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ORIGINAL ARTICLE

Association between treatment-related early changes in psychological factors and development of postherpetic neuralgia

Rie Koga[1,2] · Keiko Yamada[1,3] · Rie Ishikawa[1,4] · Yasuhiko Kubota[5] · Keisuke Yamaguchi[6] · Masako Iseki[1]

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Abstract

Purpose To examine the association between catastrophizing and pain intensity with acute herpes zoster, and the association of treatment-related early changes in depressive symptoms, anxiety, and catastrophizing with postherpetic neuralgia (PHN) development, independent of acute pain intensity.

Methods We analyzed 44 outpatient participants with acute herpes zoster who completed a 6-month follow-up. Participants completed a self-reported questionnaire with a Visual Analog Scale (VAS), the Pain Catastrophizing Scale (PCS), and the Hospital Anxiety and Depression Scale (HADS) at first visit, and 3 and 6 months, thereafter. We assessed associations between acute pain intensity and analyzed factors using univariate regression analyses. Univariate and bivariate logistic regression models were constructed to assess associations of variables at the first visit and early changes in psychological factors with PHN development.

Results Sex, severe skin rash at first visit, PCS, and HADS depression were associated with acute pain intensity {standardized regression coefficient, 0.46 [95% confidence interval (CI) 0.12–0.74], 0.36 (95% CI 0.07–0.65), 0.33 (95% CI 0.03–0.62), 0.47 (95% CI 0.19–0.74), respectively}. Acute pain intensity and early change in pain intensity were associated with PHN development [odds ratio (OR) 1.08 (95% CI 1.02–1.14) OR 2.38 (95% CI 1.10–5.16), respectively]. Decreased PCS was associated with decreased risk of PHN development, independent of acute pain intensity [OR 0.31 (95% CI: 0.12–0.80)].

Conclusion Catastrophizing was associated with acute pain intensity, and lower pain-related catastrophizing among patients with acute herpes zoster was associated with less risk of PHN development, independent of acute pain intensity.

Keywords Catastrophizing · Herpes zoster · Pain · Postherpetic neuralgia · Psychosocial risk factors

Introduction

Weakening of the immune system can reactivate varicella-zoster virus persisting in dorsal root ganglia, causing herpes zoster [1]. Postherpetic neuralgia (PHN) is a major complication of herpes zoster, with 5–30% of patients developing PHN [2], which is a type of neuropathic pain resulting from peripheral nerve injury caused by reactivation of the varicella-zoster virus. PHN often reduces patients' quality of life, and is associated with a substantial health and economic burden [3]. Thus, preventing the development of PHN among patients with herpes zoster is an important issue.

Risk factors for the development of PHN include advanced age, severe skin rash at onset, pain preceding skin rash, acute severe pain, and hyperesthesia or hypoesthesia at the skin lesion [2, 4–6]. Although some psychosocial risk factors, including anxiety, depressive symptoms, and stressful life events, have been associated with the development of

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✉ Keiko Yamada
keiko-yamada@umin.org

1 Department of Anesthesiology and Pain Medicine, Juntendo University Faculty of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

2 Department of Anesthesiology and Pain Medicine, Sada Hospital, Fukuoka, Japan

3 Department of Psychology, McGill University, Montreal, QC, Canada

4 Department of Anesthesiology and Pain Medicine, Hachinohe Heiwa Hospital, Hachinohe, Aomori, Japan

5 Osaka Center for Cancer and Cardiovascular Diseases Prevention, Osaka, Japan

6 Department of Anesthesiology and Pain Clinic, Juntendo Tokyo Koto Geriatric Medical Center, Tokyo, Japan

PHN in several previous studies [7, 8], supporting evidence is currently limited. Catastrophizing is a negative psychological characteristic involving a "fear-avoidance model" circuit, and has been suggested to be associated with pain chronicity [9–12]. A prospective multicenter study reported that pain catastrophizing was associated with the chronicity of neuropathic pain [12]. However, no previous study has investigated the association between catastrophizing and PHN development among patients with herpes zoster. In addition, no previous studies have investigated whether treatment-related changes in psychological factors among herpes zoster patients is associated with PHN development and its chronicity. Improvement in psychological factors with herpes zoster treatment might be associated with a decreased risk of PHN development and chronicity.

