Course and complications of varicella zoster ophthalmicus in a high HIV seroprevalence population (Cape Town, South Africa)

JC Richards¹, G Maartens² and AJ Davidse²

Abstract

Aim To describe the course and complications of varicella zoster ophthalmicus (VZO) in patients attending an eye clinic in a community with a high HIV seroprevalence.

Study design Prospective cohort study of consecutive patients presenting to a tertiary hospital eye clinic with VZO.

Method Patients recruited in 2001 and 2002 received standardized initial topical and systemic management, which was then modified according to complications.

Information on the course and complications of the disease was entered in a database prior to statistical analysis.

Results Information on 102 patients who had 250 visits to the eye clinic was collected. HIV serology was positive, negative, and unknown in 66, 22, and 14 patients, respectively. The most common complication was uveitis (40/102). Median delay from onset of rash to starting acyclovir was 5 days. Complications were present in 33 patients at the first visit. Complications were commoner in patients with positive Hutchinson's sign and were less common at CD4 counts <200. At CD4 counts, ≥200 HIV infection had little effect on the course and complications of VZO. Timing of commencement of Acyclovir therapy within or after 72 h had no demonstrable effect on the incidence of new complications.

Conclusion In a resource-limited setting, patients with the following characteristics should have immediate ophthalmic assessment: symptoms suggesting ocular complications or the presence of Hutchinson's

sign. All VZO patients should receive antiviral therapy at the first doctor's visit even if they present >72 h after onset of the rash.

Eye (2009) 23, 376–381; doi:10.1038/sj.eye.6703027; published online 2 November 2007

Keywords: HIV; varicella zoster ophthalmicus; herpes zoster; acyclovir

Introduction

Varicella zoster ophthalmicus (VZO) has become an increasingly common manifestation of the HIV pandemic. Its significant short- and long-term morbidity make it an important ophthalmic public health issue. African studies in recent decades have pointed to the association between HIV and VZO: HIV seroprevalence in patients with VZO in sub-Saharan Africa varies from 40 to 100% in South Africa,¹ Rwanda,² and Nigeria.³ In African countries where antiviral therapy has been unavailable, severe VZO complications with long-term morbidity have been reported: a Rwandan study reported corneal complications in 17 of 19 HIV-infected patients (89.5%),² and 25 of 100 patients developed trichiasis in an Ethiopian population.⁴

There is little published information on the course of VZO in populations with high HIV seroprevalence, in which varicella zoster affects younger patients and in which access to antiviral therapy is often limited. Management in the primary and tertiary care setting is largely based on evidence from the pre-HIV era. While

¹Division of Ophthalmology, Department of Surgery, University of Cape Town, Cape Town, South Africa

²Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa

Correspondence: JC Richards, Department of Ophthalmology, Royal Perth Hospital, Box X2213, GPO, Perth, Western Australia 6847, Australia
Tel: +61 8 94423083;
Fax: +61 8 92241391.
E-mail: diastella@iinet.net.au

Received: 1 April 2007
Accepted in revised form: 2 October 2007
Published online: 2 November 2007

complications, in our experience, appear to be severe in HIV-infected patients who are not treated with antiviral therapy, it is not certain whether or not such treatment obviates these poor outcomes.

In this paper, we describe the course and complications of VZO in a consecutive cohort of patients, from a community with a high HIV seroprevalence, attending an eye clinic with access to antiviral therapy. We make recommendations for improving management and referral patterns.

Materials and methods

We conducted a prospective 2-year cohort study of consecutive patients presenting in 2001 and 2002 with VZO to Groote Schuur Hospital eye clinic, a tertiary referral centre for patients older than 13 years serving a community with high HIV prevalence. Antenatal HIV seroprevalence in our province was 8.6% in 2001 and 12.4% in 2002. There were no specific public health referral criteria for shingles, but acyclovir was not available at public sector primary care clinics during the study period. Referral to our tertiary hospital was thus the only way of accessing antiviral treatment for patients with shingles. Primary care doctors generally referred all patients with suspected VZO to our clinic. They were managed by trainee and consultant ophthalmologists. Patients were collected prospectively. A standardized data capture form, consent procedure, counselling service, management regimen, and investigation protocol, was used. The variable severity of disease manifestations, as well as socioeconomic limitations, meant that consultations subsequent to the initial evaluation were on an 'as needed by assessment' basis rather than at uniform intervals.

