

Natural history of herpes zoster ophthalmicus: predictors of postherpetic neuralgia and ocular involvement

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SUMMARY Seventy-one patients presenting with acute herpes zoster ophthalmicus were followed up for six months for a prospective analysis of the natural history of the disease. Acute and chronic ocular complications, nasociliary nerve involvement, age, sex, rash, and pain were assessed, and the results are presented. Acute pain was measured by a visual analogue scale. Postherpetic neuralgia (PHN) was more likely in patients over 80 and in those who scored their pain highly at presentation. Duration of rash was longer in patients who developed PHN. No other associations between the parameters studied were found. Nasociliary nerve involvement was associated with subsequent ocular disease.

Ophthalmic involvement has been considered the most important and potentially serious of all sites for herpes zoster. It is reported as occurring in 33¹ to 50%² of cases and has the highest incidence of postherpetic neuralgia (PHN).³ As a result it is the site that most often requires treatment, and this is usually prolonged.

A number of retrospective studies have looked at the natural history of herpes zoster. deMoragas and Kierland³ reviewed 916 cases, of which 149 (16.3%) were trigeminal. Burgoon *et al.*¹ reviewed 206 cases, of which 36 (17.5%) were ophthalmic. Both reported a higher incidence of complications in trigeminal involvement than elsewhere. Leisegang⁴ and Womack and Leisegang⁵ have more recently reviewed respectively 94 and 86 patients with acute herpes zoster for ocular complications.

This study we believe for the first time prospectively analyses the natural history of acute herpes zoster ophthalmicus. In view of their high incidence and morbidity we have in addition looked for predictive indicators of ocular involvement and PHN in order to allow early identification and treatment of those patients most at risk.

Patients and methods

Between January and August 1984 53 patients presenting to the Accident and Emergency Department

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of St Paul's Eye Hospital, Liverpool, with acute herpes zoster ophthalmicus were examined. In addition a further 25 patients were examined at Manchester Royal Eye Hospital in the same period. Seven patients were excluded, four at Liverpool and three at Manchester: three patients could not understand standardised questions; two were taking homoeopathy at the time of presentation, rendering analysis of subsequent progression potentially unreliable; one died of an unrelated cause; one was admitted to another hospital and lost to follow-up. A total of 71 patients were studied.

Standardised assessment forms were completed at presentation and at subsequent visits. Pain was assessed by visual analogue scale (VAS). The patient was asked to look at a 100 mm horizontal line with a zero at one end and three pluses at the other, with the instruction that the latter represented the worst pain he could possibly imagine. He was then asked to indicate with a mark along the line the severity of any pain being experienced at the time of the interview, and a measurement was taken in millimeters. At subsequent interviews a fresh line was presented. Ocular involvement, nasociliary nerve (NCN) involvement at presentation, rash severity, and duration were also assessed.

Assessment of pain by a VAS has been shown to be reproducible for the same individual and a method that allows reliable statistical analysis.⁶ Like all pain assessment it is subjective, and hence direct comparisons between patients cannot be made. However,

Table 2 Nature of ocular complications in 71 patients

Anterior uveitis	33
Keratitis	16
Disciform keratitis	9
Neuropathic corneal ulcer	3
Secondary glaucoma	2
Cranial nerve palsy	2
IVth nerve	1
VIth nerve	1
Contralateral herpes zoster ophthalmicus	1
Orbital apex syndrome	1
Total involved	36

was a difference in mean time of onset of involvement between those under 60 (1.10 weeks) and those aged 60 and over (2.23 weeks), and this achieved a high level of significance ($t=9.379$; $p<<0.001$). There was no significant difference in incidence of ocular involvement in relation to age: under 40 compared with over 40 ($\chi^2_1=0.530$; $p>0.1$); under 60 with over 60 ($\chi^2_1=0.295$; $p>0.5$); under 80 with over 80 ($\chi^2_1=2.613$; $p>0.1$). There was no significant difference in incidence of ocular involvement between the sexes ($\chi^2_1=0$) (Table 3).

