

## Ocular complications of herpes zoster ophthalmicus and post herpetic neuralgia- A clinical study

Nivedita Choudhary<sup>1</sup>, Dinesh Kumar Bhagat<sup>1\*</sup>, Anirban Chakrabarti<sup>2</sup>, Pranaya Kunal<sup>2</sup>

<sup>1</sup>Assistant Professor, Department of Ophthalmology, Mata Gujri Memorial Medical College & Lions Seva Kendra Hospital, Kishanganj, Bihar- 855107, India

<sup>2</sup>Associate Professor, Department of Psychiatry, Mata Gujri Memorial Medical College & Lions Seva Kendra Hospital, Kishanganj, Bihar- 855107, India

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### Abstract

**Background:** Herpes Zoster Ophthalmicus (HZO) affects the eye and adenexa and is often associated with severe ocular morbidity and neuralgic pain. It primarily affects the elderly and immunosuppressed people. Atypical clinical manifestations are more likely to occur in HIV positive patients than in immunocompetent individuals. Post herpetic neuralgia (PHN) forms one of the most chronic and distressing non-ocular complication of HZO. **Objectives:** To determine the spectrum of ocular complications, factors influencing visual prognosis, the effect of HIV-AIDS on the spectrum of ocular complications and the spectrum of post herpetic neuralgia in patients with Herpes Zoster Ophthalmicus. **Materials and Methods:** In this prospective interventional study, all patients who presented to the Department of Ophthalmology within 3 weeks of the onset of active zoster-vesicle formation affecting the ophthalmic branch of the trigeminal nerve were included. Patients with post herpetic neuralgia were referred to the Department of Neuropsychiatry. Patients with pre-existing ocular disorders were excluded from the study. **Results:** The most common predisposing condition seen in this study was HIV infection, which was seen in 44.2% (19/43) of the patients. A peak incidence was seen in the age group, between 21-60 years. A positive Hutchinson's sign correlated significantly with the ocular manifestations of decreased corneal sensation, acute corneal lesions and uveitis. Corneal involvement was seen in 95.3% (41/43). Uveitis was seen in 44.2% (19/43) of the patients. The visual outcome in most of the patients was good with maximum patients having no visual loss. Acute herpetic pain was seen in 97.7% (42/43) patients. Post-herpetic neuralgia was seen in 41.9% (18/43) patients. About 53% of the patients had no visual loss at 6 months follow-up, while 27.9% had mild-moderate visual loss and only 13.9% had severe visual loss. There were only 6 patients who had severe visual loss. **Conclusion:** HZO is more frequently presenting at a younger age, due to an increasing incidence of HIV AIDS. Patients with nasociliary and lacrimal nerve involvement and the presence of Hutchinson's sign are more likely to have serious ocular complications. Visual loss is more likely in this group, warranting close follow-up and prompt treatment. The spectrum of ocular complications in immunosuppressed did not significantly differ from the immunocompetent patients. The overall good outcome in this study is due to the use of early intensive antiviral therapy.

**Keywords:** Acyclovir, Herpes Zoster Ophthalmicus, HIV-AIDS, Hutchinson's sign, Post-herpetic neuralgia

### Introduction

Herpes Zoster Ophthalmicus is the term used for shingles involving the dermatome supplied by the ophthalmic division of trigeminal nerve. It is caused by the reactivation of varicella zoster virus. Involvement of the ophthalmic nerve by herpes zoster ranges in frequency from 8% to 56% in various series [1]. In HZO, ocular

\*Correspondence

**Dr. Dinesh Kumar Bhagat**

Assistant Professor, Department of Ophthalmology,  
Mata Gujri Memorial Medical College & Lions Seva  
Kendra Hospital, Kishanganj, Bihar- 855107, India

**E-Mail:** [drpranayakunal2@gmail.com](mailto:drpranayakunal2@gmail.com)

involvement is seen in more than 50% of the patients[1]. Classically, HZO begins with flu-like symptoms including fever, myalgia, and malaise for approximately one week. Typically, patients then develop a painful unilateral dermatomal rash in the distribution of one or more branches of V1: supraorbital, lacrimal, and nasociliary. The skin manifestations usually begin as an erythematous macular rash, progressing over several days into papules, vesicles, and then pustules[1,2]. In this study, the spectrum of ocular complications in patients with HZO was studied. Factors influencing ocular complications and visual outcome were evaluated. The effect of HIV-AIDS on the spectrum of ocular complications in HZO was also evaluated. Patients of post herpetic neuralgia were referred to Neuropsychiatry for appropriate management.

