Original
article

Necrotising herpetic retinopathy in patients with advanced HIV disease

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Objectives: To describe the presenting features, clinical and laboratory diagnosis, response to treatment, and outcome of necrotising herpetic retinopathy (NHR) in HIV infected patients.

Methods: Retrospective case records/laboratory data review of five HIV infected patients presenting to the specialist HIV/AIDS unit at UCL Hospitals, London from April 1994 to August 1996 with a clinical diagnosis of NHR.

Results: All patients had advanced HIV disease with a median CD4 count of $20 \times 10^6/l$. Three patients had cutaneous varicella zoster virus (VZV) infection within the preceding 8 weeks. All had uniocular loss of visual acuity; one also had headache and another ocular pain. All had typical retinal appearances. VZV DNA was detected in cerebrospinal fluid of four patients (and in vitreous fluid of one of the four) and in vitreous fluid of one other. One patient refused therapy and rapidly became blind. Four patients received intravenous foscarnet with intravenous aciclovir for 6 weeks: three subsequently received oral famciclovir and one oral valaciclovir; two patients also had intravitreal injections of foscarnet. In none of the four did treatment bring about improvement in visual acuity, but in all four visual loss from retinitis was halted.

Conclusions: NHR occurs in HIV infected patients with advanced HIV disease and is strongly associated with evidence of VZV infection. With aggressive use of antiviral drugs the outcome is not uniformly poor.

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Keywords: necrotising herpetic retinopathy; varicella zoster virus; HIV infection; DNA amplification

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Introduction

Herpesviruses are well described causes of ocular disease, including retinitis and keratitis, in both immunocompetent and immunosuppressed patients. While cytomegalovirus (CMV) is the most frequent cause of retinitis in HIV infected patients,¹⁻³ varicella zoster virus (VZV) and herpes simplex type 1 (HSV-1) have been reported as causing necrotising herpetic retinopathy.⁴⁻⁶ Acute retinal necrosis (ARN) was first described in immunocompetent patients.^{6,7} Six years after this term was coined, Holland discussed the classification of a variety of clinical appearances of retinitis, all thought to be associated with herpes viruses, which were subsequently described in patients both with and without underlying immunosuppression such as AIDS.⁷

Retinal necrosis secondary to herpes virus infection is recognised by multifocal and well demarcated whitening which begins in the peripheral areas of retina, becoming confluent and progressing both circumferentially and towards the centre. Patients with AIDS may lack the marked vitreous cell reaction and occlusive vasculopathy found in other patients and so the umbrella term necrotising herpetic retinopathy (NHR) is used to include a heterogeneous group of clinical descriptions, of which ARN and progressive outer retinal necrosis are subtypes.

Progressive outer retinal necrosis (PORN) is chiefly found in AIDS patients and is usually caused by VZV. It differs from ARN in having necrosis which underlies the retinal blood ves-

sels within the deeper layers of retina, little vitreous inflammation, a notably more rapid progression, and a particularly poor prognosis for vision^{5,6} as two thirds of eyes have no perception of light within 4 weeks of onset. The multiple foci may include central as well as peripheral retina at an early stage.

Thus, AIDS patients can develop NHR either as a modified form of ARN or as PORN, perhaps depending on the individual immune response to the herpes virus involved.⁵

Viral culture of vitreous or aqueous ocular fluid has not been shown to be clinically useful, because of the minute volume of fluid obtained in the sample and its relative insensitivity. In contrast, the technique of DNA amplification, using the polymerase chain reaction affords a rapid, highly sensitive, and specific technique for detection of herpesvirus DNA in cerebrospinal fluid (CSF) and ocular samples from HIV infected patients.⁸⁻¹¹ Detection of herpesvirus DNA in both CSF and ocular fluid strongly correlates with the presence of neurological and ocular disease respectively.⁸⁻¹⁰

In this study we describe the presentation, molecular diagnosis, treatment, and outcome in five HIV infected patients who presented with NHR.

