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Case Report

Relief of Paroxysmal Sharp Pain and Allodynia in Postherpetic Neuralgia by Intravenous Selenium: A Case Report

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Abstract

Postherpetic neuralgia (PHN) is a neuropathic pain. PHN patients experience various types of pain, suggesting multi-pathophysiologic mechanisms. Gabapentinoids are first-line therapy for PHN. However, PHN is often refractory to the treatment. Mechanisms of gabapentinoids on pain include altering calcium channels, inhibiting N-methyl-D-aspartate (NMDA) receptors and reducing inducible *nitric oxide* synthase (iNOS). Selenium mediates neuroprotection through modulating NMDA receptors and reducing iNOS. We reported that a PHN patient with a low normal selenium level received intravenous selenium as an add-on therapy to pregabalin and responded well. More studies are required to determine the analgesic effects of selenium on PHN.

Keywords: Postherpetic neuralgia; Intravenous; Selenium

Abbreviations: Ca2+- calcium ions; HZ- herpes zoster; iNOS- inducible nitric oxide synthase; NMDA- N-methyl-D-aspartate; NO- nitric oxide; NRS- numeric rating scale; PHN- Postherpetic neuralgia; ROS- reactive oxygen species; VZV- varicella zoster virus

1. Introduction

Postherpetic neuralgia (PHN) is neuropathic pain as a result of damage to peripheral nerve caused by the reactivation of the varicella zoster virus (VZV). Patients with PHN may experience a constant or paroxysmal pain. The pain is manifested as a tingling, shooting, *electric-shock,* or stabbing sharp pain along with *burning* and/or itching *sensation*. Gabapentinoids and opioids are first- and second-line drugs for PHN respectively. However, some patients are refractory to the current pharmacotherapy. It indicates an unmet need in the treatment of PHN. Selenium has antioxidant and neuroprotective effects [1, 2]. Herein, we reported that intravenous selenium in a PHN patient with a low normal selenium level made effective responses in paroxysmal sharp pain and allodynia, defined as a reduction of 2 points on an 11-point numeric rating scale (NRS 0–10).

2. Case Presentation

A 76-year-old female (145 cm, 46 kg) developed herpes zoster (HZ) involving the right eighth to tenth thoracic dermatomes one year ago. She had a history of cervical carcinoma in situ with a surgical treatment one month prior to the outbreak of HZ. She had an inadequate response to monotherapy of pregabalin and was intolerant to the side effect (constipation) of combined therapy of pregabalin and opioids. When pregabalin (300 mg daily) alone was prescribed, paroxysmal spontaneous electric-shock/stabbing pain (>10 times/day with a duration of 2-3 minutes) and brush-evoked pain (allodynia) were graded as 5 and 4 on an 11-point NRS, respectively. She refused invasive treatments including nerve blocks and pulsed radiofrequency therapy. She has been taking vitamin C 1000 mg, zinc 25 mg and vitamin D3 4000 iu daily from the over-the-counter supplement for 6 months as a suggestion - these nutrients were identified as risk factors of PHN [3, 4]. She was referred to our pain clinic for nutritional survey and alternative therapy for PHN. Blood tests revealed high normal levels of vitamin C, D and zinc. The reference range of serum selenium concentration in our hospital is from 70 to 190 µg/L. Her selenium level (128.9 µg/L) was within the low normal range (70-130 µg/L) based on a dichotomous classification. (Table 1) She received a 2-hour infusion of sodium selenite (selenium 200 µg) in 100 ml normal saline twice a week as an add-on therapy to pregabalin (300 mg daily). Two weeks later, paroxysmal sharp pain and brush-evoked allodynia were rated as 3 and 2 on the 11-point NRS, separately. After three weeks of intravenous selenium treatment, the paroxysmal sharp pain was rated less than 3 on the 11-point NRS with a decreased frequency 2-3 times a day. Allodynia disappeared. Serum selenium level increased to 186.8 µg/L. Selenium treatment was switched to daily oral supplementation containing 100 µg of selenium. Pregabalin was decreased to 150 mg daily. At 1-month follow-up visit, the frequency of paroxysmal sharp pain was reported only once a day. Medication was tapered off at 3-month follow-up without recurrence of pain. No complications were reported.