#### **Aims and objectives**

1. To determine the spectrum of ocular complications in patients with Herpes zoster ophthalmicus
2. To determine the factors influencing visual prognosis in patients with herpes zoster ophthalmicus.
3. To evaluate the effect of HIV-AIDS on the spectrum of ocular complications in patients with herpes zoster ophthalmicus
4. To evaluate the spectrum of post-herpetic neuralgia

#### **Materials and methods**

This study was conducted in the Department of Ophthalmology, M.G.M Medical College & L.S.K Hospital, Kishanganj, Bihar during the period August 2014 to July 2015 on patients who presented to the Department of Ophthalmology or were referred from the departments of Dermatology, General Medicine and Neuropsychiatry. All patients who presented to the Department of Ophthalmology within 3 weeks of the onset of active zoster vesicle formation affecting the ophthalmic branch of the trigeminal nerve were included. Patients with pre-existing corneal diseases, glaucoma, uveitis and severe retinal diseases were excluded. Forty three patients were included in the study.

A detailed history including information regarding past medical disorders, ocular diseases and drug history was obtained. History of blood transfusions and sexual history were specially asked for. All the details were collected on a proforma specially designed for this study. They underwent a complete physical, dermatological, neuropsychiatric and ophtha-

lmologic examination. Laboratory investigations like hemoglobin, total and differential count, blood sugar, renal function tests and ELISA for HIV (with informed consent) was done. Tzanck smear on the vesicular fluid was done for all the patients and the diagnosis confirmed. The ophthalmological examination included assessment of visual acuity, anterior segment using slit lamp bio-microscopy and fundus examination with the indirect ophthalmoscope.

Herpetic pain was recorded at each visit based on ratings on a 4-point verbal scale as described by Zaal et.al [3]. These were then classified as acute, to include pain at the initial visit and then at 1, 2 and 4 week visits. Post-herpetic neuralgia was the chronic pain that persisted one month after the rash onset. There is controversy regarding the definition of post-herpetic neuralgia. The definition of post-herpetic neuralgia differs in literature. Some studies consider neuralgic pain persisting 3 months after rash onset as post-herpetic neuralgia, while in ophthalmic literature it is considered as pain persisting one month after rash onset. In our study, the definition most commonly used in ophthalmic literature was used.

**Follow-up visits:** Patients were recalled for a complete ophthalmic, neuropsychiatric and general physical examination at 1, 2 and 4-week intervals, then at 3 months and finally at 6 months. At each visit the ophthalmological examination included best-corrected visual acuity (BCVA), corneal sensitivity, slit lamp examination, ocular motility testing and fundus examination.

**Treatment:** All patients received oral acyclovir (800 mg, five times daily) for 7-10 days. Antibiotic drops, cycloplegics and lubricating eye drops for ocular surface protection were also prescribed. Patients, who developed stromal keratitis or iridocyclitis, were started on topical steroids. If the skin involvement was severe, oral steroids were administered in the dose of 1 mg/kg body weight.

Most of the patients were seen as outpatients although few were admitted for severe edema, intractable acute herpetic pain and treatment of other systemic conditions-like uncontrolled sugars etc. Post herpetic neuralgia was managed with tricyclic antidepressants and analgesics by neuropsychiatrists. All data were analyzed by standard statistical procedures.

#### **Results**

**Age Distribution:** The study showed that the range of age group was between 6-75 years, the median of

which is 44 years. A peak incidence was seen in the age group, between 21-60 years.

