

A Study on the Connection between the Incidence of Postherpetic Neuralgia and Serum Ionized Calcium

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Herpes zoster (HZ) is an acute virus infectious disease mainly affecting middle-aged and elderly people. The morbidity rates of HZ in the age group of 50–59 years and 60–69 years are, respectively, 46 and 69 (per year, per 10,000 people). The age groups of 70–79 years and 80–89 years have a much higher rate of 95 and 109 (per year, per 10,000 people), respectively.^[1,2] Postherpetic Neuralgia (PHN) is a neuropathic syndrome which manifests as ongoing pain along the cutaneous nerve/s located in the area of prior HZ rash and typically involves one or more of the following types of pain: spontaneous aching or burning; paroxysmal shooting; and allodynia and hyperalgesia. While in the majority of cases, this pain will resolve within a year of initial rash presentation, for some patients the pain may persist for 5 years or more. As expected, given the relationship to HZ, the incidence of PHN increases markedly with age. However, the incidence is also linked to the severity of the pain experienced during the HZ episode. Those patients experiencing the highest levels of acute pain during HZ presentation are most at risk of developing PHN. PHN is also more prevalent among female than male HZ patients.

Data from the zoster quality of life study provide further evidence that, as a common and chronic complication of HZ, PHN has a significant impact on patients' lives and may result in significant costs for healthcare providers. Data from this study also highlight current unmet needs among PHN patients and inadequacy of current treatments in the management of PHN, reinforcing the need for effective means of prevention, and alternative strategies for pain management.^[2]

There are 2.25–2.75 mmol/L of calcium in the plasma (or serum) of every adult, accounting for <0.1% of the

human weight, among which half is free Ca²⁺, the other half is protein-combined calcium, calcium combined mostly with albumin, and slightly with globulin. Free calcium and protein combined calcium are dynamically balanced in the plasma. The serum calcium level within the normal range plays an important role in maintaining salt in the bone, blood coagulation, and neuromuscular excitement.^[3]

Recent research has revealed that Ca²⁺ metabolic disorder in critical PHN patients has a close connection with the attack and the severity and prognosis of this disease.^[4] It is estimated that in China there are 60–80 million senior citizens suffering osteoporosis due to low ionized calcium (ICa).^[5] Therefore, the purpose of this study was to investigate whether there is a relationship between the pathogenesis of PHN and the concentration of ICa.

METHODS

The inclusion criteria of HZ were: Patients were diagnosed according to criterion stipulated in clinical dermatology;^[6] patients aged 60 years and above; patients willing to accept various treatments; and arrangements by this research team.

The exclusion criteria of HZ were: (1) Patients treated with calcium within 3 months; (2) Patients with serious cardiac, hepatic, and renal insufficiency or failure; (3) Patients

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with serious hypertensive disease, active peptic ulcer, and diabetes heavily depended on insulin; (4) Patients treated systematically with corticosteroid hormone within a month; and (5) Patients unable to complete the treatments for various reasons.

The inclusion criteria of PHN were patients selected previously; patients with pain lasting 3 months or longer after being clinically cured.

In this study, we collected complete clinical data of 128 cases of the HZ patients, among whom 79 were men and 49 were women; 63 cases were in 61–70 years age group; 51 cases in the 71–80 years age group; and 14 cases in the 81–90 years age group. PHN patients reported experiencing pain in the area of their HZ rash for an average of 12 days. The PHN pain most commonly affected more than one site of the body (61.2%; $n = 78$) and most frequently presented on the chest/rib cage (66.4%; $n = 84$), head and neck (49.3%; $n = 63$), and abdomen/flanks (31.6%; $n = 41$). Eventually, 74 cases developed into PHN.

Japanese Jokoh Ex-Z Electrolyte Analyzer (JOKOH Co., Ltd, Japan) and its corollary reagent were used. The investigators collected the fasting venous blood of 128 patients in their early stages of HZ, separated the serum within 2 h, and then examined the ICa value of each blood sample at room temperature. All the patients received regular treatment, and no calcium was applied. Thirty days later, 54 patients were cured and 74 developed into PHN. All their ICa values were re-examined. The reference range for the patients aged over 60 was 1.13–1.35 mmol/L.

According to the World Health Organization, pain is divided into the following scale: 0 - no pain; I - mild pain, intermittent, and medicine not necessary; II - moderate pain, continuous, and affecting sleep, painkiller needed; III - severe pain, continuous, and pain cannot be relieved without medicine; and IV - serious severe pain, continuous acute pain with changes in blood pressure and pulse.

The investigators used SPSS 13.0 statistical software (SPSS Inc., USA) for data analysis. All data were tested by Chi-square test and Spearman rank correlation methods. The number of incidences, the pain scale, and the distribution area is shown in tables.

RESULTS

In Figure 1, “II,” “III,” and “IV” represent the pain scale of second-degree, third-degree, and fourth-degree, respectively. As the HZ patients and PHN patients are suffering from relatively severe pain, the pain scales of 0 and I degree do not exist, so the 0 and I are not shown in the Figure 1.

From the Figure 1, it can be clearly seen that the patients with the HZ and PHN are mainly distributed in the low-ICa area. Moreover with the normalization of ICa values, the number of incidences is on the decrease [Tables 1 and 2].