The current study had two main aims: (1) to examine the association between catastrophizing and pain intensity with acute herpes zoster, and (2) to investigate the association of treatment-related early changes in depressive symptoms, anxiety, and catastrophizing, with PHN development, independent of acute pain intensity. Reducing pain-related catastrophizing for patients with acute herpes zoster might prevent PHN development.

Methods

Study population

We identified 55 patients with acute herpes zoster within 30 days from the onset of skin rash at the Pain Clinic of Juntendo University Hospital from July in 2013 to September in 2015, without cancer or psychiatric disorders. Participants completed a self-report questionnaire at the first visit, and 3 and 6 months from the first visit. All participants were treated with medication or nerve block from the first visit. We asked participants who discontinued their examinations to answer a questionnaire by mail. Finally, of the 55 participants, 44 participants completed a 6-month follow-up and were included in the analyses. There were no significant differences in baseline characteristics between the 44 included patients and the 11 excluded patients (Online Resource 1).

Measures

Visual Analog Scale (VAS)

We used a visual analog scale (VAS) to measure pain intensity [13]. The VAS consisted of a 10-cm line with endpoints indicating a range from no pain to the worst possible pain. We converted the scale so that scores ranged from 0 (no pain) to 100 points (the worst possible pain) [13].

Pain Catastrophizing Scale (PCS)

We measured catastrophizing using the Pain Catastrophizing Scale (PCS), which consists of 13 items related to catastrophic thinking.[14] The PCS uses a 5-point Likert-type scale, ranging from 0 (never) to 4 (all the time). The PCS total score is calculated by totaling the scores for the 13 items, thus, the final score ranges from 0–52 points [14]. The Japanese version of the PCS was validated in a previous study [15].

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) consists of 14 items; 7 items assess anxiety and the other 7 items assess depression [16] The validity and reliability of the Japanese version of the HADS have been evaluated elsewhere [17]. The HADS uses a 4-point scale ranging from 0 to 3, and each anxiety and depression score is calculated by totaling the points for the 7 items. Thus, each scale score for anxiety or depression ranges from 0 to 21 points.

Procedure

Descriptive statistics were used for all study variables.

Assessment during the acute phase

Univariate regression analyses were used to evaluate the associations between demographic variables, physical factors, or psychological factors, and acute pain intensity.

Assessment during the development of PHN

T tests for paired variables were used to examine early changes in pain intensity and psychological factors within 3 months from the first visit. We constructed univariate logistic regression models to examine whether sex, severe skin rash, VAS, PCS, and HADS anxiety, and HADS depression at the first visit, early changes in VAS, PCS, and HADS anxiety/depression during the acute phase were associated with PHN development. We defined PHN development as a score $\geq$ 30 mm on the VAS within 6 months from the first visit.

We used bivariate logistic regression analyses to find a determinant factor for PHN development independent of pain intensity (VAS) at the first visit among early changes in pain intensity, catastrophizing, depression, or anxiety. Because pain intensity at the first visit could be a confounding factor between early changes in the listed variables and PHN development, it might be necessary to consider the influence of pain intensity when assessing a determinant factor for PHN development. Because of the small sample size

in the current study ($n = 44$), we selected bivariate logistic regression instead of multivariable logistic regression.

P values < 0.05 in two-tailed tests were considered statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical concerns

All procedures were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2013. Written informed consent was obtained from all participants. The Juntendo University Faculty of Medicine Institutional Review Board (no. 13-060) approved this study on 23 July 2013.

Results

Demographic information, mean values and standard deviations for all study variables including treatment are presented in Table 1.

Factors associated with pain intensity in the acute phase

We investigated the associations between demographic variables, physical factors, or psychological factors, and acute pain intensity (Table 2). Explanatory variables were age, sex, severe skin rash at the first visit, pain before skin rash, pain site, and PCS, HADS anxiety, and HADS depression scale scores. Sex, severe skin rash at the first visit, and PCS and HADS depression scores were significantly associated with acute pain intensity.

Factors associated with PHN development

T tests for paired samples were performed to examine treatment-related early changes (within 3 months from the first visit) in scores for pain intensity, catastrophizing, anxiety, and depression (Online Resource 2). All measurement scores decreased from the first visit compared with 3 months later.