Treatment of keratitis and uveitis was initially with acyclovir ointment, and topical steroids were introduced only later in severe unresponsive cases and in several of those which went on to chronicity.

Ocular involvement when still active at six months was defined as chronic and occurred in eight of 28 initially involved patients (28.6%). Chronic eye disease occurred in 14.3% of the 56 patients studied, with an age range of 54–91. However, the difference in incidence between those under 54 and those aged 54 and over did not achieve significance ($\chi^2_1=2.734$; $p>0.05$). Seven patients had keratouveitis still active at six months, two of these with an associated secondary glaucoma; a further three had neuropathic corneal ulcers. All had chronic anterior uveitis.

NASOCILIARY NERVE

NCN involvement was assessed at presentation and was defined as involvement by rash of the external nasal nerve. It occurred in 21 of 56 patients (37.5%). There was a highly significant association between presence of NCN involvement at presentation and the subsequent development of ocular complications

Table 3 Factors related to ocular involvement

Ocular involvement	Sex		NCN		Mean rash severity	PHN	
	M	F	+	-		+	-
+	13	15	16	12	2.04	7	21
-	12	16	5	23	1.86	5	23

($\chi^2_1=7.619$; $p<0.01$) (Table 3). If NCN involvement existed at presentation, there was a 76.2% chance of subsequent ocular involvement. If there was no NCN involvement at presentation, there was only a 34.3% chance of the eye developing complications.

There was no significant association between NCN involvement and chronicity of ocular complications in already involved eyes ($\chi^2_1=0.616$; $p>0.1$).

RASH

Severity of rash was estimated on a 1–3 scale, 1 representing mild, 2 moderate, and 3 severe. There was no significant difference between severity of rash and age: under 40 compared with 40 and over ($t=1.365$; $p>0.1$) (Table 1). There was no significant difference between rash severity in patients who went on to develop ocular involvement compared with those who did not ($t=0.924$; $p>0.1$) (Table 3).

Duration of rash was measured by duration of crusts in days, with a mean of 22.0 days and a range of 6–35 days. The mean duration of rash in each age group (Table 1) increased with age. Patients under 40 had a significantly shorter duration of rash than those aged 40 and over ($t=2.292$; $p<0.05$), and this held for those aged under 60 and 60 and over ($t=2.489$; $p<0.02$).

PAIN

Ten patients out of 56 were pain free at presentation (18%). Six of these developed pain at some time later (60%) and two of these went on to develop PHN. Four of the 56 patients (7%) were pain free throughout the course of the disease.

Table 1 shows the mean VAS scores at presentation and during subsequent time bands for each of four age groups. For the 20–39 age group the mean VAS scores fell dramatically by two weeks to one month ($p<0.01$), while this fall had occurred only by six weeks to three months for the 40–59 age group ($p<0.01$). For the 60–79 age group there was a fall in mean VAS by six weeks to three months, but this was of lesser significance ($p<0.05$). For the patients aged 80 and over there was no significant fall at any time during the acute phase ($p>0.05$).

An analysis was performed by comparing pain scores at presentation with those in subsequent time bands within each group by paired *t* tests.

Table 4 shows that compared with presentation there was a fall in incidence of pain at each subsequent time band. This achieves significance by six weeks to three months ($\chi^2_1=12.72$; $p<0.001$) and is very highly significant by six months ($\chi^2_1=41.34$; $p<<0.001$).

POSTHERPETIC NEURALGIA

Twelve of the 56 patients developed PHN (21%).

Table 4 Factors related to the development of postherpetic neuralgia

PHN	Sex		Chronic eye disease		NCN		Rash		Mean onset ocular involvement (weeks)	Mean VAS at presentation	
	M	F	+	-	+	-	Mean severity	Mean duration (days)		All ages	Over 60
+	5	7	2	5	2	10	2.17	25.08	2.20	47.42	53.10
-	20	24	6	15	19	25	1.88	21.25	1.71	34.80	30.78

Factors that might influence or be associated with this development were sought.