Methods

We retrospectively reviewed the case records of five HIV infected patients with NHR who

Table 1 Ophthalmic features at presentation in patients with necrotising herpetic retinopathy

Patient	Right eye		Left eye		Type of retinitis
	Presenting features	Visual acuity	Presenting features	Visual acuity	
1	↓ acuity floaters	6/9	Nil	6/6	NHR
2	Nil	6/6	↓ acuity floaters, blurred vision, ocular pain, optic neuritis	CF	NHR
3	↓ acuity floaters	6/9	Nil	6/6	NHR
4	blurred vision ↓ acuity blurred vision unilateral headache	6/9	Nil	6/6	PORN
5	↓ acuity blurred vision	HM	Nil	6/6	NHR

↓ = reduced; CF = able to count fingers; HM = able to perceive hand movements; NHR = necrotising herpetic retinopathy; PORN = progressive outer retinal necrosis (for definitions see text).

Table 2 Clinical features and results of investigations in patients with necrotising herpetic retinopathy

Patient	Recent cutaneous zoster	Interval cutaneous zoster-NHR (weeks)	Interval onset (weeks) of NHR to		DNA amplification	
			LP	Vitreous tap	CSF	Vitreous fluid
1	Yes	8	0	ND	VZV + CMV, HSV-1, HSV-2 all -	ND
2	No	/	2	4	VZV + CMV, HSV-1, HSV-2 all -	VZV + Insuff
3	Yes	3	1	4	VZV - CMV, HSV-1, HSV-2 all -	VZV - HSV-1 - HSV-2 -
			8		VZV + CMV, HSV-1, HSV-2 all -	
4	No	/	1	ND	VZV + CMV, HSV-1 HSV-2 all -	ND
5	Yes	3	6	2	VZV - CMV, HSV-1 HSV-2 all -	VZV + HSV-1 - HSV-2 -

NHR = necrotising herpetic retinopathy; ND = not done; LP = lumbar puncture.
+ = Positive; - = not detected; Insuff = insufficient sample for testing for other herpesviruses.

presented to the specialist HIV/AIDS in-patient unit at University College London Hospitals between April 1994 and August 1996. We also recorded the total number of diagnoses of CMV retinitis made during this period. The clinical diagnosis of NHR was made by one of us (PF), an ophthalmologist experienced in the diagnosis of retinal disease in HIV infected patients. The following criteria were used for making a diagnosis of NHR in four patients⁷:

- (1) peripheral multifocal necrosis with rapid circumferential and centripetal progression towards the posterior pole
- (2) scanty or absent inflammation of the vitreous.

A further patient had clinical features of PORN, with multifocal deep retinal opacification in the peripheral retina which was rapidly

progressive, becoming confluent. Vitreal inflammation was scanty and vasculitis absent.^{5 6}

At the time of their presentation all patients had been investigated using a unit protocol. Following ophthalmic assessment a magnetic resonance imaging (MRI) scan of the head was performed at 1.5 Tesla using a standard clinical system (Siemens Magnetom 63SP, Erlangen, Germany), and a lumbar puncture was carried out. In addition to routine microbiological and biochemical analysis an aliquot of CSF was used for the nested polymerase chain reaction (nPCR) for detection of VZV gene 29, CMV *gB*, HSV-1 *gD*, and HSV-2 *gG* sequences as previously described.^{8-10 12 13}

In three patients a vitreous tap was also performed; this was subjected to nPCR for detection of herpesvirus DNA (as above).^{8-10 12 13}

Right fundus of patient 44 soon after presentation and before retinal detachment, showing multifocal white confluent necroses without haemorrhages. These appearances are typical of progressive outer retinal necrosis.

Results

Of the five patients four were male (three white homosexuals and one heterosexual of African origin); the female was white and heterosexual. Their mean age was 34.5 years (range 31-41 years). Two patients had a previous AIDS defining diagnosis (*Pneumocystis carinii* pneumonia); three had no previous HIV associated problems. The median CD4 lymphocyte count was 20 × 10⁶/l (range 10-80 × 10⁶/l); normal range 350-2200 × 10⁶/l.