Univariate odds ratios for PHN development are shown in Table 3. Of the 44 participants who completed follow-up, 11 (23%) developed PHN. Acute pain intensity and change in pain intensity were associated with PHN development (OR 1.08, 95% CI 1.02–1.14 and OR 2.38, 95% CI 1.10–5.16, respectively).

Table 4 shows the detected associations between treatment-related early changes in psychological factors and PHN development. We found that a decrease in PCS was associated with a decreased risk of developing PHN, independent of acute pain intensity; the OR was 0.31 (95% CI 0.12–0.80).

Discussion

The current results revealed that 11/44 patients (25%) developed PHN from acute herpes zoster. We found that catastrophizing in the acute phase was associated with acute pain intensity. Of several psychological factors, only early change in catastrophizing was associated with a decreased risk of developing PHN, independent of acute pain intensity. Although depression in the acute phase was associated with acute pain intensity, depression in the acute phase and early changes in depression were not associated with PHN development. To our knowledge, this is the first study reporting an association between treatment-related early changes in catastrophizing and a decreased risk of developing PHN.

The proportion of patients developing PHN in the current study was similar to that reported in a previous systematic review [2]. Although the previous study reported that PHN development was significantly associated with anxiety and depression [8], we found that depression was associated only with acute pain intensity and not PHN development, whereas anxiety was associated with neither acute pain intensity nor PHN development, in the current study. Differences in the duration of herpes zoster at baseline between the previous study (> 3 months in the chronic phase) and the current study (< 1 month in the acute phase) may have caused this discrepancy. Generally, psychological factors were very different between the acute and chronic phases. A previous study of patients suffering whiplash syndrome participating in a 10-week behavioral intervention reported that pretreatment scores for psychological factors (e.g., catastrophizing and fear of movement) were significantly higher in the chronic (6–18 months) group compared with those in the subacute (4–12 weeks) and early chronic (3–6 months) groups [18]. In the present study, the mean HADS anxiety score of 6.2 for participants at baseline was under the cutoff, whereas that for HADS depression of 14.9 was above the cutoff [16]. Low anxiety may not be a risk factor for increasing acute pain intensity, but we could not explain why participants' anxiety scores were lower than scores for depression.

The current findings suggest that reducing pain-related catastrophizing for patients with acute herpes zoster might prevent PHN development. Previous studies have suggested that behavioral interventions targeting psychological factors such as catastrophizing might be beneficial to help employees on administrative leave with chronic low back pain or whiplash syndrome return to work [19, 20], although these conditions do not constitute neuropathic pain.

The current study involved several limitations that should be considered. First, we examined only age, severe

Table 1 Characteristics at the first visit

Variable	Mean values	SD
Age, years (SD)	65.4	16
	n	(%)
Women	28	(63.6)
Severe skin rash at the first visit	13	(29.5)
Pain before skin rash	39	(88.6)
Pain site		
Trigeminal nerve	7	(15.9)
Cervical nerve	11	(25.0)
Thoracic spinal nerves	22	(50.0)
Lumbar nerve	3	(6.8)
Sacral nerve	1	(2.3)
Treatment		
Medication, $n=44$, 100%		
Antiviral	44	(100)
NSAIDs	28	(63.6)
Acetaminophen	18	(40.9)
TCAs	12	(27.3)
Antidepressant other than TCAs	2	(4.5)
Gabapentin or pregabalin	42	(95.5)
Antiepileptic other than gabapentin/pregabalin	3	(6.8)
Weak opioid	13	(29.5)
Potent opioid	1	(2.3)
An extract from inflammatory rabbit skin inoculated by vaccinia virus	24	(54.5)
Japanese kampo medicine	9	(20.5)
Nerve block plus above medications, $n=26$, 59.0%		
Epidural block	15	(57.7)
Nerve root block	2	(7.7)
Stellate ganglion block	7	(26.9)
Brachial plexus block	3	(11.5)
Trigeminal nerve block	3	(11.5)
Other nerve block	5	(19.2)
	Mean values	SD
VAS (0–100)	68.5	21.1
PCS (0–52)	30.2	9.0
HADS anxiety (0–21)	6.2	4.0
HADS depression (0–21)	14.9	4.5