**Table 1: Demographic and Clinical Characteristics of Study Participants**

Range of age group	6-75 years
Median age	44 years
Male	23%
Female	20%
Predisposing factors	
HIV infection	44.2%
Age	20.9%
hypertension	13.9%
diabetes mellitus	11.6%
tuberculosis	9.3%)

**Sex Distribution:** Almost equal sex distribution (male-23% and female 20%) was found.

**Predisposing Factors:** HIV infection was the most common (44.2%) predisposing factor seen among the patients, followed by age (20.9%), hypertension (13.9%), diabetes mellitus (11.6%) and tuberculosis (9.3%) [Table 1].

**Visual Outcome:** The visual outcome in most of the patients was good with 56.09% of the patients having no visual loss. About 56% of the patients had no visual loss at 6 months follow-up, 28% had mild-moderate visual loss and only 13.9% had severe visual loss. There were only 6 patients who had severe visual loss.

**Table 2: Visual Outcome among Study Participants**

Visual Outcome	Percentage
No visual loss at 6 months follow-up	56.09%
Mild-moderate visual loss	28%
Severe visual loss	13.9%

**Ocular Complications:** In the acute phase of ophthalmic zoster, conjunctival hyperaemia was seen in 41 (95.3%), which subsided within 2 weeks. Punctate keratitis was seen in 41 (95.3%) patients at the initial visit, it subsided by 4 weeks in most of the patients except in 3 patients in whom it was present even at 6 months. One of these patients had showed severe upper lid scarification, which led to constant inferior keratitis. The other two patients had associated keratoconjunctivitis sicca. Acute dendritic keratitis was seen in most patients in the first 2 weeks, which gradually subsided. None of the patients had persistent dendritic keratitis. None of these patients demonstrated late corneal epithelial keratitis suggestive of prolonged viral activity. At 2 weeks follow-up, corneal stromal infiltration was seen in four patients and increased to six patients at 4 weeks. Among the six patients who developed stromal keratitis, four had nummular and two had disciform keratitis. This however subsided in all patients by 6 months. None of these patients developed persistent corneal edema or neurotrophic ulceration [Table 3].

Acute iridocyclitis was seen at mostly the first and second follow-ups at 1 and 2 weeks respectively. At the end of 6 months, none of these patients had persistent uveitis and none of the patients were found to be steroid-dependent. Secondary glaucoma was seen only in two patients.

**Table 3: Complications among Study Participants**

Visual Outcome	Percentage
Conjunctival hyperaemia	41 (95.3%)
Punctate keratitis	41 (95.3%)
Uveitis	44.2% (19/43)
Constant inferior keratitis	2.33% (01/43)
Acute herpetic pain	97.7% (42/43)
Post-herpetic neuralgia	41.9% (18/43)

**Herpetic pain and post herpetic neuralgia:** About 25 patients had severe acute herpetic pain at the onset, and this persisted in the first week. However, at 6 months follow-up, only 5 patients had severe post-herpetic neuralgia. Post herpetic neuralgia was also found to be higher in the older patients with a mean of 53.1 years.

Age did not correlate significantly with the other ocular manifestations like conjunctival signs, corneal sensation, acute or chronic corneal signs, uveitis and acute herpetic pain.

**Correlation of diabetes mellitus with ocular manifestations and post herpetic neuralgia:**Diabetes

Mellitus did not correlate significantly with the ocular manifestations like conjunctival signs, corneal sensation, acute or chronic corneal signs, uveitis and acute or post herpetic pain.

**Correlation of HIV-AIDS with ocular manifestations and post herpetic neuralgia:** HIV-AIDS did not correlate significantly with the ocular manifestations like conjunctival signs, corneal sensation, acute or chronic corneal signs, uveitis and acute or post herpetic pain.

**Correlation of HIV-AIDS with age:** It was found that HIV-AIDS was seen more often in the younger age group with a mean of about 36.8 years.

