

# Risk Factors for Postherpetic Neuralgia in Immunocompetent Patients

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Submitted: 04.02.2020  
Accepted: 25.03.2021

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**Keywords:** Herpes zoster;  
postherpetic neuralgia;  
risk factors.



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## ABSTRACT

**Objective:** The most common and important complication of herpes zoster (HZ) is postherpetic neuralgia (PHN). PHN generally affects the elderly and immunocompromised populations. Many studies investigated the risk factors for PHN; however, these studies were generally performed among immunocompromised patients. This study aimed to quantify risk factors for PHN in immunocompetent zoster patients.

**Methods:** We retrospectively reviewed the records of 106 patients diagnosed with HZ and aged  $\geq 18$  years between January 2017 and May 2019. Eight participants with immunocompromised status or under immunosuppressive treatment were excluded. Our underlying definition of PHN was pain persisting for more than 90 days following the diagnosis of zoster. Patients were divided into the PHN group ( $n=18$ ) and the non-PHN group ( $n=80$ ) on the basis of occurrence of PHN. Variables that can affect the development of PHN were investigated by comparing these two groups.

**Results:** In total, 98 eligible patients were included in this study. The mean age of the patients was  $58.62 \pm 17.53$  years. PHN was determined in 18.4% of the patients. PHN was mostly seen in the autumn. Patients in the PHN group were significantly older (mean age 68.72 years) than patients in the non-PHN group (56.35 years). PHN was higher in patients with chronic diseases. Patients with nonthoracic dermatome involvement were more likely to get PHN. There were no proportional differences detected between genders, and there were no differences between antiviral drug groups for PHN incidence.

**Conclusion:** In this study, having chronic disease, increased age, and nonthoracic dermatome involvement were found to be risk factors for developing PHN among immunocompetent hosts. As a new finding, we found that PHN has a higher incidence in autumn.

## INTRODUCTION

Herpes zoster (HZ) occurs as a result of the reactivation of the varicella zoster virus (VZV).<sup>[1]</sup> The diagnosis of HZ is usually based on the recognition of the typical presentation of rashes. A polymerase chain reaction may be required only when rashes are unusual.<sup>[2]</sup> Dermatomal rashes usually start as macules and papules and turn into vesicles and pustules. These rashes crust in 7–10 days and typically do not cross the midline.<sup>[3]</sup> HZ can cause severe pain in the affected area due to sensory damage, and it is known as postherpetic neuralgia (PHN).<sup>[4]</sup>

The most common and important complication of HZ is PHN.<sup>[5]</sup> The definition of PHN is “a dermatomal pain that continues at least 90 days after the acute HZ rash appears.”<sup>[6]</sup> The mechanism by which PHN occurs is not fully understood.<sup>[7]</sup> In patients with immune deficiency, randomized studies have shown that orally administered antiviral drugs can reduce acute pain duration.<sup>[8]</sup>

According to the literature, age, female gender, having had a prodrome, and severe rash are generally considered risk factors for PHN. Some studies found an increased risk for PHN in individuals with ophthalmic HZ.<sup>[9,10]</sup> However, these studies were generally performed among immunosuppressed patients. This study aimed to quantify risk factors for PHN in immunocompetent HZ patients.

## MATERIALS AND METHODS

We retrospectively reviewed the records of 106 patients diagnosed with HZ between January 2017 and May 2019. All recruited participants fulfilled the following criteria: (1) age  $\geq 18$  years and (2) diagnosed clinically with acute HZ. Participants with immunocompromised status and under immunosuppressive treatment were excluded. Our study was conducted in accordance with the principles of the Declaration of Helsinki and has been approved by the Institutional Review Board (No: 2011-KAEK-2)

Patients were divided into the PHN group and the non-PHN group on the basis of occurrence of PHN. Our underlying definition of PHN was pain persisting for more than 90 days following the diagnosis of HZ.<sup>[6]</sup> Acyclovir, brivudine, or valacyclovir was used to reduce acute HZ. The data on age, gender, season of admission to the hospital, involved dermatomes (thoracic and nonthoracic), antiviral therapy given to patients, and comorbidities of patients in these two groups were collected and statistically analyzed. Statistical analyses were performed using SPSS 22.0 software. The results were shown as mean±standard deviation (SD). For categorical variables, the chi-squared test was used for comparisons between the groups. The t-test analysis was performed to estimate the association of age factor with PHN. A p-value less than 0.05 was considered statistically significant.

