Ocular Manifestations in Acute Herpes Zoster Ophthalmicus

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ABSTRACT

Objective: To determine the prevalence and clinical predictors of ocular involvement in acute herpes zoster ophthalmicus.
Methods: A retrospective chart review of 167 patients presenting with acute herpes zoster ophthalmicus at the Outpatient Department of Ophthalmology, Siriraj Hospital, was performed. All skin lesions along the ophthalmic branch of the trigeminal nerve (CN V_1) and ocular inflammatory signs were observed and documented.
Results: A total of 160 cases were analyzed. The prevalence of ocular inflammation in acute herpes zoster ophthalmicus was 73.1% (117/160). The types of ocular inflammations included conjunctival injection (99.1%), keratitis (51.3%), and iridocyclitis (21.4%). Nasociliary skin lesions (Hutchinson's sign) were the best predictor of ocular inflammation in acute herpes zoster ophthalmicus (p = 0.006, OR = 3.6, 95% CI: 1.5-9.1). Other factors associated with ocular inflammation were a period of longer than 4 days from the onset of rash to an eye examination (p = 0.007, OR = 3.2, 95% CI: 1.4-7.5), and the initiation of systemic acyclovir treatment after 3 days from rash onset (p = 0.037, OR = 2.3, 95% CI: 1.05-4.96).
Conclusion: There is a high prevalence of ocular inflammation in acute herpes zoster ophthalmicus, especially among individuals with Hutchinson's sign and delayed systemic acyclovir treatment. General practitioners should be aware of ocular involvement and refer high-risk patients for a complete ophthalmologic assessment.

Keywords: Herpes zoster ophthalmicus; Hutchinson's sign; acyclovir; ocular inflammation; uveitis (Siriraj Med J 2019; 71: 364-369)

INTRODUCTION

Herpes zoster ophthalmicus (HZO) is a reactivation of the varicella-zoster virus (VZV), a DNA-virus in the Herpesviridae family, along the ophthalmic division of the trigeminal nerve (CN V_1) after a previous infection such as chickenpox.[1-2] The clinical course usually starts with prodromal symptoms like fever, malaise, headache, and dysesthesia for approximately 1-4 days prior to the development of skin lesions. The skin manifestations are characterized by maculopapular rashes and vesicles along the CN V_1 dermatome, including the forehead, eyelids, and nose. The vesicles can progress to pustules and occasionally hemorrhagic vesicles, with the formation of crusts in 7-10 days.

The nasociliary nerve, a branch of the ophthalmic nerve, supplies both the nasociliary dermatome and intraocular tissue. The nasociliary dermatome extends from the tip and sides of the nose to the nasal bridge and medial canthus. The involvement of the nasociliary nerve presents as a variety of vesicular eruptions at the periorbital area, which can lead to a wide range of ocular inflammations (for instance, conjunctivitis, episcleritis, scleritis, keratitis, uveitis, optic neuritis, and oculomotor palsy). The subsequent ocular complications consist of

chronic uveitis, neuralgia, and neurotrophic keratopathy.[1,3,7-8] The intraocular involvement of HZO, especially uveitis and optic neuritis, can lead to multimorbidity, including blindness, if HZO is not recognized early or treatment is delayed.

The involvement of this dermatome (Hutchinson's sign) is considered a highly sensitive sign for ocular involvement in patients with HZO.[3-4] The immune status of the patients is another factor that can dictate the likelihood and types of ocular presentation of HZO.[5-7] To the best of our knowledge, there has been no study of the prevalence and risk factors of ocular involvement in acute HZO in Thailand. Therefore, this study collected the clinical data of Thai patients with acute HZO to determine the prevalence of ocular involvement in HZO and the predictors associated with ocular inflammation.

