Family Practice
© Oxford University Press 2002

Vol. 19, No. 5
Printed in Great Britain

Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database

Wim Opstelten, Jan W Mauritz, Niek J de Wit, Albert JM van Wijck[a], Wim AB Stalman[b] and Gerrit A van Essen

Opstelten W, Mauritz JW, de Wit NJ, van Wijck AJM, Stalman WAB and van Essen GA. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. *Family Practice* 2002; **19:** 471–475.

Background. Postherpetic neuralgia (PHN) is a frequent complication of herpes zoster (HZ). Treatment results of this severe and long-lasting pain syndrome are often disappointing. From the point of view of possible prevention and early treatment, it is important to identify HZ patients who have an increased risk of developing PHN.

Objectives. Our goals were to determine the incidence of HZ and PHN in a primary care population and to identify risk indicators for the occurrence of PHN.

Methods. A search for HZ and PHN was conducted in a general practice research database, comprising 22 general practices and representing 49 000 people, over a 5-year period. Potential risk indicators were analysed using multivariate logistic regression.

Results. A total of 837 patients had been diagnosed with HZ [incidence 3.4/1000 patients/year, 95% confidence interval (CI) 2.9–3.9]. The risk of developing PHN 1 month after the start of the zoster rash was 6.5% (95% CI 4.9–8.3). This risk was 11.7% (95% CI 8.5–14.9) for patients aged $\geqslant$55 years. Independent risk indicators for the occurrence of PHN were age [55–74 years, adjusted odds ratio (OR) 4.2, 95% CI 1.8–9.7; $>$75 years, OR 10.7, 95% CI 4.6–25.1] and ophthalmic localization (OR 2.3, 95% CI 1.0–4.6).

Conclusions. The risk of developing PHN increases with age. Preventive strategies should focus on patients with herpes zoster aged $>$55 years and with ophthalmic localization.

Keywords. Herpes zoster, incidence, neuralgia, primary care, risk factors.

Introduction

Herpes zoster (HZ) or shingles is a common disease, with a reported incidence varying from 2.2 to 3.4/1000 patients/year.[1–3] This incidence increases with age.[2,4] HZ is caused by a localized infection with the varicella zoster virus and represents a recrudescence from a latent phase in which the virus is dormant in sensory ganglia after a primary infection (chicken pox). Reactivation of the virus and its spread to the corresponding dermatome result in HZ. The symptoms include a painful, vesicular rash with erythema. HZ is a self-limiting disease for most patients: healing of the skin and resolution of pain generally occur within 3–4 weeks. The most common complication of HZ is persistent pain, also called postherpetic neuralgia (PHN), which may last for several months to years.

Although associated with HZ, PHN is considered a distinct disorder with its own pathogenesis.[4–6] Some controversy exists, however, about the exact definition of PHN. Most authors define PHN as pain persisting beyond a specified interval (1[4,7] or 3[8] months) after the outbreak of the rash. Others define it as pain persisting beyond a specified interval after rash healing.[9] There is also disagreement with regard to the classification of PHN. For example, Dworkin and Portenoy have proposed a classification of HZ pain into an acute phase (first month after the onset of the rash), a subacute phase

Received 14 August 2001; Revised 18 December 2001; Accepted 13 May 2002.
Julius Center for General Practice and Patient Oriented Research and [a]Department of Postoperative Care, Anaesthesiology and Pain Treatment, University Medical Center Utrecht, University Medical Center Utrecht and [b]Institute for Research in Extramural Medicine, Vrije Universiteit Medical Center, Amsterdam, The Netherlands. Correspondence to W Opstelten, Julius Center for General Practice and Patient Oriented Research, University Medical Center Utrecht, PO Box 85060, 3500 AB Utrecht, The Netherlands; E-mail: w.opstelten@med.uu.nl