$n=44$

SD, standard deviation; VAS, Visual Analog Scale; PCS, Pain Catastrophizing Scale, HADS, Hospital Anxiety and Depression Scale; NSAIDs; Non-Steroid Anti-Inflammatory Drugs, TCAs; Tricyclic Antidepressants

skin rash at onset, and pain before skin rash onset as explanatory variables, and were not able to measure hyperesthesia and hypoesthesia at skin lesions or stressful life events, which were suggested risk factors for PHN development, in previous studies [2, 4–8]. Second, we cannot exclude the possibility that low statistical power caused the lack of a significant association between changes in anxiety and depression, and pain development. Third, we used mainly univariate analysis because of the small sample size in the current study, which might have overestimated the association with PHN development. Finally, we did not control physicians' procedures with patients.

In conclusion, pain-related catastrophizing was not associated with pain intensity with acute herpes zoster. However, reduction in pain-related catastrophizing among

Table 2 Univariate regression analysis examining predictors of pain intensity

Dependent = VAS (T1)	β (95% CI)	R^2_{change}	F_{change} (*df*)	*p*
Age	− 0.06 (−0.37 to − 0.25)	0.004	4.3 (1,42)	0.70
Sex	0.46 (0.18–0.74)**	0.21	11.2 (1,42)	0.002
Severe skin rash at the first visit	0.36 (0.07–0.65)*	0.13	6.3 (1,42)	0.02
Pain before skin rash	0.14 (− 0.17 to 0.45)	0.02	0.8 (1,42)	0.37
Pain site	0.11 (− 0.20 to 0.42)	0.01	0.5 (1,42)	0.47
PCS (T1)	0.33 (0.03–0.62)*	0.11	5.0 (1,42)	0.03
HADS anxiety (T1)	0.99 (− 0.05 to 0.56)	0.07	2.9 (1,42)	0.09
HADS depression (T1)	0.47 (0.19–0.74)**	0.22	11.8 (1,42)	0.001

$n = 44$

β; standardized regression coefficient, CI; confidence interval, VAS; Visual Analog Scale, PCS; Pain Catastrophizing Scale, HADS; Hospital Anxiety and Depression Scale

*$p < 0.05$, **$p < 0.01$

Table 3 Univariate odds ratios of visual analog scale > 30 mm after 6 months from the first visit

	Univariate OR (95% CI)
Number	44
Number of VAS scores > 30 mm after 6 months	11
Sex	8.33 (0.96–72.75)
Severe skin rash at the first visit	1.52 (0.36–6.48)
VAS (T1)	1.08 (1.02–1.14)**
PCS (T1)	0.98 (0.90–1.05)
HADS anxiety (T1)	0.98 (0.83–1.17)
HADS depression (T1)	1.17 (0.99–1.38)
ΔVAS	2.38 (1.10–5.16)*
ΔPCS	0.58 (0.29–1.16)
ΔHADS anxiety	0.70 (0.32–1.52)
ΔHADS depression	1.05 (0.50–2.20)

$n = 44$

OR; odds ratio, CI; confidence interval, VAS; Visual Analog Scale, PCS; Pain Catastrophizing Scale, HADS; Hospital Anxiety and Depression Scale

*p < 0.05, **$p < 0.01$

Table 4 Bivariate odds ratios of Visual Analog Scale scores > 30 mm after 6 months from the first visit

	OR (95% CI)
Number	44
Number of VAS scores > 30 mm after 6 months	11
VAS (T1)	1.12 (1.02–1.24)*
ΔVAS	0.42 (0.09–1.98)
VAS (T1)	1.10 (1.03–1.18)**
ΔPCS	0.31 (0.12–0.80)*
VAS (T1)	1.08 (1.02–1.11)**
ΔHADS anxiety	0.59 (0.26–1.35)
VAS (T1)	1.09 (1.03–1.15)**
ΔHADS depression	0.64 (0.27–1.56)

$n = 44$

OR; odds ratio, CI; confidence interval, Δ; Standardized Residualized Change score, VAS; Visual Analog Scale, PCS; Pain Catastrophizing Scale, HADS; Hospital Anxiety and Depression Scale

*$p < 0.05$, **$p < 0.01$

patients with acute herpes zoster was associated with a decreased risk of developing PHN, independent of pre-treatment pain intensity, suggesting that reducing pain-related catastrophizing might prevent PHN development.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in this work.

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