## RESULTS

Of the total 106 patients with HZ, 98 were found eligible for inclusion (8 patients were excluded for their immunosuppression). Almost 55% of the participants were females (n=54), and the median age was 58.62±17.53 years (range 19–90). The hospital admission of HZ patients was mostly seen in summer (33%) and spring (31%). In this study, thoracic dermatome was involved in 79 (81%) cases followed by cervical in 7 (7.1%) cases, lumbar in 5 (5.1%) cases, sacral in 3 (3.1%) cases, lower extremity in 3 cases (3.1%), and upper extremity in one case. In our study, 49 patients (50%) had underlying comorbid conditions, which included hypertension in 23 (21%), diabetes mellitus in 11 (10%), chronic obstructive pulmonary disease in 5 (4%), congestive heart failure in 2 (1%), depression in 2 (1%), and other diseases in 6 (5%) patients. Patients with HZ were treated using brivudine (59%), valacyclovir (24%), or acyclovir (17%).

It was found that PHN developed in 18.4% of HZ patients. According to the occurrence of PHN, the patients were divided into the PHN group (n=18) and the non-PHN group (n=80). Variables that affect the development of PHN in the two groups are shown in Table 1.

When we investigated the season of admission of the PHN patients, we found that more patients were admitted in autumn than in other seasons. The number of non-PHN patients was higher in winter and spring (p=0.01). HZ patients with chronic disease are more likely to acquire PHN than patients who do not have any chronic diseases, which was found to be statistically significant (p=0.03). This study showed that gender has a similar role in the development of PHN. However, we observed that patients in the PHN group (mean age 68.72 years) were significantly older (p=0.01) than patients in the non-PHN group (mean age 56.35 years).

When we examined the dermatomal involvement in patients, we found that PHN was more prevalent in patients with thoracic HZ although patients in nonthoracic group were more likely to get PHN (p=0.02). Rates of antiviral

**Table 1.** Variables that can affect the development of PHN

	PHN				p
	Non PHN (n=80)		PHN (n=18)		
	n	%	n	%	
<b>Gender</b>					
Male	36	45.0	8	44.4	0.93
Female	44	55.0	10	55.6	
<b>Dermatome</b>					
Thoracic	68	85.0	11	61.1	0.02
Nonthoracic	12	15.0	7	38.9	
<b>Seasons</b>					
Winter	13	16.3	2	11.1	0.04
Spring	28	35.0	2	11.1	0.01
Summer	26	32.5	6	33.3	0.92
Autumn	13	16.3	8	44.4	0.01
<b>Chronic diseases</b>					
Without	42	52.5	7	38.9	0.03
With	38	47.5	11	61.1	
<b>Antiviral drugs</b>					
Brivudine	47	58.8	11	61.1	0.09
Acyclovir	13	16.3	4	22.2	
Valacyclovir	20	25.0	3	16.7	

Chi-square test. PHN: Postherpetic neuralgia.

drugs received by patients in the PHN group were: brivudine by 61%, acyclovir by 22%, and valacyclovir by 17%. Those received by patients in the non-PHN group were: brivudine by 59%, acyclovir by 16%, and valacyclovir by 25%. There were no statistical differences between the antiviral groups for PHN incidence (p=0.09).

## DISCUSSION

PHN is one of the most common and important complications of VZV infection.<sup>[5]</sup> It is more common in individuals over the age of 50 years, with immune deficiencies, and using immunosuppressive drugs.<sup>[11]</sup> It is known that PHN affects the daily activities of patients and reduces their quality of life. Although many studies investigated the risk factors for PHN, they were generally performed among immunocompromised patients. This article aimed to quantify risk factors for PHN in a retrospective study among immunocompetent HZ patients.

In one study, the incidence of developing PHN was 10–25%.<sup>[12]</sup> Gauthier et al.<sup>[13]</sup> reported that 13.7% of HZ patients developed PHN. Our study found a similar ratio (18.4%) for immunocompetent HZ patients. Many studies showed that the ratio of HZ patients was higher in spring and summer, similar to our study. The reason for these seasonal variations could be an association between the occurrence of VZV infection and various environmental factors.<sup>[14,15]</sup> There are not enough studies about the seasonal variations of PHN occurrence. Remarkably, it was found in our study that PHN was higher in autumn and not

in spring or summer in Turkey. Having none or very little information about seasonal variation, a large-scale population-based prospective study is required.

This study found that HZ patients with chronic disease are more likely to get PHN, confirming the results of many studies in the literature.<sup>[16,17]</sup> The incidence of PHN increased with age and this observation was supported by many studies in the literature.<sup>[16]</sup> Also, further risk for developing PHN was found to be directly related to increasing age among the immunocompetent hosts. Increased age is a well-recognized risk factor, whereas the role of gender is highly uncertain. The female gender has been demonstrated to be a risk factor for PHN. It is assumed that females may have a different response to latent viral infections.<sup>[17]</sup> In our study, no statistical differences were found between male and female patients, similar to some studies in the literature.<sup>[18]</sup> Nevertheless, further research is needed to elucidate the difference in the immune response between genders. As known thoracic dermatomal involvement is the most commonly affected area in HZ patients. Therefore, PHN is more common in patients with thoracic HZ is predictable. In this study, the involvement of nonthoracic dermatome was found to be most commonly associated with the occurrence of PHN. However, in a longitudinal study, Gupta et al.<sup>[19]</sup> showed a relationship between thoracic involvement and PHN. Some studies observed that ophthalmic involvement had a higher risk for developing PHN.<sup>[9]</sup> The reason for this difference may be geographical features, but in this respect, large studies involving many patients in different geographical areas are needed.