**Correlations of involvement of various branches of ophthalmic nerve with severity of ocular complications and post herpetic neuralgia:** The involvement of the frontal nerve, a branch of the ophthalmic nerve did not correlate significantly with the ocular manifestations of conjunctival signs, corneal sensation, acute or chronic corneal signs, uveitis and acute or post herpetic pain. The involvement of the nasociliary nerve, a branch of the ophthalmic nerve correlated significantly with the ocular manifestations of corneal sensation, acute corneal signs like punctate and dendriform keratitis, uveitis and post herpetic pain. The involvement of the lacrimal nerve, a branch of the ophthalmic nerve correlated significantly with the ocular manifestations of decreased corneal sensation and uveitis. It did not correlate with conjunctival lesions, acute or chronic corneal lesions, and acute or post herpetic pain. The Hutchinson's sign being positive correlated significantly with the ocular manifestations of decreased corneal sensation, acute corneal lesions like punctate and dendriform keratitis and uveitis. It did not correlate with conjunctival lesions, chronic corneal lesions, and acute or post herpetic pain.

**Correlation of visual acuity with various ocular complications:** Visual acuity was lower in patients who had decreased corneal sensation. Visual acuity was also found to be decreased in patients with acute corneal lesions like punctate and dendriform keratitis, uveitis and in severe post herpetic neuralgia.

#### Discussion

The commonest predisposing condition seen in this study was HIV infection, which was seen in 44.2% of the patients. Age is the commonest predisposing factor in most studies[4,5]. A peak incidence was seen in the younger age group (21-60 years) in our study, unlike the previous studies where the older people (>60 years) were predominantly affected. This was because we had included both immunocompromised and immunocompetent patients. HIV-AIDS was seen more often in the younger age

group with a mean of about 36.8 years. In this series, the frontal nerve, branch of the ophthalmic nerve, was most commonly involved (86%). This concurs with various other studies including Karbassi et.al[6]. The nasociliary and lacrimal branches were almost equally involved, in 55.8% and 53.5% of the patients respectively. Isolated frontal nerve involvement was more common than the classic distribution along the ophthalmic branch of the trigeminal nerve. As expected only frontal nerve involvement did not correlate significantly with any ocular complications. However, the presence of nasociliary nerve involvement correlated significantly with the ocular manifestations of corneal sensation, acute corneal signs like punctate and dendriform keratitis, uveitis and post herpetic pain. The involvement of the lacrimal nerve, a branch of the ophthalmic nerve also correlated significantly with the ocular manifestations of decreased corneal sensation and uveitis[7]. This finding has not been reported in the other studies.

In our study, a positive Hutchinson's sign correlated significantly with the ocular manifestations of decreased corneal sensation, acute corneal lesions like punctate and dendriform keratitis and uveitis. Zaal et al have found Hutchinson's sign to be a powerful predictor of ocular inflammation in HZO, with a relative risk of 3.35[3]. Corneal involvement was seen in 95.3% (41/43), which is much higher than most other studies. However most of these corneal lesions were resolved completely without any sequelae. Leisegang found 65% (61/94) of the patients to have corneal involvement[4]. Zaal et al, reported 63% corneal involvement, which included mainly acute epithelial keratitis and stromal keratitis.<sup>5</sup> Kestelyn et al[8] and Sandor et.al[9] found a very high incidence of corneal complications in HIV positive patients at 89.4% (17/19) and at 43% (23/54) respectively.

The acute corneal lesions were seen in 70.7% (29/43) of the patients in our study and dendriform keratitis. They responded well to oral acyclovir, topical antibiotics and lubricants. Corneal lesions of a chronic nature were observed in only 14% (6/43) of the patients. These chronic corneal lesions are mainly stromal keratitis, which included nummular keratitis (in 4 patients) and disciform keratitis (in 2 patients). At 2 months follow-up, these stromal lesions, possibly attributed to a delayed immune response to persisting virus antigen, were still observed in the eyes of two patients. They were treated with topical steroids for several weeks and subsided within the six months follow-up period. Visual acuity was also significantly lowered in these patients. McGill reported a 40% incidence for nummular keratitis in HZO[10]. More recently Zaal et al reported an incidence of 50%[3].

