).

**VISUAL OUTCOMES AT 6 MONTHS' FOLLOW-UP**

The number of legally blind eyes did not differ between patients with necrotizing and those with nonnecrotizing variants of herpetic uveitis (15 of 29 [52%] and 2 of 9 [22%], respectively; \(P = .15\)), nor between patients from the ARN and non-ARN groups (13 of 25 [52%] and 4 of 13 [31%], respectively; \(P = .31\); Table 3). The most important reasons for loss of vision in the ARN group were RD (7 of 13 [54%]) and retinal atrophy with scarring (6 of 13 [46%]). The reasons for vision loss in the non-ARN group were retinal atrophy (2 of 4 [50%]), RD (1 of 4 [25%]), and undetermined (1 of 4 [25%]). In all

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**Figure 3.** Herpetic papillitis in 2 patients with a non–acute retinal necrosis variant of posterior segment involvement.

**Figure 4.** A non–acute retinal necrosis panuveitis variant of herpetic posterior segment infection. No distinctive retinal features are visible.

**Figure 5.** Papillitis and severe cystoid macular edema with exudates in a 28-year-old patient who also has a slowly progressing peripheral retinal lesion (not visible in this image).
In a previous report, the presence of occlusive vasculitis was associated with worse VA at 6 months follow-up; patients with vasculitis had, on average, a VA of 0.05 compared with 0.5 in patients without vasculitis \( (P = .001) \). In our series, VA of less than 0.1 was not associated with sex, age, viral species, hypotony, cystoid macular edema, presence of necrotic lesions or speed of progression of these lesions, or time to diagnosis. In patients in the ARN group, the start of antiviral treatment longer than 3 weeks after the onset of symptoms was associated with worse VA at 6 months’ follow-up (VA of 0.05 and 0.3; \( P = .03 \)). In patients in the non-ARN group, the VA at 6 months was 0.8 when treated within 3 weeks of the onset of symptoms and 0.3 when treated after 3 weeks of onset \( (P = .11) \).

Our study shows that intraocular infection with VZV or HSV can result in a wide spectrum of clinical manifestations ranging from fulminant ARN to milder, nonnecrotizing uveitis. In addition to classic ARN, we observed 3 additional types of herpetic uveitis with posterior involvement: (1) a slow type, with ARN-like necrotic lesions located in the retinal periphery but characterized by slow progression, (2) vasculitis/papillitis, with absence of retinal necrotic lesions, and (3) panuveitis with lack of necrotic lesions and no obvious vasculitis or papillitis.

Case reports of nonnecrotizing herpetic uveitis variants have been published sporadically. Bodaghi et al described 5 patients with positive test results for HSV or VZV in aqueous humor who had nonnecrotizing retinitis consisting mainly of vasculitis, papillitis, or vitritis. In addition, several case reports of atypical variants of ARN have been published. Our subdivision of the non-ARN group into the proposed variants is also applicable to these previous reports.

Our primary purpose was to describe the clinical features of the non-ARN variants of herpetic uveitis. In our series, the posterior segment findings between the ARN and non-ARN variants obviously differed because the presence of rapidly progressing peripheral retinal necrotic lesions was also a diagnostic criterion of ARN. Surprisingly, the extent of inflammation in the anterior and posterior segments did not differ between ARN and non-ARN variants. However, these findings are clearly biased by the treatment, the retrospective character of our study, and our limited number of patients. With more patients included and early treatment of all variants, a difference in inflammation severity (and other potential differences) may appear. Occlusive vasculitis was more prominent in the group with ARN. Moreover, the patient from the non-ARN group with occlusive vasculitis also had been diagnosed with Wegener disease.

The occurrence of VA of less than 0.1 in patients in the ARN group (13 of 25 [52%]) was similar to that shown in a previous report. More importantly, in the non-ARN group, 4 of 13 patients (31%) developed VA of less than 0.1, which is higher than for the general uveitis population in whom the prevalence of a legally blind eye was 18%. This finding may be explained partly by the late recognition and late treatment of viral infection.

