Original Article

Risk Factors Associated with Comorbidities and Complications in Patients with Herpes Zoster Ophthalmicus: A Retrospective Analysis

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Abstract

Aim: The incidence of herpes zoster ophthalmicus (HZO) has been increasing in recent years. Although HZO is a self-limiting disease with an excellent response to treatment, it may cause significant neurological and ocular complications. We aim to identify the demographic and clinical characteristics of patients with HZO and determine the risk factors for ocular involvement and postherpetic neuralgia (PHN). Additionally, we investigate how these risk factors might inform early diagnostic and therapeutic interventions, ultimately guiding strategies to prevent HZO-related complications.

Materials and Methods: Eighty-six patients diagnosed with HZO and hospitalized at our institution were evaluated. All patients underwent inpatient follow-up to monitor for potential ocular complications. PHN was defined as either the documented persistent pain or use of analgesic medications three months post-HZO onset.

Results: A total of 86 patients were included, with a mean age of 67.2±13.0 years and a male-to-female ratio of 0.91. Ocular involvement was observed in 57.0% of cases. No significant associations regarding age, sex, immunosuppression status, or Hutchinson's sign were found between patients with and without ocular involvement. However, patients with maxillary or combined maxillary-mandibular branch involvement had a significantly lower risk of ocular complications ($P < 0.001$). PHN occurred in 46.5% of patients and was significantly linked to greater clinical severity ($P = 0.026$) and neurologic symptoms ($P = 0.005$).

Conclusion: Whereas Hutchinson's sign did not predict ocular involvement, involvement of the maxillary and mandibular branches was linked to a reduced risk of ocular complications. Clinical severity was positively correlated with PHN.

Keywords: Herpes zoster ophthalmicus, Hutchinson sign, ocular complications, postherpetic neuralgia, varicella zoster virüs

Introduction

Herpes zoster ophthalmicus (HZO) results from the reactivation of the varicella-zoster virus within the ophthalmic branch of the trigeminal nerve and can cause significant ocular morbidity. Approximately 10-15% of herpes zoster cases involve the ophthalmic division, and nearly half of these develop complications such as keratitis, uveitis, and conjunctivitis.[1,2] In patients with ocular involvement, long-term complications such as postherpetic neuralgia (PHN) may occur, contributing to chronic neuropathic pain. PHN significantly reduces the quality of life, particularly in older patients, often requiring prolonged management.[3] While systemic antiviral therapy has proven essential in reducing HZO-related complications,[1,4] the risk factors for ocular involvement and PHN in HZO are still

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not fully understood. We aim to identify the demographic and clinical characteristics of patients with HZO and determine the risk factors for ocular involvement and PHN. Additionally, we investigate how these risk factors might inform early diagnostic and therapeutic interventions, ultimately guiding strategies to prevent HZO-related complications.

Materials and Methods

Study Design and Patient Selection

In this single-center, retrospective study, we evaluated 86 patients diagnosed with HZO admitted to our institution between 2007 and 2023. Demographic and clinical data were collected from electronic medical records. The inclusion criteria mandated a clinically confirmed diagnosis of HZO, while patients with incomplete medical records or pre-existing ocular disorders were excluded from the study. The retrospective study was approved from the Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 368, date: 25.11.2022).

Data Collection

Collected data included demographic characteristics (age, sex), duration of symptoms prior to hospital presentation, and presence of immunosuppression. Photographic documentation is a part of standard clinical practice at our institution. All hospitalized patients have photographs taken at admission and during their inpatient stay. In this study, these photographs were reviewed to document and verify the presence of clinical severity, periorbital edema, Hutchinson's sign, laterality (right or left-sided involvement), and specific facial area involvement (eyelid and scalp), including maxillary and/or mandibular branch involvement. Clinical severity was classified based on the presence of hemorrhagic and necrotic crusting. Mild cases were defined by minimal or absent crusting, moderate by prominent crusting without significant necrosis, and severe by extensive hemorrhagic and necrotic crust formation. Ocular manifestations and systemic dissemination were recorded. The following were documented: antiviral treatment regimens, neurological symptoms, and systemic markers such as elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels.

Outcome Measures

All patients were closely monitored during hospitalization for the emergence or progression of HZO-related ocular complications through consultations with ophthalmologists. PHN was defined as any persistent pain symptom or the continued use of analgesic medications documented in medical records at least three months after HZO onset.

Primary Outcomes

Incidence of ocular complications: To determine the overall rate of ocular involvement (e.g., keratitis, kerato-uveitis, conjunctivitis) in HZO.

Incidence of PHN: To quantify the prevalence of PHN.

