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Predictors of postherpetic neuralgia in patients with herpes zoster: a pooled analysis of prospective cohort studies from North and Latin America and Asia

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SUMMARY

Objectives: The most common complication of herpes zoster (HZ) is postherpetic neuralgia (PHN), a persistent pain that can substantially affect quality of life (QoL). This analysis aimed to evaluate predictors of PHN in HZ patients.

Methods: A pooled analysis of prospective cohort studies of HZ patients aged ≥50 years from North America (Canada), Latin America (Brazil, Mexico, and Argentina), and Asia (Taiwan, South Korea, and Thailand) was performed. Patients within 14 days of rash onset were included. The incidence of PHN was defined as a worst pain score of ≥3, persisting/appearing at >90 days after rash onset. Socio-demographics, HZ disease characteristics, treatment, pain-related interference with activities of daily living, and health-related QoL were assessed.

Results: Of 702 patients with HZ, 148 (21.1%) developed PHN. Similar risks of PHN were observed across geographic regions. On multivariate analysis, older age, greater severity of pain at rash onset, employment status, walking problems at enrollment, and pain interference affecting social relationships were significantly associated with the development of PHN.

Conclusions: In addition to older age and severe acute pain, this study suggests that impaired physical and social functioning from acute zoster pain may play a role in the development of PHN in this prospective cohort study of HZ patients from North and Latin America and Asia.

1. Introduction

Herpes zoster (HZ) is caused by reactivation of the latent varicella zoster virus (VZV) in sensory ganglia and is typically characterized by painful, blistering rashes.[1] The lifetime risk of HZ is approximately 30%.[2] For some patients, pain continues to persist after the rash heals and develops into postherpetic neuralgia (PHN). PHN is the most common complication of HZ and occurs in approximately 5% to 30% of HZ patients.[3] The risk of PHN increases with age. PHN can persist for several months to several years, and even up to 10 years. PHN substantially affects patient quality of life (QoL) and can cause physical disability, emotional distress, and social isolation.[4] PHN patients experience different types of pain including a steady burning pain, intermittent stabbing or shooting pain, and stimulus-evoked pain (allodynia). Treatments for PHN include anticonvulsants, topical lidocaine or capsaicin, tricyclic

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antidepressants, and opioid analgesics.[4–6] However, each treatment has limited efficacy and patients are often refractory to these treatments. As an effective preventive strategy, a live-attenuated VZV vaccine (Zostavax by Merck) has been demonstrated to significantly reduce the risk of HZ and PHN.[7]

Understanding the predictors of PHN is important to enable healthcare professionals to identify patients at risk of PHN who might benefit from early treatment. It may also help researchers to better understand the pathophysiology of PHN. It is recognized that older age, greater acute pain severity, and greater rash severity increase the risk of developing PHN.[6,8–23] However, other factors, such as prodromal pain, female sex, and functional and psychosocial status, have rarely been evaluated or have not been consistently associated with the risk of PHN.[8,11,15] Conflicting results could be due to differences in the definition of PHN, study population, and methodology. Furthermore, prior research has been conducted mostly in North America and Europe, but less frequently in other geographic regions.

The objective of this study was to evaluate the predictors of PHN from a pooled analysis of prospective cohort studies of patients with HZ from North America (Canada), Latin America (Mexico, Brazil, and Argentina), and Asia (Taiwan, South Korea, and Thailand).

2. Methods

2.1. Study design and population

Data from the MASTER study (Monitoring and Assessing Shingles Through Education and Research), a prospective cohort study of patients with HZ conducted in seven countries (Canada, Brazil, Mexico, Argentina, Taiwan, South Korea, and Thailand) using the same methodology, were pooled.[20,24–28] Eligible participants were patients with a physician-confirmed diagnosis of HZ rash or zoster-associated pain with documented date of rash onset in the medical chart, ≥50 years of age, and capable of completing the study questionnaires. Patients were recruited at different time points during the course of their disease. However, the current analysis was restricted only to patients enrolled within 14 days of rash onset. Patients were followed prospectively for 6 months to assess their zoster-associated burden of illness, including severity and duration of pain, impact on health-related QoL, and healthcare utilization. All participants signed an informed consent form prior to any study-related procedure. The study was approved by local institutional review boards in each country.