Information on the course and complications of the disease was entered in an MS Access® database. Statistical analysis was performed using Intercooled Stata 8.2 for Windows.

Ethical approval was obtained from the University of Cape Town Research Ethics Committee.

HIV testing was done with informed consent following counselling. All patients received prescriptions for oral acyclovir 800 mg five times daily for 7 days, and topical chloramphenicol twice daily to the involved eye. Skin lesions were treated with potassium permanganate soaks followed by silver sulphadiazine 1% ointment twice daily. Analgesia was provided with paracetamol and codeine as needed, with addition of amitriptyline if required. Further treatment was given according to complications. Patient follow-up was determined by the nature and severity of complications.

Results

Demographics

During the study, 102 consecutive patients with VZO were assessed. In the case of three patients whose hospital folders were untraceable, only partial information was available. Demographic details are shown in Table 1. The median CD4 count was 280 cells/ μ l (range 48–1180) in the 44 HIV-infected patients who had CD4 counts measured.

Disease characteristics, course, and complications

There were 250 visits: 6 patients required only one appointment and 41 patients did not return for their final follow-up appointment, including 20 patients who were only seen once. Median follow-up was 13 days (range 0–491). There was no significant difference in the number of outpatient visits between HIV-infected and HIV-uninfected patients ($P = 0.81$; Wilcoxon's rank-sum test).

In 33 cases, a positive Hutchinson's sign was documented (characterized by a vesicle on the tip or side of the nose). Eight patients had simultaneous involvement of the first and second trigeminal divisions. Of these, five were HIV-infected, two HIV-uninfected, and one unknown. In the HIV-infected group, four had $CD4 < 200$ and two of these developed complications. Too few patients had multidermatomal disease to permit statistical analysis. No other cranial nerve involvement was diagnosed in any of our patients.

Table 1 Demographic data of study cohort of 102 patients

	HIV status			Comparison between HIV-positive and -negative
	Unknown	Positive	Negative	
Number	14	66	22	
Median age	36	33.2	55.3	$P < 0.01$
Sex		44 female, 22 male	10 female, 12 male	$P = 0.08$
African ethnicity	1	55 (83.33%)	10 (45.45%)	$P < 0.01$

P = difference between HIV-positive and -negative groups.

Patients presented to the primary care doctor a median of 5 days after the onset of pain and 4 days after the onset of rash. Patients were assessed by an ophthalmologist 24 h later and received acyclovir on the same day as the ophthalmology consultation (ie median 5 days after the onset of rash). There was no significant difference in time to presentation between HIV-infected and -uninfected patients ($P = 0.21$; Wilcoxon's rank-sum test). The median time from onset of paraesthesia to rash was 1 day (interquartile range (IQR) 0–2, maximum 7 days).

A total of 102 complications were seen in 58 patients, of whom 33 had a complication evident on the first visit (Table 1). More HIV-infected patients (25/66 37.99%) had complications at the first visit than HIV-uninfected patients (3/22 14%) ($P = 0.03$; two sample test of proportions). Fewer HIV-infected (15/66) than HIV-uninfected (15/22) patients received acyclovir within 72 h of onset of the rash ($P < 0.01$). Kaplan–Meier analysis showed no significant difference in the occurrence of new complications in patients receiving acyclovir within 72 h compared with those receiving it after 72 h ($P = 0.96$; log-rank test) (Figure 1). In Cox regression analysis, there was no significant relationship between the number of patients developing complications and age, HIV status, or delay in acyclovir treatment. Kaplan–Meier analysis of available data (obtained after relatively late presentation of the total group) showed that the onset of complications was no more rapid in HIV-infected than HIV-uninfected patients ($P = 0.5$; log-rank test) (Figure 2).

Of 33 patients with positive Hutchinson's sign of vesicles in the distribution of the nasociliary nerve, 25 (78.1%) developed complications. This was significantly more common than in the group with negative Hutchinson's sign of whom only 32/69 (46.4%) developed complications ($P = 0.01$).

Secondary infections developed in eight patients of whom six were HIV-infected. In this small group, HIV infection did not significantly influence the number of secondary infections ($P = 0.46$).