Risk factors for ocular involvement and PHN: To identify demographic, clinical, and treatment-related variables associated with developing ocular complications or PHN.

Secondary Outcomes

Symptom duration and treatment timing: To explore the effect of early vs. delayed presentation on clinical severity, ocular outcomes, and PHN incidence.

Clinical severity, immunosuppression, and neurological symptoms: Investigate the impact of overall clinical severity (e.g., hemorrhagic or necrotic crusting), immunosuppression status, and neurological symptoms on ocular involvement and PHN development.

Treatment regimens: To assess whether the choice or duration of antiviral therapy correlated with ocular involvement or PHN.

Statistical Analysis

All data analyses were conducted using SPSS version 28.0 [IBM Corp., Armonk, NY, United States of America (USA)] with a significance level set at $P < 0.05$. Statistics were computed, including means, standard deviations, medians, minimum and maximum values, frequencies, and percentages. The normality of data distributions was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Depending on the distribution, independent quantitative variables were analyzed using either t-tests or Mann-Whitney U tests. Chi-square or Fisher's exact tests were employed for categorical variables to identify associations. Spearman's correlation analysis was applied to explore relationships between variables of interest.

Results

Demographic and Clinical Characteristics

Eighty-six patients were included in the study, with a mean age of 67.2±13.0 years (30-98 years). Of these patients, 52.3% were female. The duration of symptoms before hospital presentation ranged from 1 to 20 days, with a median of 5 days. Most patients (62.8%) sought medical attention more than three days after symptom onset. Immunosuppression

was present in 14.0% of the patients. Periorbital edema was observed in 88.4% of cases, predominantly ipsilateral (74.4%).

Hutchinson's sign was observed in 24.4%, while 8.1% of patients showed disseminated disease. Elevated ESR and CRP levels were common, with 59.3% and 64.0% of patients showing elevated levels, respectively. Neurological symptoms (headache, transient confusion, ophthalmoplegia, and hypoesthesia) were present in 23.3% of patients. Table 1. Summarizes the demographic and clinical data of the patients diagnosed with HZO.

Primary Outcome Measures

Ocular involvement and its risk factors: Ocular involvement was documented in 57.0% of the patients, with keratitis being the most prevalent manifestation (30.2%), followed by kerato-uveitis (20.9%) and conjunctivitis (5.8%). There were no significant differences in age, sex, symptom duration prior to presentation, immunosuppression, periorbital edema, laterality, Hutchinson's sign, ESR, and CRP level between patients with and without ocular complications ($P > 0.05$). However, individuals with maxillary or combined maxillary-mandibular branch involvement were significantly less likely to experience ocular involvement compared to those with only ophthalmic branch involvement ($P < 0.001$) Table 2 provides a detailed comparison of patients with and without ocular involvement.

PHN and its risk factors: PHN developed in 46.5% of patients. There were no statistically significant differences in age ($P = 0.082$), sex ($P = 0.434$), or symptom duration prior to presentation ($P = 0.286$) between patients with and without PHN. However, PHN was significantly associated with greater clinical severity ($P = 0.026$), with 35.0% of patients in the severe group developing PHN compared to 10.3% in the mild and moderate groups. Additionally, neurological symptoms were markedly more frequent in the PHN group (37.5%) than in the non-PHN group (10.3%) ($P = 0.005$). Elevated ESR and CRP levels were not significantly associated with the development of PHN ($P > 0.05$ for both). Table 3 provides a detailed comparison of patients with and without PHN.

Secondary Outcome Measures

Symptom duration and treatment timing: Most patients (62.8%) presented more than three days after symptom onset (median of five days). There was no statistically significant difference between delayed presentation (> 3 days) and ocular involvement ($P = 0.358$) or PHN incidence ($P = 0.286$).

Clinical severity, immunosuppression, and neurological symptoms: Clinical severity was categorized as mild (26.7%), moderate (46.5%), or severe (26.7%) based on the extent of hemorrhagic or necrotic crusting. Severe clinical involvement was significantly associated with PHN ($P = 0.026$) but not with ocular complications ($P = 0.155$). Immunosuppression did not correlate with either outcome (both $P > 0.05$). Neurological symptoms were more common in the PHN group (37.5% vs. 10.3%, $P = 0.005$), underscoring their potential value as an early indicator of chronic pain risk.

Treatment regimens: All patients received antiviral therapy, predominantly acyclovir (70.9%), for a mean duration of 9.1±2.9 days. Neither the choice of antiviral agent ($P = 0.160$) nor total treatment duration ($P = 0.557$) had a significant impact on ocular complications. Similarly, no significant differences were found in treatment duration ($P = 0.401$) or antiviral choice ($P = 0.212$) between patients with and without PHN.