2.2. Definition of postherpetic neuralgia

The incidence of PHN was defined as a worst pain score of ≥3, persisting or appearing more than 90 days after the onset of rash. A previous validation study has shown that worst pain scores of ≥3 occurring ≥90 days after rash onset significantly impair QoL and activities of daily living.[29] This definition was used in a clinical trial of zoster vaccination and other studies.[7]

2.3. Assessment

A physician reviewed the patient's characteristics of HZ and treatment at the time of recruitment. To assess zoster-associated pain and its impact on activities of daily living from the patient's perspective, the Zoster Brief Pain Inventory (ZBPI) and the Initial Zoster Impact Questionnaire (IZIQ) were used. The ZBPI is a validated self-administered questionnaire that assesses the severity of pain associated with HZ using a scale from 0 (no pain) to 10 (pain as bad as you can imagine).[29] The ZBPI also assesses the interference of pain with daily activities, including general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.

The following socio-demographics, characteristics of HZ, and health indicators were evaluated as potential predictors of PHN: age, sex, level of education, employment status, living alone, immune status, presence of other pain conditions, and pre-existing problems in the EQ-5D five health domains. The following HZ characteristics were also examined as predictors: severity of rash (number of lesions), worst pain score at rash onset, prodromal pain (duration and severity of pain), problems in EQ-5D health domains at rash onset, pain interference with daily activities at rash onset, and use of antiviral medications.

2.4. Statistical analysis

Baseline characteristics of HZ patients by PHN status were compared using the Chi-square test or Fisher's exact test, as appropriate, for categorical variables. To examine factors associated with the risk of developing PHN, binomial regression models were used with a log-link function and computed risk ratio (or relative risk, RR) and associated 95% confidence intervals (CI). The parsimonious multivariate regression model was built using a backward selection procedure. Variables with $p < 0.20$ in the univariate analysis were considered as candidates for the multivariate model, and variables with $p < 0.05$ were kept in the final model.

3. Results

A total of 702 patients with HZ were included in the analysis (Table 1). Approximately 38% of participants were aged 50–59 years, 31% were aged 60–69 years, and 31% were aged ≥70 years. The majority of patients were women (62%), and 32% reported being employed. The baseline clinical characteristics of HZ disease were generally comparable across the three geographic regions. About 58% of patients reported a severe worst pain score at rash onset (≥7). The majority of patients reported taking antiviral medications (87%).

Of 702 patients with HZ, 148 (21.1%) developed PHN. The age-specific risk of PHN ranged from 14.0% in adults 50–59 years of age and 20.6% in adults 60–69 years of age, to 29.7% in adults ≥70 years of age. In the univariate analysis, older age, employment status, greater severity of pain at rash onset, severe prodromal pain, problems in health domains in the EQ-5D at enrollment (except being anxious or depressed), and reported pain interference from acute HZ on activities of daily living (all seven items of ZBPI) were significantly associated with an increased risk of PHN (Table 2). No significant differences in the risk of PHN were found by geographic region, sex, level of education, living alone, immune status, presence of other pain conditions, pre-existing problems in the EQ-5D health domains, severity of rash, or use of antiviral medications during the acute phase.

In the multivariable regression model (Table 3), older age (60–69 vs. 50–59 years, RR 1.20, 95% CI 0.81–1.79; ≥70 vs. 50–59 years, RR 1.72, 95% CI 1.18–2.51), greater severity of pain at rash onset (moderate vs. no/mild, RR 2.46, 95% CI 0.91–6.66; severe vs. no/mild RR 3.58, 95% CI 1.36–9.45), employment status (RR 0.58, 95% CI 0.38–0.89), walking problems at enrollment (RR 1.47, 95% CI 1.11–1.93), and pain interference affecting relationships with other people (RR 1.69, 95% CI 1.27–2.25) were significantly associated with the development of PHN.

4. Discussion

The risk of developing PHN, defined as a pain score of ≥3 lasting or appearing more than 90 days after rash onset, was approximately