MATERIALS AND METHODS

The study was approved by the Siriraj Institutional Review Board (Si 179/2009). A retrospective chart review of patients who were clinically diagnosed with HZO and attended the Outpatient Department of Ophthalmology, Siriraj Hospital, between 2005 and 2008 was performed. All patients underwent an eye examination under a slit-lamp biomicroscope within 1 month of the onset of skin lesions. The degree of conjunctival injection was referenced from the Cornea and Contact Lens Research Unit grading scale (none, mild, moderate, and severe).[9] However, the clinical grading of the intraocular inflammations was modified from the cell grading system of the Standardization of Uveitis Nomenclature (SUN) Working Group by using a 1 mm x 1 mm slit beam under a slit-lamp examination (grade 0 = none; grades 0.5–1+ = mild; grade 2+ = moderate; and grades 3–4+ = severe).[10] Excluded were patients with previous ocular diseases, ocular trauma, or ocular surgery, or patients who had an eye examination later than 1 month after the onset of their skin lesions.

The diagnoses of HZO were based on the presence of a unilateral group of vesicles on an erythematous base and a painful skin rash within the ophthalmic dermatome. The following data were collected and recorded: demographic data (age, sex, and race), pre-existing diseases (acquired immune deficiency syndrome, diabetes mellitus, tuberculosis, autoimmune diseases, lymphoma, pregnancy, and others), and the date of onset of the skin rash. The extent of herpes zoster skin lesions was documented by marking anatomical drawings at the eyelids, forehead, alar, and tip of the nose.

The patients were treated with systemic oral acyclovir as soon as the diagnosis of HZO was established, and the time interval between the onset of HZO and the administration of the oral antiviral drug was recorded. Oral acyclovir (800 mg, 5 times per day) was prescribed for a period of 7–10 days, as per the guidelines of the American Academy of Family Physicians.[5]

The quantitative data were analyzed using the unpaired t-test method. The qualitative data were analyzed with the Chi-square and Fisher's exact tests. Multivariate analysis was performed with a backward stepwise logistic regression method. The odds ratio (OR) with 95% confidence interval (95% CI) and p-values were calculated. Two-sided p-values ≤ 0.05 were considered statistically significant.

RESULTS

Having been diagnosed with HZO, 167 patients were referred to the Ophthalmology Department to undergo an eye examination. Of those, seven were excluded (two due to an incomplete examination, one with a history of ocular surgery, and four with incomplete records). Data on the remaining 160 patients were summarized and analyzed.

Table 1 shows the demographic data of the 160 patients, who comprised 103 females (64.4%) and 57 males (35.6%) with a mean age of 51.5 ± 18.8 years (range 5-88). The median age of our subjects was also 51 years (interquartile range 39.0-65.7). There were no differences between including or excluding patients with extreme ages. The HIV patients tended to be younger than the non-HIV patients (mean age 46.37 ± 17.63 years versus 40.32 ± 7.25 years, respectively). The study revealed 22 patients (33.8%) who were anti-HIV positive from the 65 patients who underwent an anti-HIV test; 23 patients (14.4%) with hypertension; 11 patients (6.9%) with diabetes mellitus; 8 patients (5.0%) with tuberculosis; 8 patients (5.0%) with immunodeficiency; 4 patients (2.5%) with lymphoma; and 3 patients (1.9%) with systemic lupus erythematosus. The skin lesions were confined to the forehead in 134 patients (83.8%), the eyelids in 138 patients (86.3%), and the tip of the nose (or Hutchinson's sign) in 54 patients (33.8%). The median time from the appearance of the rash to acyclovir treatment was 3 days (range 1-30 days), and from the rash appearance to eye examination was 4 days (range 1-30 days).

Ocular involvement was found in 117 patients (73.1%) with a female predilection (74 females and 43 males), but there was no difference in laterality. Almost all patients (116/117) had a conjunctival injection with mild severity (70.1%). About half of the HZO patients with ocular involvement demonstrated corneal lesions that were dendritic, stromal keratitis, or both. Iridocyclitis

TABLE 1. Demographic data of all 160 patients with acute herpes zoster ophthalmicus.

Characteristics	N (Total = 160)
Age (years)	51.5 ± 18.8
Gender: Female	103 (64.4%)
Male	57 (35.6%)
Underlying diseases	
Acquired immunodeficiency syndrome	22/65 (33.8%)
Hypertension	23 (14.4%)
Diabetes mellitus	11 (6.9%)
Tuberculosis	8 (5.0%)
Other immunodeficiency	8 (5.0%)
Lymphoma	4 (2.5%)
Systemic lupus erythematosus	3 (1.9%)
Skin involvements	
Forehead	134 (83.8%)
Eyelids	138 (86.3%)
Tip or alar of nose (Hutchinson's sign)	54 (33.8%)
Median duration (days)	
Rash to acyclovir treatment (min, max)	3 (1, 30)
Rash to eye examination (min, max)	4 (1, 30)

was the only intraocular involvement seen in this cohort, accounting for 21.4% (25/117; Table 2).