Discussion

In this cohort of HZO patients, maxillary and mandibular branch involvement emerged as an unexpected factor reducing ocular complications, while classical markers such as Hutchinson's sign were not significant predictors of ocular involvement. This finding diverges from some previous studies[1,5] that emphasize the prognostic role of Hutchinson's sign. It is possible that variations in patient populations, timing of antiviral treatment, or early ophthalmologic consultation influenced our results. Our study also highlights the strong association between PHN development and severe clinical presentation. The presence of hemorrhagic or necrotic crusting may reflect a more aggressive viral reaction, potentially increasing nerve damage and chronic neuropathic pain.

While some studies have reported that HZ and HZO occur more frequently in females than males, our results did not indicate a significant difference in occurrence between sexes.[6-8] Several reports suggest a higher incidence of zoster in immunocompromised states; however, there are limited data regarding the role of immunosuppressive risk factors in developing HZO manifestations.[9-11] In our study, immunosuppression was present in only 14% of patients and was not associated with an increased risk of ocular involvement, PHN, or disseminated disease. Severe manifestations of HZO have been documented more frequently in immunocompromised individuals, such as those with human immunodeficiency virus/acquired immunodeficiency syndrome.[2,12] HZO typically presents as an acute, painful eruption of erythema, vesicles, macules, papules, and blisters around the periorbital region, often accompanied by periorbital edema and ptosis.[5] In our study, 14% of patients also exhibited periorbital edema in the non-involved contralateral eye. Although the underlying cause is unknown, it is thought that bilateral periorbital swelling

Table 1. Demographic and clinical characteristics of patients with herpes zoster ophthalmicus

		Mean ± SD/n(%)
Age		67.2±13.0
Gender	Male	41 (47.7)
	Female	45 (52.3)
Symptom Duration (Days)		5.3±3.2
	≤ 3 days	32 (37.2)
	> 3 days	54 (62.8)
Immunosuppression		12 (14.0)
Malignancy		11 (12.8)
Periorbital edema	None	10 (11.6)
	İpsilateral	64 (74.4)
	Bilateral	12 (14.0)
Hutchinson's sign		21 (24.4)
Involved side	Right	43 (50)
	Left	43 (50)
Eyelid involvement		79 (91.9)
Scalp involvement		56 (65.1)
Maxillary/mandibular involvement	None	59 (68.6)
	Maxillary	18 (20.9)
	Maxillary + mandibular	9 (10.5)
Ocular involvement		49 (57.0)
	Conjunctivitis	5 (5.8)
	Keratitis	26 (30.2)
	Keratouveitis	18 (21.0)
Onset of ocular involvement (days)		6.0±3.8
Dissemination		7 (8.1)
Neurological symptom		20 (23.3)
Postherpetic neuralgia		40 (46.5)
Clinical severity	Mild	23 (26.7)
	Moderate	40 (46.5)
	Severe	23 (26.7)
Erythrocyte sedimentation rate	Normal	30 (34.9)
	High	51 (59.3)
C-reactive protein	Normal	28 (32.6)
	High	55 (64.0)
Antiviral treatment	Acyclovir	61 (70.9)
	Valacyclovir	14 (16.3)
	Acyclovir + valacyclovir	8 (9.3)
	Brivudine	1 (1.2)
	Acyclovir + brivudine	2 (2.3)
Duration of antiviral treatment (days)		9.1±2.9
Length of hospitalization (days)		9.2±3.3

Min.: Minimum, Max.: Maximum, SD: Standard deviation, PHN: postherpetic neuralgia