All patients reported loss of visual acuity; in

Table 3 Treatment and outcome in patients with necrotising herpetic retinopathy

Patient	Treatment	Survival (weeks)	Right eye		Left eye	
			Outcome	Final acuity	Outcome	Final acuity
1	Nil (refused)	8 died of HIV wasting disease	Retinitis	NPL	Retinitis	NPL
2	IV foscarnet and aciclovir → oral famciclovir	78 died of CMV encephalitis	Retinitis halted	6/6	Retinitis halted	6/9
3	IV foscarnet and aciclovir → oral valaciclovir	12 died of HIV wasting disease	Retinitis and RD	NPL	No retinitis	HM
4	IV foscarnet and aciclovir → oral famciclovir	43 (continues)	Retinitis and RD	PL	Optic neuritis	6/6
5	IV foscarnet and aciclovir IVit foscarnet and IV cidofovir → oral famciclovir	35 (continues)	Retinitis and RD	NPL	No retinitis	6/9

IV = intravenous; IVit = intravitreal injection; RD = retinal detachment; NPL = no perception of light; PL = perception of light only; HM = hand movements.

addition one had unilateral headache and another had ocular pain (table 1). All were seen by an ophthalmologist (PF) within 1–14 days of onset of symptoms (mean duration of symptoms at first presentation 7.5 days). Initial ophthalmic signs included absent or mild inflammation of the vitreous and peripheral retinal necrosis in all patients. NHR was unilateral in all five patients at presentation (table 1). One patient (No 2) also had optic neuritis in the eye affected by NHR with no retinitis but pain on eye movement and visual acuity which recovered to 6/36 within 3 weeks. Three patients had a history of recent cutaneous unidermatomal varicella zoster infection, ophthalmic in one (table 2) and had received oral aciclovir 800 mg × 5 per day for 7–10 days for treatment of these episodes. General examination revealed no focal neurological abnormalities. The figure shows the fundal appearances of patient No 4.

Magnetic resonance imaging showed normal cerebral appearances in three patients and minor cerebral atrophy in two. In addition, in one patient (No 2) the optic nerve of the eye affected by NHR and optic neuritis was swollen, and in another (No 1) the optic nerve showed increased signal, indicative of inflammation, on the side affected by NHR, but this patient already had loss of visual acuity attributable to retinitis.

Lumbar puncture was performed in all patients within 6 weeks of onset of NHR (table 2). Routine biochemical and microbiological analyses gave normal or negative results in all patients. Only one patient (No 1) had a pleocytosis, the CSF showing 14 lymphocytes × 10⁶/l.

Conventional viral culture of CSF was done in patients 2–5; no herpesviruses were detected. DNA amplification for herpesvirus gave negative results for CMV, HSV-1, and HSV-2 in all five patients; VZV DNA was detected in CSF from four patients (table 2). In one patient (No 3) no detectable VZV DNA was present in a sample of CSF obtained 1 week after onset of NHR, but was present in a subsequent CSF sample obtained 7 weeks later (table 2). A vitreous tap was performed in three patients (table 2). VZV DNA was detected in two patients (Nos 2 and 5). No HSV-1 or HSV-2 DNA was detected in either of the samples assayed (Nos 3 and 5); there was an insufficient sample from the third

patient (No 2) for further analysis.

One patient (No 1) refused treatment. He presented with poor vision and rapidly became blind in the affected eye; subsequently the other eye became involved and progressed to total blindness within 1 month. The four other patients were treated initially with a combination of intravenous foscarnet 60 mg/kg three times daily and intravenous aciclovir 10 mg/kg three times daily for 6 weeks (table 3).