Cobo et al found that those treated with antiviral agents were less likely to get stromal keratitis at 25% as compared to the non-treated group at 56%[10]. The lower incidence of stromal keratitis and their resolution in most of our patients without complications is due to the intensive antiviral therapy and the prompt instillation of topical steroids at an early stage.

In this study, none of patients developed long term corneal complications like bullous keratopathy, mucous plaques or neurotrophic keratitis. However, corneal sensitivity was reduced in 30.2% (13/43) of the patients. This decreased sensation was significantly associated with the involvement of the nasociliary and lacrimal branches of the trigeminal nerve and a positive Hutchinson's sign[11]. Visual acuity was also significantly lowered in patients who had decreased corneal sensation. But this did not lead to treatment-refractory corneal ulceration or perforation in herpes zoster-affected eyes, suggesting permanent nerve damage. Leisegang and Womack found 17.44% (15/86) of the patients to have neurotrophic keratitis, and these patients did not receive antiviral therapy[12].

Uveitis was seen in 44.2% (19/43) of the patients. Among these patients, 47.39% (9/19) of the HIV patients had uveal involvement as compared to 41.6% (10/24) of the non-HIV patients. Anterior uveitis is fairly common in HZO and has been reported in nearly 30% of the patients by Zaal et al[3], however, Womack et al. encountered a slightly larger number at 43%, which was similar to our study[12]. Use of antiviral agents did not decrease the incidence of uveitis, however it reduced the severity of inflammation thereby improving visual outcome in the series reported by Severson EA et.al[13]. Acute non-granulomatous iridocyclitis was seen at mostly the first and second follow-ups at 1 and 2 weeks respectively. Uveitis is never seen at the initial presentation as seen in our study. Hence it is important to inform the patient regarding the possibility of developing uveitis during the course of the disease and the need for regular follow-up. These patients were started on topical corticosteroids and cycloplegics to which they responded well. At the end of 6 months, none of these patients had persistent uveitis. Secondary glaucoma was seen only in two patients. This does not concur with the trial by Cobo et al who reported elevated IOP in 43% of patients early in the course of the disease[10,14]. Acute herpetic pain was seen in 97.7% (42/43) patients. Post-herpetic neuralgia was seen in 51.2% (21/41) patients. This value was found higher than that seen in the other series. Post herpetic pain was seen more often in the older age group with a mean of about 53.1 years. The more severe cases were elderly patients and in those with involvement of the

nasociliary nerve. Harding et al[15]. found an increased incidence of PHN in their study with increasing age, male sex and severe acute pain as the risk factors. Involvement of nasociliary nerve and ocular involvement did not increase the risk in their study. The pain resolved with medical management only. They were treated with tricyclic antidepressants and analgesics. The patients who had post-herpetic neuralgia had a significantly lower visual acuity, an observation not reported in other studies. However, this finding is not unexpected as PHN is more likely to occur in severe disease, which is also associated with more visual loss. Various studies report incidence rates ranging from 15-20% for post herpetic neuralgia. Harding et al[15] found 21% incidence of PHN in their study, which was less than that seen in our study. Severity and the incidence of PHN were also found to be higher in HIV positive patients by Kestelyn et al[8] However Margolis et al do not concur with this with only 2.4% (2/74) of patients developing PHN in their study, which included only patients with HIV[16].

