Thermography as a predictor of postherpetic neuralgia in acute herpes zoster patients: a preliminary study

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Background/purpose: Infrared thermal images in patients suffering from herpes zoster (HZ) may exhibit thermal asymmetry due to the unilateral distribution of HZ lesions. This study examined the usefulness of infrared thermography in acute HZ as a predictor for the development of postherpetic neuralgia (PHN).

Methods: The authors collected demographic and clinical data including age, sex, onset of skin lesion, pain intensity by a visual analogue scale (VAS) and the development of PHN from a total of 55 patients diagnosed with HZ. We evaluated the body surface thermographic parameters between the lesion and contralateral normal skin: maximal difference in the temperature ($\Delta T$) and the size of the body surface area (BSA) showing thermal asymmetry.

Results: Temperatures of the lesions were found to be warmer than the control side in most patients with acute HZ. We compared the patient group who developed PHN with those who did not. In univariate analysis, patients with PHN were older ($P = 0.004$), had a higher VAS score for pain ($P < 0.001$), higher $\Delta T$ ($P < 0.001$) and larger BSA ($P = 0.001$). In logistic regression analysis to identify independent risk factors of PHN, older age (> 60 years old) and $\Delta T$ more than 0.5°C were found to be statistically significant.

Key words: herpes zoster – postherpetic neuralgia – risk factors – temperature difference – thermography

Accepted for publication 13 March 2011

The skin surface temperature distribution of a healthy human body exhibits a bilateral symmetry. Asymmetric distribution of skin temperature usually indicates abnormality of the body, although some pathologic conditions may exhibit bilateral thermal dysfunction (1).

Herpes zoster (HZ) is a relatively common condition, which is characterized by blistering skin eruption and neuropathic pain in dermatomal distribution. Concomitant inflammation of the peripheral nerve and damaged skin is thought to be responsible for the acute pain of HZ (2). Also, these inflammatory changes are expected to cause an alteration in skin infrared emission. Because of the unilateral distribution of HZ lesions, infrared thermal images in patients suffering from HZ may exhibit thermal asymmetry.

Postherpetic neuralgia (PHN) is the most common and most challenging to treat neurologic complication of HZ. PHN has been variably defined as any pain after rash healing or any pain 1 month, 3 months or 6 months after rash onset; the overall incidence of PHN is 8–19%, depending on the definition (3–5). Various studies revealed the following factors as predictors for the development of PHN: older age, females, greater acute pain severity, greater rash severity and having prodromal symptoms (3, 6, 7).

The aim of this study was to observe the thermal asymmetry in patients with acute-stage HZ and to determine whether the thermal images can provide prognostic information for the management of HZ patients.

Subjects and Methods

A total of 55 patients diagnosed with HZ from October 2008 to May 2010 were included in this study. Only the patients whose skin lesions developed between 1 and 7 days before the hospital visit were included, in order to observe changes in the acute phase of HZ. Biographic data, such as age, sex, affected area and interval between the onset of skin rash and hospital visit, were collected. Pain intensity was measured by a visual analogue scale (VAS), ranging from 0 (no pain) to...
10 (pain as bad as you can imagine). After the patients were diagnosed as having acute HZ clinically, all patients had a thermogram (IRIS-5000, Medicore, Seoul, Korea) taken on the corresponding dermatome. Patients were acclimatized for 15 min without clothing at a temperature of 24 °C, and then thermograms were recorded. Between lesional and contralateral normal skin, we observed two parameters on the thermogram: maximal temperature difference (ΔT) in degrees Celsius and the size of the body surface area (BSA) showing thermal asymmetry in percentage (rule of nine). Also, we followed the patient for the development of PHN: we defined PHN as a pain persisting or appearing 30 days after rash onset.

Statistical analyses performed were as follows: χ²- and t-test were used to identify the relevant factors for the development of PHN in univariate analysis. To determine the risk factors independently associated with PHN, logistic regression analysis was performed.

**Results**

We collected demographic, clinical and thermographic data from a total of 55 patients (20 males and 35 females; ages 12–86 years). As expected, the distribution of zoster lesion was reflected as thermal asymmetry on the thermogram (Fig. 1). The mean temperature difference in the affected dermatome and contralateral control was $0.53 \pm 0.41 ^\circ C$, which was regarded as abnormal considering other reports on the thermogram (8) or the manufacturer’s guideline for clinically significant thermal asymmetry ($\Delta T > 0.5 ^\circ C$). The skin surface temperature of the lesion was higher than that of the control side in most of the patients. Only three patients had a lower temperature than the control side, but the degree of the differences was $< 0.5 ^\circ C$, and was thus regarded as not having clinical significance. The temporal change of temperature difference showed a monophasic pattern, showing peaks at day 4 after the development of skin rash, and subsiding subsequently (Fig. 2). Interestingly, when compared with the patient group who did not develop PHN (blue dot in Fig. 2), patients who developed PHN showed a higher temperature difference (green dots in Fig. 2).