A univariate analysis demonstrated that the prevalence of ocular involvement increased significantly if a patient presented with Hutchinson's sign (p = 0.008, OR = 3.5, 95% CI: 1.4-8.4) or an HIV infection (p = 0.024, OR = 9.1, 95% CI: 1.1-7.5); if the period from the onset of rash to an eye examination was > 4 days (p = 0.009, OR = 3.1, 95% CI: 1.4-7.1); or if the period from the rash onset to acyclovir treatment was > 3 days (p = 0.044, OR = 2.3, 95% CI: 1.08-4.9; Table 3). There was no statistical significance for the age of onset, sex, or other pre-existing diseases.

As to the multivariate analysis, HIV infection showed no statistically significant association with ocular involvement. In contrast, the 3 remaining factors (Hutchinson's sign, a period from rash onset to eye examination > 4 days, and a period from rash onset to acyclovir treatment > 3 days) significantly increased the risk of ocular complications (Table 4).

A subgroup analysis for different types of ocular involvement revealed associations between Hutchinson's sign and conjunctivitis (OR = 3.6, 95% CI: 1.48-8.76), keratitis (OR = 1.97, 95% CI: 1.0-3.85), and anterior

TABLE 2. Ocular findings in acute herpes zoster ophthalmicus patients.

Characteristics	N = 117
Laterality	
Right eye	67 (57.3%)
Left eye	50 (42.7%)
Conjunctival injection	
No	1 (0.9%)
Yes	116(99.1%)
Mild	82 (70.1%)
Moderate	32 (27.3%)
Severe	2 (1.7%)
Keratitis	
No	57 (48.7%)
Yes	60 (51.3%)
Dendrite	47 (40.2%)
Stromal	7 (6.0%)
Combined	6 (5.1%)
Iridocyclitis	
No	92 (78.6%)
Yes	25 (21.4%)
Mild	14 (12.0%)
Moderate	7 (6.0%)
Severe	4 (3.4%)

uveitis (OR = 2.74, 95% CI: 1.13-6.62). After adjusting for three factors (HIV status; a period from rash onset to eye examination > 4 days; and a period from rash onset to acyclovir treatment > 3 days), there were changes in the associations between Hutchinson's sign and conjunctivitis (OR = 4.17, 95% CI: 1.58-10.97), keratitis (OR = 2.18, 95% CI: 1.07-4.42), and uveitis (OR = 3.23, 95% CI: 1.28-8.18).

TABLE 3. Univariate analysis of factors associated with ocular involvement in acute herpes zoster ophthalmicus.

Factors	Ocular involvement (N = 117)	No ocular involvement (N = 43)	Odds ratio (95% confidence interval)	P-value#
Age (years)	50.4 ± 18.6	54.5 ± 19.4	–	0.227
Gender: Female	74 (63.2%)	29 (67.4%)	1.3 (0.5–3.1)	0.76
Duration of rash to eye examination >4 days	53 (45.3%)	9 (20.9%)	3.1 (1.4–7.1)	0.009*
Duration of rash to acyclovir treatment >3 days	60/114 (52.6%)	13/40 (32.5%)	2.3 (1.08–4.9)	0.044*
Underlying diseases				
HIV infection**	21/51 (41.2%)	1/14 (7.1%)	9.1 (1.1–75)	0.024*
Hypertension	15 (12.8%)	8 (18.6%)	0.6 (0.2–1.6)	0.503
Diabetes	9 (7.7%)	2 (4.7%)	1.7 (0.4–8.2)	0.729
Tuberculosis	7 (6.0%)	1 (2.3%)	2.7 (0.3–22.4)	0.683
Immunodeficiency	5 (4.3%)	3 (7.0%)	0.6 (0.1–2.6)	0.444
Lymphoma	4 (3.4%)	–	–	0.575
Systemic lupus erythematosus	3 (2.6%)	–	–	0.564
Skin involvement				
Forehead	99 (84.6%)	35 (81.4%)	1.3 (0.5–3.1)	0.804
Eyelid	103 (88.0%)	35 (81.4%)	1.7 (0.7–4.3)	0.411
Tip or alar of nose (Hutchinson's sign)	47 (40.2%)	7 (16.3%)	3.5 (1.4–8.4)	0.008*