Patients with prolonged PHN often suffer ongoing disturbances in physical and psychosocial functioning. In severe cases, PHN can lead to drug dependency, depression and even suicide. Effective pain management programs for these patients need to be developed. Combinations of all these medications and not a 'single drug was in help managing the PHN. Older patients and patients with visual loss, who are more likely to develop PHN according to our findings, require careful follow-up and early treatment for PHN. In this series, we did not encounter any posterior segment complications. The visual outcome seen in our series concurs with the various other studies, where HZO has a good visual outcome unless serious retinal lesions occur[12]. About 53% of the patients had no visual loss at 6 months follow-up, while 27.9% had mild-moderate visual loss and only 13.9% had severe visual loss. There were only 6 patients who had severe visual loss. One was due to phthisis bulbi in a HIV patient due to severe inflammation resulting from non-compliance of medication. The other 5 patients had complications like posterior subcapsular cataract in 4 and secondary glaucoma in 1 patient. Visual acuity was lower in patients who had decreased corneal sensation. Visual acuity was also found to be decreased in patients with acute corneal lesions like punctate and dendriform keratitis, uveitis and in severe post herpetic pain. Patients with HZO should be monitored frequently to detect these ocular complications associated visual loss to prevent permanent visual loss.

HIV-AIDS was the most common predisposing factor seen among the patients in this series. The spectrum of ocular complications in HIV

patients, seen in our series was similar to that seen and reported by Kestelyn where 89.4% patients had corneal involvement and 52.6% had uveitis[8]. Sandor et al reported keratitis and uveitis in 57% of their patients, which was less than that seen in our series[9]. Margolis et al reported stromal keratitis in 35% of the patients, which was more than that seen in our series[16]. They reported iritis in 50% of their patients, which concurs with our study. But they had a low incidence of PHN at 4% compared to our series. They also reported that 4 % of the patients had developed necrotizing retinitis, which was not seen in our series.

Presence of HIV infection did not increase the incidence of ocular complications like acute or chronic keratitis, uveitis, acute herpetic pain or PHN. There was no significant difference in the occurrence of ocular complications in the immunocompromised and immunocompetent patients, except in the severity of rash[17]. The HIV patients in our series had involvement of the adjacent maxillary and mandibular dermatome along with the ophthalmic dermatome more often than the immunocompetent patients. This was not reported in the other studies. None of our patients had posterior segment complications of HZO like ARN and PORN. These conditions were important causes of visual loss in HIV patients in the series reported by Margolis et al[16]. We have no explanation for this difference. The anterior segment complications seen in the HIV positive patients in our series concurs with the findings of Margolis et al[16]. This is because the patients in both the studies received early intensive antiviral therapy. In contrast patients reported by Kestelyn et al[8] and Sandor et al[9] had more severe ocular complications resulting in poor visual outcome as their patients did not receive antiviral therapy. Although the incidence of anterior segment complications was comparable or more than these two series, the final visual outcome was better in our study. This could be attributed to the early intensive antiviral therapy. In this series, none of the HIV positive patients developed chronic infective dendriform corneal lesions as reported by Margolis et al[16]. These lesions occur only in HIV positive patients with HZO and are cause for severe distressing intractable pain in these patients.

### Conclusion

The involvement of the nasociliary nerve, lacrimal nerve and the Hutchinson's sign being positive were associated with an increased incidence of ocular complications, including stromal keratitis and uveitis. With the increasing incidence of HIV infection, HZO is increasingly presenting at a younger age, as seen in our series. Thus, all young patients with HZO need serological testing for HIV. Visual loss was associated

with the presence of decreased corneal sensation. Visual acuity was also found to be decreased in patients with acute corneal lesions like punctate and dendriform keratitis, uveitis and in severe post herpetic pain. PHN was more likely to occur in the older age group. The presence of nasociliary nerve involvement and visual loss were more likely to be associated with PHN, an observation not reported earlier. Early treatment with tricyclic antidepressants will help in early resolution of this distressing complication of HZO. Serious visual loss could be prevented in most patients suffering from acute ophthalmic herpes zoster disease if vigorous acyclovir treatment is instituted early. The inflammatory and immune-mediated lesions of HZO respond well to topical steroids. The drug has a definite role in the treatment of corneal, scleral or uveal inflammation. The non-administration or inadequate use of steroids in the presence of inflammatory complications may lead to permanent visual loss in these patients.

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