Details of the nature and number of complications are shown in Table 2. The most common were uveitis, punctate corneal staining, and frank corneal ulceration. In the whole group, median time from onset of rash to onset of uveitis was 11 days (IQR 6.5–21), and to corneal punctuate staining was 9 days (IQR 3–17). The longest time from the onset of rash to a new complication was 121 days preceding presentation of a patient with a corneal ulcer. In one patient, a recurrent acute uveitis attack occurred more than 200 days after the initial rash. One patient had an initial attack of uveitis lasting over 3 months. In all other patients, the uveitis was acute and lasted less than 8 weeks. It is possible that some chronic cases may have been missed as a result of failure of some patients to return for follow-up.

Figure 1 Time from acyclovir administration to new complication ($P = 0.96$; log-rank test).

Figure 2 Time to first complication by HIV status. Time in days where day 0 is the day of rash onset ($P = 0.50$; log-rank test).

Table 2 Complications by HIV status

Complications	HIV status		
	Positive	Negative	Unknown
Uveitis	31	6	4
Punctate staining	13	4	2
Corneal ulcer	10	2	1
Nummular keratitis	8	2	
Intraocular pressure >21	4	3	1
Disciform keratitis	2	2	
Dry eye	3		
Vasculitis	1		
Scleritis	1		
Episcleritis	1		
Trichiasis		1	
Total complications	74	20	8
Number of patients with complications	42	10*	6
Total number of patients	66	22**	14

*Comparison with the HIV-positive group ($P = 0.10$; two-sample test of proportions).

**Comparison with the HIV-positive group ($P = 0.25$; two-sample test of proportions).

For both HIV-infected and -uninfected patients, the timing was similar for the onset of uveitis at 10.5 (IQR 7–21) vs 11 days (IQR 10–17) ($P = 0.91$) and for corneal punctuate staining at 10.5 (IQR 3.5–17.5) vs 11 days ($P = 0.77$).

Figure 3 Time to first complication by CD4 count. Time in days where day 0 is the day of rash onset ($P=0.88$; log-rank test).

A statistically significantly lower number of HIV-infected patients with $CD4 \leq 200$ (18/36) developed complications than did those with $CD4 > 200$ (22/29) ($P=0.03$). Individually the only factor, that did not follow this trend was raised intraocular pressure. This was seen in three patients with $CD4 \leq 200$ compared with only one with $CD4 > 200$. There were no cases of dry eye in patients with $CD4 \leq 200$ compared with three in the group with $CD4 > 200$. Numbers were too small for statistical analysis. Among the 44 HIV-infected patients with uveitis who had CD4 counts available, only one had $CD4 < 100$. This patient had a CD4 count of 48 and was the only patient in the study with $CD4 < 100$. Kaplan-Meier analysis of HIV-positive patients in whom CD4 counts were performed showed that there was no significant difference in time to onset of first complication in patients with $CD4 \leq 200$ and those with $CD4 > 200$ ($P=0.88$; log-rank test) (Figure 3).

The diagnosis of VZO was associated with considerable visual morbidity. In many cases, the eyelids were too swollen to allow measurement of visual acuity on the involved side. In the 82 cases where visual acuity was recordable, 15 had visual acuity worse than 6/60 at presentation. At the final visit, 7/44 patients with recordable visual acuity still had visual acuity worse than 6/60. Out of 41 patients with two documented visual acuity tests, 21 improved, 13 got worse, and 7 were unchanged at the final follow-up.

Discussion

This study reflects an increasing proportion of younger HIV-infected patients presenting with VZO in South Africa. In 2001–2002, in Cape Town 66/102 (64.7%) were HIV-infected compared with 40% in Johannesburg in 1992.¹ As is the case in the general population, the majority of HIV-infected patients were black women. Only 22/102 (11.4%) were in the older HIV-uninfected

group to whom available antiviral studies based on the elderly population would be applicable.