Two patients (Nos 3 and 5) developed retinal detachment during the initial phase of treatment with resultant poor vision. In two patients (Nos 2 and 5), despite treatment, the other eye became involved and was treated with the addition of intravitreal foscarnet (dose 2.4 mg/0.1 ml or 1.2 mg/0.1 ml) to the above regimen. Subsequently, in one patient (No 5) intravenous cidofovir was used to control progressive retinitis. A retinal detachment occurred in the second eye which was treated initially with laser retinopexy and then with vitrectomy and oil tamponade. With the combination of these manoeuvres there was stabilisation of vision at 6/9. Following initial treatment three patients received maintenance therapy with oral famciclovir, 750 mg once daily and one with oral valaciclovir, 500 mg twice daily (table 3). During follow up patient No 3 became blind in the eye unaffected by NHR as a result of optic neuritis shortly before death. This may have been the result of VZV as no other pathogen was identified. Necropsy was not performed. Of the four treated patients, two continue follow up, at 43 and 35 weeks respectively. Two died at 12 and 78 weeks from the time of diagnosis of NHR from unrelated causes: the retinitis remained stabilised in both patients (table 3).

Over the 28 month period of the study 66 new diagnoses of CMV retinitis were made in this centre.

Discussion

In this study we found that NHR is much less common than CMV retinitis in this group of HIV infected patients. All our patients presented with typical ocular abnormalities and in keeping with previous reports all our patients had advanced HIV disease and low CD4 lymphocyte counts,^{14 15} although three had no previous HIV associated problems. Previous studies have commented on the strong associa-

tion between NHR and antecedent cutaneous zoster infection.^{16 17} In our study the association was less clearly defined, as only three of the five patients had recent cutaneous zoster infection. A similar observation was made in a retrospective study of 26 HIV infected patients with NHR from five ophthalmology units in Paris in whom only 45% had a recent past history of cutaneous zoster.¹⁴

In addition to making the diagnosis by clinical criteria we were able to demonstrate evidence of VZV infection in CSF and/or vitreous fluid in all five patients by DNA amplification. VZV DNA was detected in the vitreous fluid of two of the three patients in whom samples were taken. This demonstrates the important role of molecular techniques in the diagnosis of ocular disease caused by herpesviruses. Prior administration of aciclovir in two patients did not influence detection of VZV DNA in vitreous fluid. Strikingly, none of our patients had detectable HSV-1 or HSV-2 in CSF or vitreous fluid. This observation is not unique to our patients and evidence of VZV infection has been demonstrated by antigen detection¹⁸ and PCR techniques¹⁰ in previous studies of immunocompetent and immunodeficient patients.

Detection of VZV DNA in CSF of HIV infected patients with advanced disease and acute neurological presentations is an infrequent finding.^{9 11} In one prospective study of 120 HIV infected patients undergoing diagnostic lumbar puncture only eight (6.6%) had detectable VZV DNA. All eight, who had a range of neurological disease including VZV associated meningoencephalitis, transverse myelitis and encephalopathy, and CMV retinitis/encephalitis, had concurrent or a history of recent cutaneous zoster.⁹ The infrequent detection of VZV DNA in CSF was also reported in a study of 500 patients from Milan, Italy.¹¹ Seventy two patients were studied retrospectively and 428 were studied prospectively, all underwent diagnostic lumbar puncture for evaluation of clinical neurological disease. VZV DNA was detected in CSF of only 13 (3%). Only three of these 13 patients were clinically evaluable. One had presented with zoster ophthalmicus and subsequently developed a contralateral hemiparesis. The two others had recent shingles "a few weeks before presentation"; one had cryptococcal meningitis, and the other had "acute brain dysfunction". Necropsy, in these two patients and in two other non-evaluable patients, showed no evidence of VZV infection.¹¹

Detection of VZV DNA in ocular fluid in the absence of clinical evidence of NHR has not been reported. In one prospective study vitreous fluid samples were obtained from 100 patients, 50 of whom were HIV infected and had presented with retinitis and 50 who were not known to be HIV infected and were undergoing vitreoretinal procedures—for example, for diabetic retinopathy and retinal detachment.¹⁰ There was no detectable VZV DNA in vitreous fluid from the 50 immunocompetent patients or from any of the HIV infected patients with CMV retinitis (n = 41),

two of whom also had zoster ophthalmicus, ocular toxoplasmosis (n = 2), or ocular toxocara infection (n = 1). Detectable VZV DNA was however present in all six HIV infected patients with a clinical diagnosis of NHR.¹⁰