(1–4 months after the onset) and a chronic phase (>4 months),[10] while Johnson has made a distinction between early PHN (1–6 months after the onset) and late PHN (>6 months).[11] PHN occurs in 9–19% of all HZ patients. Its incidence is age dependent: the risk of PHN is low (2%) in patients younger than 50 years of age, ~20% in those older than 50 years and ~35% in those over the age of 80 years.[3,12,13]

Pain from PHN has a potentially high impact on the quality of life. To date, a number of treatment strategies, including amytriptyline,[8,14] gabapentin,[15] oxycodone[16] and a lidocaine patch,[17] have demonstrated some degree of efficacy. However, because many patients still suffer from pain despite such treatment, the value of several preventive strategies has been investigated.[18] The efficacy of antiviral medication in preventing PHN, for example, is controversial. In fact, meta-analyses have shown no or only a partial effect on the incidence of PHN, although the duration of the pain might be reduced.[19,20] In contrast, a small randomized control trial showed that early medical treatment with amitriptyline causes a reduction in the occurrence of PHN.[21] Two retrospective studies have also shown a reduction in the occurrence of PHN when an epidural injection of corticosteroids and local anaesthetics were given in the acute phase of HZ.[22,23]

Dworkin and Portenoy[6] mentioned the following risk factors for PHN in their review on HZ: older age, severity of the HZ infection, sensory dysfunction in the affected dermatome, a painful prodrome and fever ⩾38°C in the acute phase. Others have reported ophthalmic localization,[3,12,24,25] psychosocial problems,[26,27] immunoincompetence, connective tissue disease[28] and diabetes[29] as risk indicators.

Although nearly all HZ and PHN patients are diagnosed and treated by a GP, few studies have looked into the incidence and risk indicators in a primary care setting.[3,12,13,25] For this reason, we determined retrospectively the incidence of HZ and PHN in patients registered in a general practice research database and analysed the risk indicators for PHN.

Methods

Patients and setting

Data were collected from the General Practice Research Database (HNU: Huisartsen Netwerk Utrecht[30]). This research network is a co-operation between the Julius Center for General Practice and Patient Oriented Research and 22 general practices in six different locations. The participating GPs use a computerized medical record system to register all patient contacts. The general purpose of this registration is to support the GP during basic daily practice activities and to supply data for scientific research. The total patient population of the HNU consists of ~49 000 people and can be considered as a dynamic population cohort with rather stable size. Its age and sex ratios are comparable with those of the Dutch population.[31] All HZ patients diagnosed between 1 August 1994 and 31 July 1999 were identified by searching the database for the ICPC code32 S70 (HZ) and for free text ('zoster'). After the search, one of the authors (JWM) visited the general practices and reviewed the full-text medical records of the selected patients. When the diagnosis HZ was only mentioned in the differential diagnosis or in the free text (e.g. "does not look like zoster", "prodrome zoster?", "patient fears zoster"), but not confirmed afterwards, patients were excluded from the analysis.

Registration

The presented duration of pain was recorded for each HZ patient. PHN was defined in this study as any pain that persisted at least 1 month after HZ diagnosis. Those patients who still had pain 3 months after HZ diagnosis were also registered. The total duration of pain was measured as the length of time between the first and last patient contact during which pain was reported or an analgesic was prescribed. The longest follow-up was 5 years. Additional information was registered with regard to possible risk factors for PHN, including age, gender, localization, co-morbidity, medication and painful prodrome. Relevant co-morbidity included diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and having a psychological problem at the time of HZ diagnosis. Relevant pharmacotherapy comprised corticosteroids (at the time of or within 14 days before diagnosis) and psychopharmaceuticals (anxiolytics and/or antidepressants at the time of or within the 3-month period before diagnosis). We also registered the frequency of consultations the year before diagnosis and the chronic use of analgesics (three or more prescriptions in the year before diagnosis) since these two factors could affect our outcome parameters.