According to our definition of PHN as pain persisting or appearing 30 days after rash onset, 15 out of 55 patients were classified into the PHN group (27.3%). In univariate analysis, compared

![Fig. 1. Thermal asymmetry in acute herpes zoster 3 days after onset of skin lesion. (a) 74-year-old man with acute HZ of the left side of the thorax, later he developed PHN. (b) 70-year-old man with acute HZ of the right side of the thorax, he recovered without PHN. Both images were obtained at 3 days after the onset of skin lesion.](image-url)
Development of PHN

**TABLE 1. Univariate analysis of a group with PHN vs. without PHN**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Development of PHN</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Yes (N = 15)</td>
<td>No (N = 40)</td>
</tr>
<tr>
<td>Sex ratio (M:F)</td>
<td>1.0:1.5</td>
<td>1.0:1.9</td>
</tr>
<tr>
<td>VAS for pain</td>
<td>5.20±1.61</td>
<td>3.38±1.39</td>
</tr>
<tr>
<td>Onset of skin lesion (days)</td>
<td>3.60±1.88</td>
<td>4.05±1.89</td>
</tr>
<tr>
<td>BSA (%)</td>
<td>3.43±2.57</td>
<td>1.69±1.24</td>
</tr>
</tbody>
</table>

*Numerical data denotes mean ± standard deviation, except for the sex ratio for male and female (M:F).

With patients without PHN, patients with PHN were older (63.33 vs. 48.20, P = 0.004) and had a severe VAS score for pain (5.20 vs. 3.38, P < 0.001). However, other factors including female gender and medication within 72 h of development of skin eruption did not show statistically significant differences. For the thermographic data, temperature difference (ΔT) and BSA showing thermal asymmetry showed statistically significant differences, i.e., patients with PHN showed higher ΔT (0.86 °C vs. 0.40 °C, P < 0.001) and larger BSA (3.43% vs. 1.69%, P = 0.001), (Table 1). To determine independent risk factors for the development of PHN, logistic regression analysis was performed including variables found to be significant in univariate analysis (age ≥ 60 years old vs. <60, VAS score ≥ 5 vs. <5, ΔT ≥ 1.0 °C and 0.5 °C ≤ ΔT < 1.0 °C vs. ΔT 0.5 °C, BSA ≥ 3% vs. <3%), and reported prognostic factors of PHN, such as female gender and starting antiviral therapy within 72 h after the rash onset. Among these, age >60 years and temperature difference >0.5 °C were found to be independent risk factors for the development of PHN. Moreover, temperature difference showed a dose–response relationship, that is, the more the temperature difference, the greater the chance of PHN development. Other factors did not reveal statistical significance (Table 2). Although the VAS score for pain did not show a statistically significant difference, the VAS score showed a tendency for more severe pain leading to much more PHN.

**TABLE 2. Logistic regression analysis to identify the risk factors for the development of PHN**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Exp (B) [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;60 years old</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>VAS for pain</td>
<td>&lt;5</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Onset of skin rash</td>
<td>≤ 3 days</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>ΔT</td>
<td>ΔT &lt; 0.5 °C</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>BSA</td>
<td>&lt;3.0%</td>
<td>1.00 (reference)</td>
</tr>
</tbody>
</table>

Nagelkerke R-square for this regression model was 0.598.

Discussion

HZ is one of the most common dermatoses encountered in dermatologic practices. Besides controlling viral reactivation, amelioration of pain is of the utmost importance in the management of zoster patients, whether it is acute pain or PHN. As the most debilitating sequelae of HZ, the importance of controlling or preventing PHN cannot be overestimated. In this study, we inves-
tigated whether the thermogram could be used in the prediction of PHN development as other previously identified predictors of PHN development, such as older age, severe acute pain, severe rash intensity and antiviral treatment within 72 h after the rash onset (3, 6, 7).

Thermogram is well suited to detect changes in blood perfusion, which might occur due to inflammation, angiogenesis or other causes (9). Generally, if the temperature difference is higher than 0.5 °C, there might be a thermal asymmetry due to disease or suspicious pain (8). The thermal pattern of neuropathic pain is usually hyperthermia in the acute stage and hypothermia in the chronic stage (10); previous application of a thermogram to HZ patients confirmed the above-mentioned thermal pattern (10–12). It is suggested that the antidromic vasodilation triggered by neurosecretion from hyperactive nociceptors in the acute stage of neuropathic pain causes hyperthermia; meanwhile, sympathetic overactivation-driven vasoconstriction or denervation-driven muscular hypoactivity in the chronic stage causes hypothermia in a thermogram (13, 14).