We found a strong association between the presence of occlusive vasculitis and VA. The hypothetical explanation could be that vasculitis indicates a feature of severity of retinal disease. We also found an association between low VA and RD, in agreement with Sims et al and Meghpara et al. Hillenkamp et al studied the effect of early vitrectomy on the rate of secondary RD in patients with ARN. Although the rate of RD was reduced in the group that underwent early vitrectomy, final visual function was not better. Hillenkamp et al propose that retinal ischemia and optic nerve atrophy, rather than RD, are the main causes of poor visual outcome in their series of patients with ARN. This information is in agreement with our finding of worse visual outcome in patients with occlusive retinal vasculitis. We did not, however, find an association between an overt optic nerve atrophy and visual outcome. The higher rate of optic disc atrophy noted by Hillenkamp et al could be explained by a longer follow-up period in their study. Retinal detachment, vasculitis, and optic nerve atrophy are likely to relate to the severity and extent of retinitis, which has been shown to relate to worse visual outcome.

In patients in the ARN group, better VA at 6 months was achieved in those treated with antiviral therapy within 3 weeks of onset of symptoms. Given that the more severe cases are usually diagnosed and treated earlier, the real beneficial effect of early treatment could be larger than apparent from our results. In the non-ARN group, only 2 patients received antiviral treatment within 3 weeks and 10 patients received antiviral treatment after 3 weeks. The VA at 6 months was 0.8 for the ARN group and 0.3 for the non-ARN group \( (P = .11) \). Because of this small group size, however, we cannot draw any definitive conclusions from these results.

The underlying reason for the variable clinical manifestations and severity of herpetic posterior uveitis is unknown but could be, in addition to pathogen-related factors, influenced by the variation in patients’ immune capacity. Bodaghi et al hypothesized that necrotizing herpetic retinopathic variants are retinal equivalents of epithelial keratitis and assumed an intracellular presence of the viruses with subsequent cytopathic damage, whereas the nonnecrotizing variants were assumed to represent equivalents of stromal keratitis, ie, to be associated with tissue damage based on immunological processes. Obviously, more studies are required to test this hypothesis. Furthermore, it is feasible that the variation of clinical features might also be related to the number of viruses present in the eye and the capacity of the immune response of the host. Acute retinal necrosis has been thought to occur predominantly in people with competent immune systems; however, several reports indicate that depression in cellular immunity might be present in these patients. One could hypothesize that nonnecrotizing and slow-type ARN variants of herpetic posterior uveitis occur in patients who have better functioning cellular immunity than patients with full-blown ARN. This topic warrants further investigation.
Our study identified posterior uveitis variants caused by VZV or HSV that differ from the well-described ARN or progressive outer retinal necrosis syndromes. The number of patients with identified herpetic uveitis of the non-ARN type was relatively small. This may be because this type is relatively rare but it certainly also was influenced by the low clinical suspicion of, and subsequent lack of laboratory testing for, herpes viruses in patients with non-ARN types of posterior uveitis. The small group size limits the value of our conclusions, and future enlargement of the non-ARN group could reveal characteristics we were unable to identify here. In agreement with Bodaghi et al., we propose viral analysis of ocular fluids in patients with longstanding posterior uveitis, especially in those patients whose symptoms worsen while undergoing immunomodulatory treatments. Earlier diagnosis and start of therapy might improve visual outcome in these patients.

In conclusion, our findings show that HSV and VZV can cause a wide spectrum of clinical manifestations ranging from severe acute retinal necrosis to slow-progressing necrotizing and non-necrotizing types of inflammation. The non-ARN variants are currently underdiagnosed. Patients with these variants could potentially benefit from earlier recognition and treatment.

Submitted for Publication: August 9, 2010; final revision received September 21, 2010; accepted September 28, 2010.

Published Online: December 13, 2010. doi:10.1001/archophthalmol.2010.313

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Financial Disclosure: None reported.

REFERENCES