Data analysis

Data were analysed using SPSS for Windows, version 9.0 (SPSS Inc, Chicago, IL). Analyses were performed to determine if clustering (on a practice level) was an influential factor. Incidence and prevalence rates were standardized to the European standard population. We first assessed univariate associations of the potential risk indicators with PHN. Then, we used gender and all of the determinants that had a P-value <0.1 in the univariate model to build a multivariate logistic regression model. This latter model was used to assess the independent influence of potential risk factors on the occurrence of PHN. The same determinants were also used in a multivariate logistic regression analysis of PHN patients who still had pain 3 months after HZ diagnosis. The potential correlation between consultation frequency and PHN was checked using Spearman's correlation coefficient.

Results

A search of the database resulted in 1234 possible patients, 837 of whom were diagnosed as having HZ, equally distributed over the 5-year period. Of the 397 patients who did not actually have HZ, GPs initially thought the symptoms pointed to a possible or a beginning HZ and registered it as such. These patients were excluded from the analysis. The calculated incidence of HZ was 3.4/1000 patients/year [95% confidence interval (CI) 2.9–3.9]. Extrapolated to the standard European population,[33] the incidence was 3.6/1000 patients/year (95% CI 3.1–4.1). A total of 47% of all HZ patients were at least 55 years old (Table 1). In addition, the risk of PHN increased with age. Persistent pain 1 month after HZ diagnosis was reported in the medical records of 6.5% (95% CI 4.9–8.3*)* of the HZ patients and in 2.6% (95% CI 1.7–4.0) 3 months after HZ diagnosis (extrapolated to the standard European population[33] risk of pain at 1 month: 6.9%, 95% CI 5.3–8.8; risk of pain at 3 months: 2.9%, 95% CI 1.9–4.2). These percentages increased with age (Table 2). Adjustment for clustering did not essentially influence these rates.

In the univariate analysis, age, ophthalmic localization, DM, use of psychopharmaceuticals and painful prodrome appeared to be possible risk indicators for the occurrence of PHN (P-value < 0.10). After multivariate analysis, however, only age [55–74 years, adjusted odds ratio (OR) 4.2, 95% CI 1.8–9.7; >75 years, OR 10.7, 95% CI 4.6–25.1] and ophthalmic localization (OR 2.1, 95% CI 1.0–4.6) independently contributed to the risk of developing PHN (Table 3). Persistent pain 3 months after HZ diagnosis was only independently associated with age. Ophthalmic localization showed an adjusted OR of 2.3. This odds ratio, however, was not significant (Table 4).

No correlation was found between consultation frequency or analgesic use and PHN (data not shown).

TABLE 1 *Incidence of herpes zoster in different age groups*

Age group (no. of patients)	Number	Incidence (per 1000 py)[a]	(95% CI)
≤44 years (n = 30 605)	317	2.1	(1.9–2.2)
45–54 years (n = 6987)	127	3.6	(3.2–4.1)
55–64 years (n = 4782)	139	5.8	(5.2–6.5)
65–74 years (n = 3700)	121	6.5	(5.8–7.4)
≥75 years (n = 2925)	133	9.1	(8.1–10.2)

[a] py, person years.

Discussion

The HZ incidence found in this study is similar to that reported in other studies,[1–3] while the 6.5% risk of developing PHN is somewhat lower.[3,12,13] Of the potential risk indicators studied, we found that only age and ophthalmic localization contributed independently to the incidence of PHN.

Some aspects of this study, however, must be addressed in order to appreciate the results. First, the study was retrospective and therefore potentially prone to registration inadequacy, especially to under-reporting. In addition, our analysis was based on the registration of complaints that were presented actively by patients. We believe that consulting a GP is a reliable indicator that people have significant pain. Those with mild pain, however, might have bought analgesics without consulting their GP. The cumulative incidence of PHN in our study, therefore, probably includes only those patients with more severe pain. This would also explain why the

TABLE 2 *Risk of postherpetic neuralgia 1 and 3 months after diagnosis of herpes zoster in different age group*s