In this study, VZO resulted in considerable ophthalmic morbidity. Fifty-seven patients had complications, of whom 33 had complications at presentation. All had problems, which would have caused photophobia, visual loss, circumcorneal redness, or severe eye pain (not skin pain). The 45 who had no complications (and hence no warning symptoms) could have been managed by the primary care physician with immediate antiviral therapy and education about warning symptoms, which should prompt a visit to the ophthalmologist. The presence of a positive Hutchinson's sign has been shown to have strong positive predictive value for the development of ocular complications⁵ and would also have been useful as a referral criterion for the primary care physician. In this group, use of Hutchinson's sign as a referral criterion would have only led to seven extra referrals (ie patients with no ocular complication). This would have saved many unwell and infectious patients an expensive trip to the tertiary hospital. It would have also reduced the risk of disease transmission to the large number of HIV-infected patients sitting in the ophthalmology clinic waiting area who could potentially have been infected with varicella zoster after less than 5 min of respiratory exposure.⁶

The accessibility of antiviral therapy appears to have mitigated some complications seen in African studies where treatment was not available. In our study, relatively fewer corneal complications (53 complications/102 patients = 51.9%) were seen than the 89.5% rate in the HIV-infected Rwandan group.² Similarly, only 1/102 patients developed trichiasis compared with 25/100 in the Ethiopian group.⁴ This may have been partially related to appropriate local therapy, which in our group included potassium permanganate soaks and silver sulphadiazine 1% ointment to the skin and chloramphenicol ointment to the lids. It is well established that oral antiviral treatment reduces late ocular complications from 50% in untreated to 20–30% in treated^{7,8} although the majority of studies are based on commencement within 72 h of the onset of the rash. We were unable to demonstrate a benefit of starting therapy within 72 h compared with later than 72 h. This is in keeping with the finding that there is still some benefit to treatment 7 days after the onset of lesions.⁹ The incidence of ocular complications in HIV-infected patients was 63.6%. This was similar to that in the San Francisco study where 69% of HIV-infected patients with VZO developed complications.¹⁰ In that population with median CD4 of 48, it is more likely that patients received antiviral treatment sooner after the onset of rash than our patients. At the time when our study was conducted, acyclovir was not available at the primary care level. This resulted

in a 24 h delay in therapy for many patients. The drug is now available to primary care physicians so that therapy can be commenced earlier. It will be interesting to review our subsequent complication rate to establish whether an overall earlier commencement of antiviral therapy is beneficial.

A Kenyan study found that HIV prolonged the course of VZO.¹¹ We were unable to demonstrate this with the follow-up data available to us. In our study, HIV-infected patients had a shorter mean follow-up of 35.97 days (range 0–437) than HIV-uninfected patients (59.95 range 0–491) despite similar numbers of clinical visits. The difference may be related to our HIV-infected patients being too unwell or unemployed and financially unable to attend their appointments. In our clinic, patients are followed up only until the primary ophthalmic problem or resultant complication has resolved.

The incidence of varicella zoster viral (VZV) infection increases with declining CD4+ lymphocyte count in HIV-infected patients: in the Amsterdam Cohort Study,¹² the incidence of VZV was 31.2 per 1000 person years at CD4+ count >500 cells/ μ l and 97.5 per 1000 person years at CD4+ count <200 cells/ μ l. VZV was not an independent predictor of HIV disease progression.¹² Interestingly, in our study, the incidence of complications was smaller in the group with lower CD4 count, suggesting that most clinically evident complications were proportional to the activity of the immune response more than to specific viral cytopathic destruction. Exceptions were ocular hypertension and dry eye. Dry eye may have been a manifestation of HIV rather than VZV infection. (Note that in our population at the time of the study, patients with extremely low CD4 counts were rare because of the high associated mortality.) It is to be noted that active viral infection was common in a study of 16 AIDS patients with chronic epithelial keratitis where 12 were tested with PCR. Of these, nine were positive for VZV in epithelial dendrites.¹³ Also of note in our population was that uveitis was still seen when the CD4 count was extremely low. The only patient with CD4 <100 had a count of 48 and had uveitis. It will be interesting to see whether any of the non-uveal complications recur with the increased availability of highly active antiretroviral therapy in a mode similar to that of immune reconstitution uveitis.

Interestingly, in our predominantly black population, no patients developed acute retinal necrosis although one had transient retinitis, which did not progress. This is in contrast with 5/29 AIDS patients (17%) who developed acute retinal necrosis, in a Florida study of immunocompromised HIV-infected patients.¹⁴ It is not clear whether any of these had additional risk factors such as systemic steroid treatment.