Age. The mean age for those patients who developed PHN was 70.75 years (range 25–92). This was significantly higher than those who did not—58.34 years ($t=2.242$; $p<0.05$). Table 1 shows the incidence of PHN related to age. 30% of patients aged 60 and over were afflicted, while the incidence rose to 71% at 80 and over. There was a highly significant difference in incidence of PHN between patients under 80 and those 80 and over ($\chi^2=8.727$; $p<0.01$), but a significant difference did not occur at lower ages.

Sex. There was no significant difference in incidence of PHN between the sexes ($\chi^2=0.0088$; $p>0.05$). This non-significance did not change when only patients over 60 were analysed ($\chi^2=0.01$; $p>0.5$) (Table 4).

Ocular involvement. This was not significantly associated with PHN ($\chi^2=0.002$; $p>0.5$) (Table 3). PHN was not associated with chronic eye disease ($\chi^2=0.001$; $p>0.5$) (Table 4). Mean time of onset of ocular involvement after onset of rash was greater in those who developed PHN, but this did not achieve significance ($t=0.962$; $p>0.1$).

Nasociliary nerve involvement. This was not associated with subsequent development of PHN ($\chi^2=1.576$; $p>0.1$) (Table 4).

Rash. Duration of rash was longer in those patients who developed PHN but this was not significant ($t=1.793$; $p>0.05$) (Table 4). Severity of rash was greater in those who developed PHN but was also not significant ($t=1.195$; $p>0.1$).

Acute pain. Mean VAS scores at presentation were higher in those patients who subsequently developed PHN (Table 4). This was significant for patients aged 60 and over ($t=2.204$; $p<0.05$) but not for the whole group ($t=1.402$; $p>0.1$). However, VAS scores of 35 mm and over at presentation were significantly associated with PHN when compared with scores below 35 mm ($\chi^2=5.197$; $p<0.05$). This was also true of comparisons between scores of under 30 mm and those of 30 mm and over ($\chi^2=4.023$; $p<0.05$), under 40 mm with 40 mm and over ($\chi^2=4.773$; $p<0.05$), and under 50 mm with 50 mm and over ($\chi^2=4.095$; $p<0.05$).

Table 5 shows that the mean pain score falls highly significantly by six weeks to three months in those patients who did not develop PHN but stayed high in those who did (paired t tests). The presence of pain at two weeks to one month was not associated with the development of PHN ($\chi^2=0.148$; $p>0.5$) but the presence of pain at six weeks to three months was, and this highly significantly ($\chi^2=8.680$; $p<0.01$).

Discussion

Frequency of infection increased with age until 70 and decreased thereafter, but with population correction there was a steady rise in incidence (Fig. 1), conforming with previous work.^{1,3,8,9} No cases were seen below age 20, supporting the similar findings of Burgoon *et al.*¹ and deMoragas and Kierland.³ However, Edgerton² found several reports of ophthalmic zoster in infancy and concluded that there are two periods in life in which infection is most likely—under 14 and over 40. It is possible that some affected infants may have been referred elsewhere during our study, explaining the lack of young cases. However, it is certain that infantile ophthalmic zoster is uncommon in the healthy population. The mechanism of infection in this age group is usually exposure to varicella zoster virus in utero at the time of maternal chickenpox.¹⁰

Of the 71 patients 63.4% were female, and this is consistent with previous reports.¹⁵ However, our age distribution analysis shows that under age 60 there is a highly significant increase in the number of males involved, while female cases were more likely among patients aged 60 and over.