A poor outcome from NHR in HIV infected patients has been previously reported. In one study of 26 patients 22 became totally blind, despite use of antiviral therapy active against both HSV-1 and 2 and varicella zoster.¹⁴ Details of treatment regimens were given for 24 of the 26 patients described. In 16 patients (67%) intravenous foscarnet (90–120 mg/kg twice daily) was used alone and in eight patients (33%) a combination of intravenous foscarnet (dose as above) and aciclovir (given at a higher dose 15 mg/kg three times daily) was used. For 15 of these patients the interval between onset of ophthalmic symptoms and commencement of antiviral therapy ranged from 1 to 60 days (mean 12 days). In this study the single patient whose visual acuity improved with therapy the onset/treatment interval was 5 days.¹⁴

With acute medical intervention in four of our patients, using a combination of intravenous foscarnet and intravenous aciclovir disease progression occurred in all, but was eventually halted as treatment continued. Additional intravitreal foscarnet injections were given in two patients with bilateral retinitis. In our study patients began treatment within 1–14 days of onset of symptoms, the average delay was only 7 days. At present, while there is no consensus on which agent(s) to use for treatment¹⁴ nor for how long treatment should last, we recommend 4–6 weeks of combination intravenous foscarnet and intravenous aciclovir because of concerns about possible resistance of varicella zoster virus to aciclovir,¹⁹ given either for antecedent cutaneous zoster infection or previous herpes simplex infection. Intravitreal foscarnet should be added to this regimen if retinitis is progressing in the second eye. We also advocate aggressive treatment of retinal detachment in these circumstances. The role of cidofovir, a potent nucleoside analogue which is effective against a broad spectrum of herpesviruses²⁰ requires further evaluation as treatment for NHR. We used this drug in one of our patients whose retinitis was progressing despite intravenous aciclovir and intravenous and intravitreal foscarnet. Cidofovir together with a combination of surgical manoeuvres resulted in stabilisation of the patient's vision.

Following presentation with NHR there is potential for recurrence if antiviral medication is stopped or reduced.^{5 21} Most centres therefore offer maintenance antiviral therapy; the most frequently used regimens being intravenous foscarnet, ganciclovir, or aciclovir,²¹ all of which require an indwelling central venous catheter for long term access.

Oral aciclovir has also been used for maintenance therapy, obviating the need for long term venous access.²² Long term compliance with therapy which needs to be taken five times a day is a potential problem in this patient group who may also be taking combi-

nation antiretroviral therapy, *P. carinii* prophylaxis and antifungal suppressive therapy. For this reason we used valaciclovir, the L-valine ester of aciclovir in a twice day regimen. In addition, valaciclovir is better absorbed than aciclovir and thus has better bioavailability. Oral famciclovir, the prodrug of penciclovir, subsequently became available and we used this in three patients in a once daily maintenance regimen. Famciclovir has more than 75% bioavailability and a long intracellular half life. It has been evaluated in treatment of immunocompetent patients with cutaneous zoster, and has been shown to be effective and well tolerated.²³ A single case report has documented its efficacy as maintenance therapy for varicella zoster virus associated necrotising retinopathy in an HIV infected patient.¹⁵ In this report the authors used twice the United Kingdom licensed dose of famciclovir—that is, 500 mg three times daily, because of concerns about reduced absorption of the drug in patients with AIDS.

In summary, NHR is an infrequent cause of retinitis in patients with advanced HIV disease. Progressive reduction in visual acuity can be halted and visual outcome can be good with early diagnosis and aggressive treatment including intravenous, intravitreal, and surgical interventions together with subsequent oral maintenance therapy.

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