Table 2. Risk factors for ocular involvement in HZO

		Ocular involvement (-) (n = 37) Mean ± SD/n (%)	Ocular involvement (+) (n = 49) Mean ± SD/n (%)	*P*
Age		65.7±13.0	68.3±13.1	0.370[t]
Gender	Male	18 (48.6)	23 (46.9)	0.875[X²]
	Female	19 (51.4)	26 (53.1)	
Symptom duration (days)		5.5±2.8	5.2±3.6	0.358[m]
	≤ 3 days	12 (32.4)	20 (40.8)	0.426[X²]
	> 3 days	25 (67.6)	29 (59.2)	
Immunosuppression		5 (13.5)	7 (14.3)	0.919[X²]
Malignancy		5 (13.5)	6 (12.2)	0.862[X²]
Hutchinson's sign		11 (29.7)	10 (20.4)	0.319[X²]
Maxillary/mandibular involvement	None	16 (43.2)	43 (87.8)	**0.000**[X²]
	Maxillary	14 (37.8)	4 (8.2)	
	Maxillary + mandibular	7 (18.9)	2 (4.1)	
Dissemination		5 (13.5)	2 (4.1)	0.113[X²]
Clinical severity	Mild	11 (29.7)	12 (24.5)	0.155[X²]
	Moderate	13 (35.1)	27 (55.1)	
	Severe	13 (35.1)	10 (20.4)	
Neurological symptom		9 (24.3)	11 (22.4)	0.838[X²]
Postherpetic neuralgia		19 (52.8)	21 (48.8)	0.727[X²]
Erythrocyte sedimentation rate	Normal	17 (48.6)	13 (28.3)	0.061[X²]
	High	18 (51.4)	33 (71.7)	
C-reactive protein	Normal	10 (27.8)	18 (38.3)	0.315[X²]
	High	26 (72.2)	29 (61.7)	
Duration of antiviral treatment (days)		8.8±2.4	9.4±3.2	0.557
Length of hospitalization (days)		8.5±3.2	9.7±3.3	0.094[m]

[t]: Independent sample t-test, [m]: Mann-whitney u test, [X²]: Chi-square test (Fisher's exact test)
HZO: Herpes zoster ophthalmicus, SD: Standard deviation

is usually due to gravitational edema rather than the spread of infection to the opposite side of the face.[13] A minority of patients present with only ophthalmic symptoms and no skin rash, suggesting that the risk of ophthalmic complications may not be directly related to the severity of the skin rash.[14,15] Keratitis and conjunctivitis have also been reported as common ocular manifestations of HZO in previous studies.[16-19] Our study's ocular involvement rates were similar to those of previous studies. Initiating systemic antiviral therapy within the first 72 hours is associated with less severe ocular features.[8] The average duration from onset of symptoms to examination by an ophthalmologist was 4.0±2.3 days in one study.[20] In our study, the time of ocular involvement was 6.0±3.8 days. Although the timing of ophthalmologic consultations has not been widely documented, one study found an average duration of approximately five days from rash onset to clinical presentation and subsequent referral to an ophthalmologist.[21] Another analysis of a USA claims database showed that 75.8% of patients consulted an ophthalmologist within seven days of receiving an HZO diagnosis.[7] Our study underscores the crucial role of ophthalmologic consultation, which was requested for all patients at the onset of treatment. This early involvement ensures comprehensive care and better outcomes for patients. Hutchinson's sign (cutaneous involvement of the tip of the nose), indicating nasociliary involvement, is a strong predictor of ocular complications in HZO.[22] However, our study did not find a significant association between Hutchinson's sign and ocular involvement, possibly due to patient characteristics or diagnostic and treatment timing variations. Furthermore, our findings showed no significant differences in ocular outcomes between patients treated with valacyclovir and those treated with acyclovir, consistent with studies suggesting similar efficacy between these agents.[23] In our study, patients started antiviral treatment early. A cohort study conducted in the USA, involving numerous cases of HZO, found that nearly 60% of patients initiated antiviral treatment within seven days of their diagnosis diagnosis.[7] In our study, we found that 37.2% of patients initiated antiviral treatment within 72 hours of symptom onset, while 62.8% began treatment after this period, with acyclovir being the most frequently

Table 3. Risk factors for postherpetic neuralgia in HZO

		PHN (-) (n = 39) Mean ± SD/n (%)	PHN (+) (n = 40) Mean ± SD/n (%)	P
Age		69.3±13.4	64.1±12.9	0.082[t]
Gender	Male	20 (51.3)	17 (42.5)	0.434[X²]
	Female	19 (48.7)	23 (57.5)	
Symptom duration (days)		5.1±3.4	5.8±3.3	0.286[m]
	≤ 3 days	12 (32.4)	20 (40.8)	0.432[X²]
	> 3 days	25 (67.6)	29 (59.2)	
Immunosuppression		4 (10.3)	7 (17.5)	0.352[X²]
Malignancy		4 (10.3)	6 (15.0)	0.526[X²]
Ocular involvement	None	17 (43.6)	19 (47.5)	0.938[X²]
	Conjunctivitis	2 (5.1)	3 (7.5)	
	Keratitis	12 (30.8)	11 (27.5)	
	Keratouveitis	8 (20.5)	7 (17.5)	
Maxillary/mandibular involvement	None	26 (66.7)	26 (65.0)	0.546[X²]
	Maxillary	10 (25.6)	8 (20.0)	
	Maxillary + mandibular	3 (7.7)	6 (15.0)	
Dissemination		4 (10.3)	1 (2.5)	0.157[X²]
Clinical severity	Mild	12 (30.8)	11 (27.5)	**0.026**[X²]
	Moderate	23 (59.0)	15 (37.5)	
	Severe	4 (10.3)	14 (35.0)	
Neurological symptom		4 (10.3)	15 (37.5)	**0.005**[X²]
Erythrocyte sedimentation rate	Normal	16 (44.4)	13 (33.3)	0.324[X²]
	High	20 (55.6)	26 (66.7)	
C-reactive protein	Normal	11 (28.9)	13 (33.3)	0.678[X²]
	High	27 (71.1)	26 (66.7)	
Duration of antiviral treatment (days)		8.8±2.3	9.4±2.9	0.401[m]
Length of hospitalization (days)		8.6±3.2	9.5±3.2	0.183[m]