Ocular complications seen in herpes zoster ophthalmicus have been well documented^{4,5,8,11–18} and occurred in 50% of our patients. Anterior uveitis was

Table 5 Mean VAS scores at presentation and subsequent time bands compared with subsequent onset of PHN

PHN	Presentation	2/52–1/12	6/52–3/12
+	47.42	38.75	34.50
		$p>0.10$	$p>0.10$
-	34.80	23.14	10.67
		$p>0.05$	$p<0.001$

commonest, occurring in 92% of patients with ocular involvement, followed by corneal complications in 52%. These two accounted for the great majority, and all but two cases of corneal disease were associated with an underlying uveitis. Disciform keratitis occurred in 25% of involved eyes and is approximately twice the incidence reported by Leisegang⁴ and Marsh.^{11,12}

Ocular motor palsies occurred in two patients and have been reported previously.^{8,16,17} Most series report a lower incidence, but Marsh *et al.*¹⁷ found a much higher 31% of new cases after careful examination, with several being contralateral or bilateral and third nerve involvement the commonest. As is typical, both our cases resolved spontaneously and completely.

One patient developed orbital apex syndrome seven weeks after the onset of the rash, with combined external ophthalmoplegia, proptosis, and ptosis. Treatment with indomethacin was begun, with a rapid improvement in orbital signs, but three months later the disc was atrophic and the best vision was 6/36. Marsh^{11,17,19} suggested the use of systemic steroids in these cases in order to reduce the occlusive vasculitis which is the probable underlying mechanism.

Ocular complications not seen in our series but reported elsewhere include nodular episcleritis and scleritis, third nerve palsies, and several corneal manifestations including mucous plaque keratitis, nummular keratitis, perforation, and interstitial keratitis.^{4,5,10,18,20}

The development of ocular complications was not related to age, sex, or severity of rash but did occur about one week later in the patients aged 60 and over. Nasociliary nerve involvement at presentation was strongly associated with subsequent development of ocular complications (76.2%), as was the converse. This has been suggested previously¹¹ but never subjected to statistical analysis.

Rash severity was not related to age, but duration of rash was significantly shorter in younger patients, especially under 40.

Much emphasis has been placed in the past on detailed and thorough investigation of all new cases for underlying malignant disease, especially lymphomas.³ Recent work has indicated the futility of this by showing that no previously undiagnosed malignancy is likely to be found at onset²¹ and that on long term follow-up the annual incidence of new malignant lesions is similar to that in the normal population.²² Our series lends support to this, as no cases of malignant disease were noted at any stage.

Acute pain associated with herpes zoster ophthalmicus is distinct from the later development of postherpetic neuralgia. This study shows that acute

pain as measured by VAS decreases with time, and this more rapidly in younger age groups. It is common at presentation, occurring in 82.1% of patients. Of those who were pain free at presentation 60% subsequently developed pain. It is therefore apparent that the great majority experience pain at some time.

The incidence of PHN in this study was 21.4%. This is much higher than the 7% reported by Marsh^{11,19} and the 9.7% reported by Burgoon *et al.*¹ It is more in keeping with the higher incidence reported by deMoragas and Kierland.³ The development of PHN in one patient aged 25 indicates that, though less common, this is an important complication in younger patients. One patient had no pain until the onset of PHN at six months; one should not assume that the absence of acute pain implies the eventual freedom from PHN.

This study shows that patients aged 80 and over have a significantly higher chance of developing PHN than younger patients. A high VAS pain score at presentation in patients aged 60 and over was significantly associated with PHN. Analysis suggests that a high index of suspicion should be given to presentation scores in excess of 35 mm. There was a very highly significant fall in VAS scores by six weeks to three months in those who did not develop PHN, while for those who did the scores stayed high. Furthermore the presence of pain in this time band was highly significantly associated with PHN.

No association was found between PHN and ocular involvement, chronic eye disease, duration or severity of rash, sex, or nasociliary nerve involvement at presentation.

This study shows that PHN is more likely in older patients and in those who score their pain highly on VAS at presentation. These two factors therefore allow some measure of prediction of which patients should be treated. As our and other work has shown this should be early, preferably before 14 days. Furthermore the failure of VAS scores to fall as the condition progresses should alert the clinician to the impending development of PHN, one of the most severe complications of this disease.

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