Age group (no. of HZ patients)	After 1 month			After 3 months		
	n	%	(95% CI)	n	%	(95% CI)
≤44 years (n = 317)	3	0.9	(0.2–2.7)	1	0.3	(0.01–1.7)
45–54 years (n = 127)	5	3.9	(1.3–9.0)	1	0.8	(0.02–4.3)
55–64 years (n = 139)	9	6.5	(3.0–11.9)	4	2.9	(0.8–7.2)
65–74 years (n = 121)	13	10.7	(5.2–16.3)	4	3.3	(0.9–8.3)
≥75 years (n = 133)	24	18.0	(11.5–24.6)	12	9.0	(4.8–15.2)

TABLE 3 *Distribution, odds ratio and adjusted odds ratio of the potential risk indicators for postherpetic neuralgia at 1 month in primary care patients with herpes zoster (*n = *837)*

Variable		Pain/total (%)	Odds ratio (95% CI)		*P*
			Unadjusted	Adjusted	
Gender	Male[a]	22/350 (6.3)	–	–	
	Female	32/487 (6.6)	1.0 (0.6–1.8)	0.8 (0.4–1.5)	0.52
Age group	⩽54[a]	8/444 (1.8)	–	–	
	55–74	22/260 (8.5)	5.0 (2.2–11.5)	4.2 (1.8–9.7)	0.001
	⩾75	24/133 (18.0)	12.0 (5.2–27.4)	10.7 (4.6–25.1)	<0.001
Localization	Not ophthalmic[a]	41/734 (5.9)	–	–	
	Ophthalmic	13/103 (12.6)	2.4 (1.3–4.7)	2.3 (1.1–4.6)	0.026
Co-morbidity	No diabetes[a]	48/793 (6.0)	–	–	
	Diabetes	6/44 (13.6)	2.4 (1.0–6.0)	1.4 (0.6–3.8)	0.447
	No use of psychopharmaceuticals[a]	45/757 (5.9)	–	–	
	Use of psychopharmaceuticals	9/80 (11.3)	2.0 (0.9–4.3)	1.4 (0.5–3.9)	0.540
Other	No painful prodrome[a]	47/788 (6.0)	–	–	
	Painful prodrome	7/49 (14.3)	2.6 (1.1–6.2)	2.1 (0.9–5.2)	0.108

[a] Reference category in each variable.

TABLE 4 *Distribution, odds ratio and adjusted odds ratio of the potential risk indicators for postherpetic neuralgia at 3 months in primary care patients with herpes zoster (*n = *837)*

Variable		Pain/total (%)	Odds ratio (95% CI)		*P*
			Unadjusted	Adjusted	
Gender	Male[a]	8/350 (2.3)	–	–	
	Female	14/487 (2.9)	1.3 (0.5–3.1)	1.0 (0.9–1.0)	0.940
Age group	⩽54[a]	2/444 (0.5)	–	–	
	55–74	8/260 (3.1)	7.0 (1.5–33.3)	5.4 (1.1–26.5)	0.037
	⩾75	12/133 (9.0)	21.9 (4.8–99.2)	19.7 (4.3–90.9)	<0.001
Localization	Not ophthalmic[a]	16/734 (2.2)	–	–	
	Ophthalmic	6/103 (5.8)	2.8 (1.1–7.3)	2.2 (0.8–6.5)	0.141
Co-morbidity	No diabetes[a]	19/793 (2.4)	–	–	
	Diabetes	3/44 (6.8)	3.0 (0.8–10.4)	1.7 (0.5–6.2)	0.427
	No use of psychopharmaceuticals[a]	19/757 (2.5)	–	–	
	Use of psychopharmaceuticals	3/80 (3.8)	1.5 (0.4–5.3)	1.4 (0.3–5.6)	0.687
Other	No painful prodrome[a]	20/788 (2.5)	–	–	
	Painful prodrome	2/49 (4.1)	1.6 (0.4–7.2)	1.2 (0.3–5.6)	0.802