[t]: Independent sample t-test, [m]: Mann-whitney u test, [X²]: Chi-square test (Fisher's exact test)
HZO: Herpes zoster ophthalmicus, SD: Standard deviation

used antiviral agent (70.9%). The mean duration of antiviral therapy was 9.1±2.9 days, with no significant differences in treatment duration between those with ocular involvement or without it, or with PHN or without it. Intravenous acyclovir (10-15 mg/kg every 8 hours, adjusted based on creatinine clearance) is recommended for disseminated zoster, severe HZO with ocular involvement, and central nervous system zoster. At the same time, oral valacyclovir (1 g three times daily) is indicated for uncomplicated zoster and HZO without ocular involvement. Brivudine and famciclovir also serve as alternative treatment options.[24] Oral valacyclovir is as effective as intravenous acyclovir, potentially offering cost savings due to reduced hospitalization rates.[25] Clarification is needed on the total treatment duration, especially for immunocompromised patients with zoster or those with visceral or ocular involvement. PHN, the most common complication of varicella-zoster virus reactivation, is characterized by chronic, often refractory neuropathic pain persisting over three months after the HZ outbreak.[26] PHN prevalence varies between 5% and 30% depending on the study design and the specific population studied.[27] In some studies, age is a significant risk factor for PHN, along with other factors such as female sex, increased severity of prodromal or acute zoster pain, premorbid functional status, immunocompromised condition, and involvement of the head and neck regions.[28-30] Our study observed no significant differences between patients with and without PHN regarding age, sex, and immunosuppression. However, PHN was significantly associated with the clinical severity of HZO, indicating that more severe cases may require closer monitoring for potential chronic pain development. Elevated ESR and CRP were common findings, with 59.3% and 64.0% of patients, respectively, showing elevated levels. However, in our study, increased acute phase reactants were not associated with ocular involvement, PHN development, or treatment response. Limited data exist on the relationship between elevated acute phase reactants and clinical features, such as treatment response, and complication development in HZO.

Study Limitations

The retrospective nature of this study and its relatively small sample size presents limitations; however, the photographic documentation of cutaneous and ocular findings, conducted for every inpatient at our center, allowed us to verify each lesion's evolution and better correlate clinical severity with subsequent outcomes. This approach adds an objective component to the retrospective review, reducing potential errors in data interpretation. Additionally, none of our patients had received the zoster vaccine prior to infection, which prevented us from assessing its potential protective role in HZO or PHN. Furthermore, no follow-up data were available for recurrence, limiting our insights into long-term outcomes.

Conclusion

In conclusion, HZO is a self-limiting disease that responds well to antiviral treatment, but follow-up and management are critical in neurological and ophthalmological complications. In this cohort of HZO patients, maxillary and mandibular branch involvement emerged as an unexpected factor reducing ocular complications, while classical markers such as Hutchinson's sign were not significant predictors of ocular involvement. Larger, prospective studies are warranted to confirm these findings and to investigate the long-term implications of maxillary-mandibular involvement in HZO, as well as the correlation between clinical severity and PHN. Most studies of HZO are conducted by ophthalmologists. Therefore, more data are needed on HZO patients without ocular involvement. More studies involving dermatologists in relation to skin or laboratory findings with predictive value for developing complications associated with HZO are also needed.

Ethics

Ethics Committee Approval: The study received approval from the Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 368, date: 25.11.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.B.A., A.E.K.A., V.M., Design: E.B.A., B.B.D., A.K.P., M.S.G., Data Collection or Processing: B.B.D., V.M., M.S.G., Analysis or Interpretation: E.B.A., B.B.D., A.E.K.A., Literature Search: E.B.A., A.K.P., Writing: E.B.A., A.E.K.A.

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