Antivirals such as acyclovir, brivudine, and valacyclovir are used to reduce acute HZ. Many studies showed that antiviral therapy can reduce the incidence and severity of PHN, especially when administered in the early stages of the disease.<sup>[20]</sup> However, according to some studies, there is no consistent evidence that administering antivirals reduces the risk for PHN.<sup>[21]</sup> Another study compared the effect of oral brivudine and acyclovir, and it was found that the incidence of PHN was lower in the group that received brivudine.<sup>[22]</sup> In our study, antiviral therapy was administered in the early stages of the disease to each participant, and there were no differences in the impact of different antiviral drugs in the incidence of PHN.

## CONCLUSION

In this study, the incidence of developing PHN among immunocompetent HZ patients was 18.4%. It was found that HZ patients with chronic disease and involvement of nonthoracic dermatome were more likely to get PHN. We also observed that patients who developed PHN were often admitted to the hospital in autumn. Increased age has been demonstrated to be a risk factor for PHN, whereas gender had no association. There were no differences between antiviral drug groups for PHN incidence.

### Ethics Committee Approval

This study approved by the Afyonkarahisar University

of Health Sciences Clinical Research Ethics Committee (Date: 06.12.2019, Decision No: 2019/12).

### Informed Consent

Retrospective study.

### Peer-review

Internally peer-reviewed.

### Authorship Contributions

Concept: Y.N.; Design: Y.N.; Supervision: H.A.; Fundings: Y.N., H.A.; Materials: Y.N., H.A.; Data: Y.N.; Analysis: Y.N.; Literature search: Y.N., H.A.; Writing: Y.N.; Critical revision: H.A.

### Conflict of Interest

None declared.

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## İmmünkompetan Bireylerde Postherpetik Nevralji İçin Risk Faktörleri

**Amaç:** Postherpetik nevralsi (PHN), Herpes zosterin (HZ) en önemli komplikasyonudur. Özellikle yaşlı ve immünsupresif bireylerde sıklıkla görüldüğü bilinmektedir. Bu nedenle immünsupresif HZ'li hastalar arasında PHN risk faktörlerini araştıran birçok çalışma yapılmıştır. Biz de çalışmamızda immünkompetan bireylerdeki PHN risk faktörlerini araştırmayı amaçladık.

**Gereç ve Yöntem:** Bu çalışmada, Ocak 2017–Mayıs 2019 tarihleri arasında başvuran 18 yaş üzeri ve klinik olarak akut HZ tanısı alan 106 hastanın kayıtlarını geriye dönük olarak taradık. İmmünsupresif hastalığı olan veya immünsupresif ilaç kullanan sekiz hasta çalışmaya dahil edilmedi. HZ tanısından sonra en az 90 gün devam eden ağrı PHN olarak değerlendirildi ve buna göre hastalar iki grupta incelendi; PHN (n=18) ve nonPHN grubu (n=80). PHN gelişimini etkileyebilecek değişkenler bu iki grup kıyaslanarak incelendi.

**Bulgular:** Çalışmaya alınan 98 hastanın yaş ortalaması  $58.62 \pm 17.53$  yaş olarak saptandı. Bu hastaların %18.4'ünde PHN gelişti. PHN gelişen hastaların sıklıkla hastaneye sonbaharda başvurduğu gözlemlendi. PHN grubun yaş ortalaması (68.72) istatistiksel olarak nonPHN grubun yaş ortalamasından (56.35) yüksek bulundu. Kronik hastalığı olan hastalarda, olmayanlara göre PHN gelişimi daha sık saptandı. PHN gelişen hastalarda torasik tutulum daha sık görüldü de, nontorasik tutulumu olanların daha yüksek oranda PHN geliştirdiği gözlemlendi. Ancak cinsiyet ve hastaların kullandığı ilaç grupları açısından anlamlı bir farklılık bulunamadı.

**Sonuç:** Bu çalışmada, HZ'li olan immünkompetan bireylerde; ileri yaş, kronik hastalığın olması ve nontorasik dermatom tutulumunun olması PHN için risk faktörü olarak saptandı. Çalışmamızda sonbahar mevsiminde başvuran hastalarda istatistiksel olarak yüksek oranda PHN geliştiğinin gözlenmesi dikkat çekici bir bulguydu.

**Anahtar Sözcükler:** Herpes zoster; postherpetik nevralsi; risk faktörleri.