[a] Reference category in each variable.

incidence in our study is lower than that in other studies. Nevertheless, we would like to emphasize that our incidence figure is likely to reflect the clinically relevant dimension of PHN in primary care. Secondly, migration and death might also lead to underestimation of the incidences of HZ and PHN. This factor probably did not play an important role in our study since our HZ cases were equally distributed over the 5-year period and the incidence is comparable with that reported in other studies.[1–3] Thirdly, we lacked reliable information regarding the severity of pain and rash. Therefore, we were unable to analyse the influence of these potential risk indicators. Finally, the number of participating general practices was quite small, which could affect the generalizability of the study results. The practices do, however, include ~49 000 patients, and patient characteristics are comparable with those of the Dutch primary care population. This is confirmed by the HZ incidence (3.4/1000 patients/year), which corresponds to the HZ incidence in The Netherlands (2.8/1000 patients/year).[34]

Our results support a number of earlier studies[3,4,12,13,28] that reported age as a risk indicator of PHN, i.e. the older

the patient, the higher the risk. In addition, our finding that no children or adolescents developed PHN confirms the results of a study conducted in Iceland on HZ in children and adolescents.[35] This higher risk of developing PHN with increasing age has often been explained by the decreasing immunity seen in older people. Like others,[4,5] however, we did not observe that immunity-depressing factors such as DM, RA, SLE or the use of corticosteroids increased the risk of PHN. Nor could we detect any risk of reported psychological stress at the time of HZ on the development of PHN, a fact that has been noted by others.[26,27] Our finding of an ophthalmic localization of HZ as a risk indicator does support the results of earlier studies.[3,12,24,25] Moreover, we found that a painful prodrome, which could be considered a sign of more severe HZ, was associated with an increased risk of PHN. The odds ratios, however, were not significant, probably due to the small number of patients. Moreover, the data on this risk indicator should be viewed with caution as the registration of this factor by the GPs might have been incomplete.

We conclude that, so far, age and ophthalmic localization are the only factors that can help GPs identify patients at risk of developing PHN.

Acknowledgements

The authors thank the GPs of the Utrecht Network of General Practitioners for their co-operation, NPA Zuithoff, MSc, for his help with the data analysis, and ThJM Verheij, MD, PhD, professor of general practice, and RJ Stolker, MD, PhD, anaesthesiologist, for their comments on earlier versions of this article.