In this study, HZ patients developed skin eruption 1–7 days before hospital visit; therefore, most of the thermographic patterns were hyperthermia on the lesional side. The mean temperature difference ($\Delta T$) showed a variation according to the time interval between the onset of skin rash and hospital visit. From the first appearance of a skin lesion, $\Delta T$ increases, reaching a peak at day 4, and then decreases again (Fig. 2), which resembles the natural clinical course of zoster skin eruption – initially urticarial rash, then full-blown vesicular eruption with severe inflammation and resolution with crust formation. When patients with or without PHN were separately dotted on the diagram, they showed an interesting pattern. Most patients who developed PHN subsequently (green dot in Fig. 2) showed higher $\Delta T$, usually out of 1 standard deviation from the mean $\Delta T$ of the corresponding day. This observation led us to examine whether the thermography is valuable in predicting the development of PHN.

Thus, we divided the patients into two groups according to the occurrence of PHN, and compared the clinical and thermographic variables between the two groups. The results of univariate analysis are summarized in Table 1. Thermographic parameters, i.e., maximal temperature difference between lesion and normal ($\Delta T$), and percentage of BSA showing thermal asymmetry between the lesion and the contralateral side showed a statistically significant difference. The higher the temperature difference and the wider the area showing thermal asymmetry on thermogram, the higher the incidence of PHN. If we assume that severe inflammation manifests a higher $\Delta T$ and a wider area of temperature difference on a thermogram, this finding is consistent with a previous finding that identified severe skin rash as a predictive factor for the development of PHN (3, 7). To test whether these thermographic variables are independent risk factors for the occurrence of PHN, logistic regression analysis was performed including two thermographic parameters ($\Delta T$ and BSA) and the aforementioned predictors of PHN – age, sex, severity of pain (VAS for pain) and antiviral therapy within 72 h after the rash onset (Table 2). Among the variables, only age and $\Delta T$ were statistically significant risk factors for PHN. Although it did not reach statistical significance ($P = 0.091$), VAS for pain was revealed as a potential risk factor for PHN, which is consistent with the previous reports that more severe pain in the acute stage is one of the risk factors for the development of PHN (3, 6, 7). Commencement of antiviral therapy within 72 h after the onset of skin rash was one of the well-known factors for the prediction of PHN. In this study, the interval between the onset of skin rash and hospital visit was not associated with the development of PHN. There may be two possible explanations for this unexpected finding. One is recall bias – we relied solely on patients’ statement about when the first skin rash appeared. Considering the fact that the initial skin eruption of HZ can easily be missed, some of the patients who responded they visited and received antiviral therapy within 3 days of first appearance of skin rash might pass the critical time limit of 72 h. The other possibility is that the relatively milder cases presented later; meanwhile, more severe cases presented earlier in the course of HZ eruption. Compared with more severe cases of HZ, milder cases usually manifest as a limited skin eruption and less debilitating pain; thus, there is a possibility of delayed hospital visits in the case of a mild HZ attack.

Among the thermographic variables, area of BSA displaying thermal asymmetry was not a
meaningful predictor for PHN, which can be rationalized by the fact that the area innervated by each nerve is usually different in size. For example, in the case of zoster ophthalmicus, the area innervated by the V1 branch of the trigeminal nerve usually does not exceed the size of an adult hand (approximately 1% of BSA), while the skin rash from the zoster affecting the L4 or the L5 dermatome could manifest on the entire length of lower extremity. Thus, the size of thermal asymmetry on the thermogram might be misleading in the determination of the severity of skin rash. In contrast, maximal temperature difference (ΔT) may reflect the severity of skin inflammation. Thus, in this study, ΔT was found to be a marker for severe inflammation, thus leading to the development of PHN. However, this result seems to be inconsistent with a recent study by Han et al. (14). They reported that the temperature differences in the thermal image were not correlated with pain severity, disease duration and development of PHN. Because of differences in the study design, we think it is better to interpret their results more cautiously. In their report, they defined ‘acute HZ’ as HZ case <6 months after the healing of skin rash. Considering the typical time course of thermal asymmetry in a neuropathic disorder – hyperthermia in the acute phase and hypothermia in chronic phase, some of the ‘acute HZ’ patients might have been in the chronic phase in the study by Han and colleagues. Our study reflects a more specified time interval (1–7 days of skin rash development) in the acute phase of HZ eruption. Different study populations could be one of the reasons why the two studies yielded different conclusions about the predictive value of ΔT.

PHN is pain that may persist for months or even years, but there is currently no consensus on the definition of PHN. When defining PHN as lasting or appearing 30 days after the rash onset, the incidence of PHN is 27.3% in our study. Among these, 66.7% (10 out 15) had pain lasting at least 3 months. Thus, pain lasting more than 30 days would likely remain for a longer duration; therefore, our results could be applicable to the different definitions of PHN. Although further evaluation with a larger population will be needed, we suggest that the thermal images in the acute stage of HZ might be a possible assessment tool that may provide valuable prognostic information.

Conclusion

We conclude that thermal asymmetry in the acute phase of HZ attack might provide prognostic information for the development of PHN. Higher temperature differences seemed to be associated with the occurrence of PHN. Further studies are required to support our preliminary results and to understand in depth the association between thermal changes in acute HZ and the development of PHN.

Acknowledgements

Conflict of interest: None declared.

This study was supported by a grant from the KoreaHealthcare technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A091121).

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