#Unpaired t-test for quantitative data and Chi-square test, Fisher's exact test for qualitative data
*Statistical significance at p-value < 0.05, **Human immunodeficiency virus infection

TABLE 4. Multivariate analysis of factors associated with ocular involvement in acute herpes zoster ophthalmicus.

Factors	Crude odds ratio (95% confidence interval)	P-value#	Adjusted odds ratio (95% confidence interval)	P-value##
Hutchinson's sign	3.5 (1.4-8.4)	0.008*	3.6 (1.5-9.1)	0.006*
Duration of rash to acyclovir treatment >3 days	2.3 (1.08-4.9)	0.044*	2.3 (1.05-4.96)	0.037*
Duration of rash to eye examination >4 days	3.1 (1.4-7.1)	0.009*	3.2 (1.4-7.5)	0.007*
HIV infection**	9.1 (1.1-75)	0.024*	6.3 (0.8-49.9)	0.084

#Univariate analysis by Chi-square test
##Multivariate analysis by backward stepwise logistic regression
*Statistical significance at p-value < 0.05
**Human immunodeficiency virus infection

DISCUSSION

HZO is a common disease, and it may present not only as a skin manifestation but also involve ocular tissue. The ocular manifestations of HZO are variable; the acute eruptive phase can present as eyelid swelling, conjunctivitis, punctate keratitis, and/or corneal pseudodendrites. After the acute eruptive phase, the infection can cause stromal keratitis, nummular keratitis, disciform keratitis, neurotrophic keratopathy, and corneal mucous plaque. Severe ocular involvement has been reported as serpiginous keratitis, acute retinal necrosis, optic neuritis, orbital myositis, and cranial nerve palsy, but especially CN III and orbital apex syndrome, resulting in retinal detachment or a loss of vision. The clinical findings in the chronic phase include persistent corneal epithelial defects and postherpetic neuralgia.[8,11-13]

In the current report, we studied the ocular involvement of acute HZO. The age of onset of HZO for our cohort was about 50 years. This was younger than the ages found by Canadian and European studies, in which HZO was reported to occur at an age of approximately 60,[3,4,14] but it was much older than the age reported from Africa (around 35 years).[15-16] This may suggest that the age of HZO onset may have racial and/or geographic variations. Furthermore, we also found females were more predominant than males. In terms of the underlying diseases, previous studies by Nassaji-Zavareh et al. and Kaiserman et al. demonstrated a significant correlation between herpes zoster infection and diabetes mellitus, but not specific to HZO.[17-18] In our study, the proportion of diabetes mellitus patients was only 6.9% (11 patients), which is low. Therefore, we could not analyze the association between diabetes mellitus and herpes zoster infection.

We found that the most common skin lesions in HZO occurred on the eyelids, followed by the forehead and, least commonly, the tip of the nose. It is known that the virus replicates and migrates peripherally along the sensory nerve; when it reaches the skin, it can penetrate the epidermis and subsequently develop into skin lesions.[8] From previous studies, the most frequent nerve which the VZV affects is the frontal branch of the trigeminal nerve, which innervates the upper eyelid and forehead.[7,19-20] This explains why our study found those areas were the most common sites of HZO involvement.