Conclusion/recommendations

On the basis of our lower incidence and severity of complications than in settings where antivirals are unavailable, we recommend that all patients presenting with VZO should be given immediate antiviral treatment. Given the lack of demonstrable benefit to giving acyclovir within 72 h of the onset of rash, we feel that even patients with delayed presentation should be offered antivirals. Patients with features of ocular complications (reduced visual acuity, ocular ache, photophobia, or circumcorneal redness) should be referred for urgent ophthalmic assessment. All patients with a positive Hutchinson's sign should see an ophthalmologist within 1–2 weeks. The remainder of patients should be educated about the above warning symptoms of ocular complications, which should prompt urgent ophthalmic consultation. If resources permit, the remaining patients, at lower risk of complications, should see an ophthalmologist once the rash has subsided and they have recovered from the infectious phase of their acute illness. HIV status had little effect on the course and complications of VZO in our population. Nevertheless, VZO was a useful sentinel of HIV infection so that young patients and those with risk factors should be tested for HIV. Patients should be advised that new complications may occur many months after the rash and that recurrent complications are a long-term possibility. Easy access to tertiary ophthalmic care should be ensured for these patients.

We have no proprietary interests. Costs of this project were funded entirely by research funds of the Division of Ophthalmology. We have no conflicts of interest to declare. This work has neither been presented at any meeting nor submitted elsewhere for publication.

References

- 1 Palexas G, Welsh N. Herpes zoster ophthalmicus: an early pointer to HIV-1 positivity in young African patients. *Scand J Immunol* 1992; **36**(Suppl 11): 67–68.
- 2 Kestelyn P, Stevens AM, Bakkers E, Rouvroy D, Van de Perre P. Severe herpes zoster ophthalmicus in young African adults: a marker for HTLV-III seropositivity. *Br J Ophthalmol* 1987; **71**: 806–809.
- 3 Umeh RE. Herpes zoster ophthalmicus and HIV infection in Nigeria. *Int J STD AIDS* 1998; **9**: 476–479.
- 4 Bayu S, Alemayehu A. Clinical profile of herpes zoster ophthalmicus in Ethiopians. *Clin Infect Dis* 1997; **24**: 1256–1260.
- 5 Zaal MJW, Volker-Dieben HJ, D'Amato J. Prognostic value of Hutchinson's sign in acute herpes zoster ophthalmicus. *Graefes Arch Clin Exp Ophthalmol* 2003; **241**: 187–191.
- 6 Vafai A, Berger M. Zoster in patients infected with HIV: a review. *Am J Med Sci* 2001; **321**(6): 372–380.
- 7 Liesegang TJ. Herpes zoster viral infection. *Curr Opin Ophthalmol* 2004; **15**: 531–536.

- 8 Severson EA, Baratz KH, Hodge DO, Burke JP. Herpes zoster ophthalmicus in Olmstead County Minnesota. *Arch Ophthalmol* 2003; **121**: 386–390.
- 9 Nickels AF, Pierard GE. Oral antivirals in herpes zoster therapy. *Am J Dermatol* 2002; **3**(9): 591–596.
- 10 Margolis TP, Milner MS, Shama A, Hodge W, Seiff S. Herpes zoster ophthalmicus in patients with human immunodeficiency virus infection. *Am J Ophthalmol* 1998; **125**: 285–291.
- 11 Tyndall M, Nasio J, Agoki E, Malisa W, Ronald AR, Ndinya-Achola JO *et al*. Herpes zoster as the initial presentation of human immunodeficiency virus type 1 infection in Kenya. *Clin Infect Dis* 1995; **21**(4): 1035–1037.
- 12 Veenstra J, Krol A, Praag RM, Frissen PH, Schellekens PT, Lange JM *et al*. Herpes zoster, immunological deterioration and disease progression in HIV-1 infection. *AIDS* 1995; **9**(10): 1153–1158.
- 13 Chern KC, Conrad D, Holland GN, Holsclaw DS, Schwarte LK, Margolis TP. Chronic varicella-zoster virus epithelial keratitis in patients with acquired immunodeficiency syndrome. *Arch Ophthalmol* 1998; **116**: 1011–1017.
- 14 Sellitti TP, Huang AJW, Schiffman J, Davis JL. Association of herpes zoster ophthalmicus with acquired immunodeficiency syndrome and acute retinal necrosis. *Am J Ophthalmol* 1993; **116**: 297–301.