References

[1] Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. *Arch Intern Med* 1995; **155:** 1605–1609.
[2] Galil K, Choo PW, Donahue JG, Platt R. The sequelae of herpes zoster. *Arch Intern Med* 1997; **157:** 1209–1213.
[3] Hope-Simpson RE. Postherpetic neuralgia. *J R Coll Gen Pract* 1975; **25:** 571–575.
[4] Kost RG, Straus SE. Postherpetic neuralgia: pathogenesis, treatment and prevention. *N Engl J Med* 1996; **335:** 32–42.
[5] Bowsher D. Post herpetic neuralgia in older patients. *Drugs Aging* 1994; **5:** 411–418.
[6] Dworkin RH, Portenoy RK. Pain and its persistence in herpes zoster. *Pain* 1996; **67:** 241–251.
[7] Wood MJ, Balfour H, Beutner K *et al*. How should zoster trials be conducted? *J Antimicrob Chemother* 1995; **36:** 1089–1101.
[8] Max MB, Schafer SC, Culnane M, Smoller B, Dubner R, Gracely RH. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. *Neurology* 1988; **38:** 1427–1432.
[9] Tyring S, Barbarash RA, Nahlik JE *et al.* Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. *Ann Intern Med* 1995; **123:** 89–96.
[10] Dworkin H, Portenoy RK. Proposed classification of herpes zoster pain [letter]. *Lancet* 1994; **343:** 1648.
[11] Johnson RW. The future of predictors, prevention, and therapy in postherpetic neuralgia. *Neurology* 1995; **45:** S70–S72.
[12] Ragozzino MW, Melton LJ, Kurland LT, Chu CP, Perry HO. Population-based study of herpes zoster and its sequelae. *Medicine* 1982; **61:** 310–316.
[13] Helgason S, Petursson G, Gudmundsson S, Sigurdsson JA. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: prospective study with long term follow up. *Br Med J* 2000; **321:** 794–796.
[14] Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. *Neurology* 1982; **32:** 671–673.
[15] Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia. *J Am Med Assoc* 1998; **280:** 1836–1842.
[16] Watson CP, Babul N. Efficacy of oxycodone in neuripathic pain. A randomized trial in postherpetic neuralgia. *Neurology* 1998; **50:** 1837–1841.
[17] Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain* 1996; **65:** 39–44.
[18] Watson CPN. Postherpetic neuralgia: the importance of preventing this intractable end-stage disorder. *J Infect Dis* 1998; **178:** S91–S94.
[19] Lancaster T, Silagy C, Gray S. Primary care management of acute herpes zoster: systematic review of evidence from randomised controlled trials. *Br J Gen Pract* 1995; **45:** 39–45.
[20] Alper BS, Lewis PR. Does treatment of acute herpes zoster prevent or shorten postherpetic neuralgia? *J Fam Pract* 2000; **49:** 255–264.
[21] Bowsher D. The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manag* 1997; **13:** 327–331.
[22] Moesker A, Boersma FP. The effect of extradural administration of corticosteroids as pain treatment of acute herpes zoster and to prevent postherpetic neuralgia. In Erdmann W, Oyama T, Pernak MJ (eds). *The Pain Clinic, Proceedings of the First International Symposium*. Utrecht: VNU Science Press, 1985: 273–279.
[23] Gomesz FAR, Wicks MA. The use of epidural blocks and trigeminal ganglion blocks in acute HZ to prevent PHN. *2nd International Conference on the Varicella-Zoster Virus*. Paris, 1994.
[24] Millership S. Postherpetic neuralgia. *Prof Nurse* 1998; **13:** 311–313.
[25] Sanders HWA. Herpes zoster in de huisartspraktijk [Herpes zoster in general practice]. Doctoral thesis, Nijmegen: University of Nijmegen, 1968.
[26] Dworkin RH, Hartstein G, Rosner HL, Walther RR, Sweeney EW, Brand L. A high-risk method for studying psychosocial antecedents of chronic pain: the prospective investigation of herpes zoster. *J Abnorm Psychol* 1992; **101:** 200–205.
[27] Bergbom Engberg I, Gröndahl GB, Thibom K. Patients' experiences of herpes zoster and postherpetic neuralgia. *J Adv Nurs* 1995; **21:** 427–433.
[28] Choo PW, Galil K, Donahue JG, Walker AM, Spiegelman D, Richard P. Risk factors for postherpetic neuralgia. *Arch Intern Med* 1997; **157:** 1217–1224.
[29] Millerchip S. Post-herpetic neuralgia. *Prof Nurse* 1998; **13:** 311–313.
[30] Stalman W. Management of sinusitis-like complaints in general practice. Doctoral thesis, Utrecht: Utrecht University, 1997: 45–53.
[31] *Statistisch Jaarboek* [Statistical Yearbook of The Netherlands] 1999. Centraal Bureau voor de Statistiek, Voorburg /Heerlen, 1999.
[32] Lamberts H, Wood M, Hofmans-Okker J. *The International Classification of Primary Care in the European Community*. Oxford: Oxford University Press, 1993.
[33] Eurostat New Cronos Database. www.Europe.eu.int/comm/euronet.
[34] Bartelds AIM. *Continue morbiditeits registratie peilstations Nederland*. Utrecht: NIVEL, 1997: 73–75.
[35] Petursson G, Helgason S, Gudmundsson S, Sigurdsson JA. Herpes zoster in children and adolescents. *Pediatr Infect Dis J* 1998; **17:** 905–908.