The rate of ocular involvement in acute HZO in our study was 73.1%, which is comparable to the 74% involvement reported by Adam et al.[14] On the other hand, the rate is slightly higher than that found by Zaal et al. (63%).[19] However, the rate of ocular involvement in the HZO patients in the study by Zaal et al. was lower than in the present study because Zaal et al. only

included immunocompetent patients, and they were also referred to ophthalmologists earlier than in our study. The vast majority of ocular involvement in the current study was in the form of conjunctivitis (99.1%), which tended to subside gradually only after systemic oral antiviral treatment; some of the patients needed further attention. In addition, half of the patients (51.3%) with eye complications demonstrated keratitis (dendritic, stromal, or a combination), which needed topical antiviral therapy. About one-fifth of the patients (21.4%) had an intraocular involvement (iridocyclitis). As to other studies, Szwto et al. also found that conjunctivitis was the most common ocular manifestation.[21]

Our univariate analysis established a significant correlation between HIV infection and ocular involvement in HZO, but not for diabetes mellitus. Nevertheless, HIV infection did not have a significant association with ocular involvement in HZO after adjustment by the multivariate analysis. This mainly resulted from the low number of patients in the study who had undergone HIV testing. In contrast, a larger number of HIV patients was demonstrated by van Dyk et al. to have a strong association between HIV and ocular involvement.[22] It is recognized that a positive HIV status can lead to serious complications due to an individual's immunodeficiency. Therefore, even though HIV status was not significantly associated with ocular complications in our study, we suggest that all HIV patients with HZO should be examined by ophthalmologists to detect ocular complications and prevent the development of the most devastating forms.

The higher risk of ocular manifestations in HZO had a statistically significant association with Hutchinson's sign, a period > 4 days from rash onset to eye examination, and a period > 3 days from rash onset to acyclovir treatment. Hutchinson's sign (or skin involvement of the alar and tip of nose) demonstrated a statistically significant association with ocular involvement, whereas other skin involvement did not. In the study by Adam et al., ocular involvement in HZO and rash along the supratrochlear nerve distribution had a statistically significant correlation.[14] VZV is reactivated from the ophthalmic division of the CN V; the ophthalmic division gives rise to the terminal branches, namely, the supraorbital, supratrochlear, and nasociliary branches. The nasociliary branch innervates the skin of the tip of the nose and divides into the long ciliary nerve, which provides sensory innervation to the cornea and uvea.[8] This therefore explains why the common ocular complications in HZO patients are keratitis and uveitis. A previous study by Harding et al. also found that uveitis was the common manifestation in HZO (46.48%).[3] From this evidence, a rash appearing

along the nasociliary branch (Hutchinson's sign) or the supratrochlear branch could suggest that the HZO patients concerned have a high risk of ocular complications.

Treatment with an oral antiviral drug can arrest viral replication in the early phase of HZO, thereby stopping the progression and dissemination of the virus. We found there was a significant association between ocular involvement and both a duration of > 4 days from the onset of skin rash to the time of eye examination, and a duration of > 3 days from the onset of skin rash to systemic acyclovir administration. These data therefore indicate that a delayed examination or treatment allows the virus to migrate to the distant ophthalmic nerve, thereby increasing the risk of ocular involvement.

Given the low number of subjects, the current study did not find any severe ocular findings. Other studies have reported devastating forms of ocular manifestations, such as orbital myositis, ophthalmoplegia, optic neuritis, cranial nerve palsy, and orbital apex syndrome.[11-12] Nonetheless, we should take special care with HZO patients who have decreased visual acuities. This state could indicate that the patient has a chance of developing serious ocular complications.

The limitations of this study were related to its use of a retrospective chart review, which provided limited data, especially for underlying diseases such as HIV. An HIV test was performed in only 65 patients (40.6%), not all patients, and there were no records of viral loads or CD4 counts available to stage the severity of the HIV disease. Another limitation of our study was the subjective evaluation of the ocular inflammation grading (both for conjunctival and uveal involvements), which varied between the graders. However, this should not affect the main study results of the binary evaluation of ocular involvements.

CONCLUSION

HZO has been reported to cause many ocular complications. It is reactivated by an impaired host immune defense against VZV. There is a high prevalence of ocular inflammation in acute HZO, especially among individuals with positive Hutchinson's sign, delayed eye examination, and/or delayed acyclovir treatment. The data suggests that general practitioners should circumspectly assess HZO patients because any delay in diagnosis and treatment can result in severe ocular complications and increased morbidity. Patients who are suspected of having an ocular involvement should be referred to an ophthalmologist with haste.

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