DISCUSSION

First-line therapies for PHN include tricyclic antidepressants, gabapentin, and pregabalin, and the lidocaine 5% patch. Second-line therapies include strong and weak opioids and topical capsaicin cream or 8% patch. Tricyclic antidepressants, gabapentinoids, and strong opioids are effective but also associated with systemic adverse events that may limit their use in many patients, most notably with those significant medical comorbidities or advanced age.^[7] Therefore, the PHN patients need safer and more effective treatment.

The pathogenesis of PHN is still not fully known, but the dominant view traces it to the neuropathy of the central nervous system and its neighboring nerves. Rowbotham observed in 1999 that the central nervous system of PHN patients is widely and critically damaged by chicken pox – varicella-zoster virus, not only leading to the dehydration of dorsal root ganglia, the degeneration of wallerim, but clear cystic change and marked decrease in the number of the ganglion cells, especially the decrease in

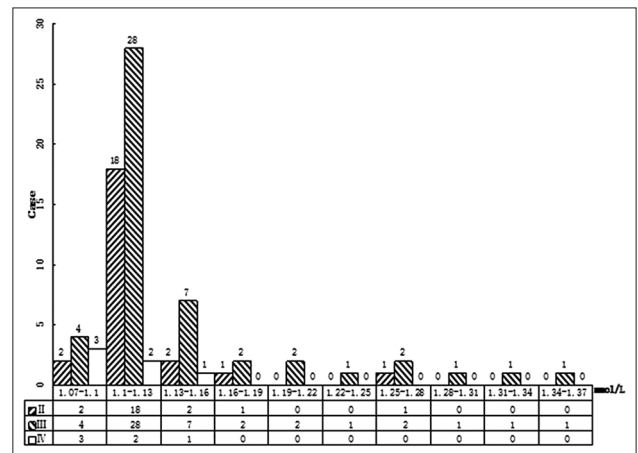


Figure 1: Connection between the incidence, the pain scale and the concentration of the ICa, concerning the 74 cases of PHN patients, 57 cases of them had ICa lower than normal, accounting for 77.03%.

Table 1: Comparison of ICa values between the PHN group and the cured group

Group	Case	ICa <1.13	ICa >1.13	Rate of incidence (%)
PHN	74	57	17	77.03
Cured	54	8	46	14.81

$\chi^2 = 24.57, P < 0.005$, the difference is statistically significant.
ICa: Ionized calcium; PHN: Postherpetic neuralgia.

Table 2: Rate of PHN incidence between the low-ICa group and normal-ICa group

Group	Case	PHN	Cured	Rate of PHN incidence (%)
ICa <1.13	65	57	8	87.69
ICa >1.13	63	8	55	12.70

$R = 6.9047, OR = 15.0882, OR > 1$. ICa: Ionized calcium; PHN: Postherpetic neuralgia; OR: Odds ratio.

and the collagenization of the thicker nerve fiber axis with the myelin sheaths. Chronic inflammatory cell infiltration can also be found in the dorsal root ganglia. This pathologic change prompts the surviving primary afferent nerve fibers, after being damaged, and to form new connections – the regeneration of the central synapse with the bone pain signal transmitting neurons. These new connections and the overactive dorsal projection neurons contribute considerably to the attack of PHN.^[8]

The calcium in the human body is widely and extensively engaged in regulating all kinds of life activities. This is especially true for the functioning activities of neurons. Under normal circumstances, Ca^{2+} is in tiny amounts within the neurons, but it exists abundantly outside the cells, 10,000 times the number of it in the neurons. Ca^{2+} maintains a stable low-level in the cells through complicated mechanisms, the functions of which include the regulation of the neuronal excitability, the release of neurotransmitters, the activation of the second messengers, and the transcription of the genes. As it is involved in passing and regulating nociception factors such as the neurotransmitters and the neuromodulators, Ca^{2+} inside of the cells plays a very important role in the passing and regulation of the pain people feel in their body. If the concentration of Ca^{2+} in the serum decreases, Ca^{2+} will flow to the inside of the cells, causing excessive amounts of Ca^{2+} to accumulate in the mitochondria, and followed by the swelling of and the damage to the mitochondria. Therefore, a series of toxic effects of the cells will be inevitable, and the neuronal cells will be functionally affected.^[9]

It can be clearly seen from Figure 1 that the patients with the HZ and PHN are mainly distributed in the low-ICa area. Moreover with the normalization of ICa values, the number of incidences is on the decrease. Continuous low-level of Ca^{2+} in the serum will lead to functional damage to the neuronal cells. If, in this state, the chicken pox – varicella-zoster virus attacks, the damage afflicted to the neuronal cells will be aggravated and accelerated.

Spearman rank correlation test methods were adopted to analyze the connection between the pain scale of PHN patients and the concentration of ICa. The test results

$ps = 0.007$, $P = 0.950$ showed that no obvious connection was found between ICa and the pain scale of PHN patients.

Comparing the PHN group and the cured group: $\chi^2 = 24.57$, $P < 0.005$, the results are statistically significant. The incidence rate between patients with low ICa and those with normal/high ICa: $R = 6.9047$, Odds ratio (OR) = 15.0882, $OR > 1$, the HZ patients with low ICa face a greater risk of developing PHN. Therefore, the low ICa value of geriatric HZ patients is a key factor to the incidence of PHN.

We prescribed calcium agents such as Caltrate D and calcium gluconate for some PHN patients with low-ICa values, and their intractable pain was cured. In the next stage of our research, we will study the curative effect of treating PHN with calcium agents to pursue an effective remedy.

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Conflicts of interest

There are no conflicts of interest.

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