Blood tests (reference ranges)	**1st**	**2nd**	**3rd**
Vitamin C (4-15 mg/L)	14.5		
25-OH Vit. D (30-100 ng/mL)	65.6		
Vitamin E (5.0-18 mg/L)	13.3		
Zinc (70-120 µg/dL)	95.8		
Selenium (70-190 µg/L)	128.9	186.8	174.9
Varicella-zoster IgG (<110 mIU/mL)	3701.5		
Varicella-zoster IgM-positive ratio (>1.0)	0.24		
C-reactive protein (<5 mg/L)	2.5	1.0	

1st: the blood test at the referral day before selenium treatment; 2nd: the serum selenium level after three weeks of intravenous selenium treatment; 3rd: the serum selenium level at 1-month follow-up visit.

Table 1: Results of the blood tests in the patient with postherpetic neuralgia.

3. Discussion

PHN is a chronic neuropathic pain impairing the quality of life. Although both of gabapentin and *pregabalin* are first-line drugs for PHN, some PHN patients have inadequate therapeutic responses. Based on individual's preference, this patient visited our pain clinic for nutritional survey and alternative treatments for PHN. Selenium supplement was found to be an effective add-on therapy to pregabalin for relieving paroxysmal *electric-shock*/stabbing sharp pain and allodynia in this PHN patient with a low normal selenium level.

In this patient suffering from on-year herpetic pain, effective responses of intravenous selenium therapy on paroxysmal sharp pain and allodynia occurred within two weeks. The dramatic therapeutic responses of PHN to intravenous selenium therapy should not be considered as the natural course of PHN. *Pregabalin* takes 4 - 6 weeks for full benefit. This patient has taken pregabalin 300 mg/day for more than three months before her referral. A delayed therapeutic effect of pregabalin was considered unlikely. A placebo effect was also unlikely because of differential therapeutic improvement on spontaneous sharp pain and allodynia in this case.

This patient has had a vegetarian diet for more than ten years. Low serum selenium levels are common in old Taiwanese as a reduced dietary intake of selenium since most of the elderly become vegetarians due to religious reasons [5]. She was diagnosed with cervical carcinoma in situ one month before the outbreak of HZ. The increased risk of cervical cancer was found to be associated with decreased serum selenium which might lead to an impaired serum antioxidant system in the pathogenesis of cervical carcinoma [6]. Her low serum selenium level was likely to exist prior to outbreak of shingles. However, chronic herpetic pain decreased the appetite and food intake. Viral infection increases the demand for micronutrients and causes the loss of selenium [1]. As a result, serum selenium level declined more over the

course of HZ and participated in the pathogenesis of PHN probably.

The effects of suboptimal selenium status on PHN are unclear. Nonetheless, selenium deficiency can be restored by selenium supplementation [1]. There is good evidence for the benefit of intravenous selenium from 60 to 400 μg/day in parenteral nutrition and burn patients [7]. Intravenous selenium therapy attenuated paroxysmal *electric-shock/*stabbing sharp pain and allodynia effectively in this PHN patient with a low selenium level. Some explanations are made. In a PHN rat model, VZV infection up-regulates inducible *nitric oxide* synthase (iNOS) to produce excessive nitric oxide (NO) which thereby activates spinal astrocytes. Activated astrocytes enhance interleukin-1β expression resulting in overactivation of N-methyl-D-aspartate (NMDA) receptors in spinal dorsal horn neurons [8] with increasing responsiveness to mechanical stimuli [9]. The major neurotransmitter released by sensory afferents in spinal dorsal horn neurons is glutamate**.** Peripheral nerve injury produces excessive glutamate release in the dorsal horn leading to excitotoxicity via overactivation of NMDA receptors [10, 11] and mitochondrial dysfunction [12]. Overactivation of NMDA receptors increases cytosolic concentrations of free calcium ions (Ca^{2+}) which consequently enter mitochondria. Mitochondrial Ca^{2+} overload promotes production of reactive oxygen species (ROS) as important upstream inducers of spinal synaptic plasticity underlying chronic pain [13]. Taken together, peripheral nerve injury caused by VZV-infection leads to excessive glutamate release, activated NMDA receptors, mitochondrial dysfunction, excessive ROS, synaptic plasticity and neuronal hyperexcitability. All changes in the nerve system are associated with the initiation and maintenance of neuropathic pain. In animal models, selenium deficiency increases susceptibility to glutamate-induced excitotoxicity, enhances the expression of iNOS, increases the NO content and the mitochondrial apoptosis [14], which can be reversed by adequate selenium treatment [15]. Accordingly, selenium mediates neuroprotection through the aforementioned effects, indicating selenium as a potential therapeutic for neuropathic pain. For safety, selenium status should be monitored by measurement of serum selenium when intravenous selenium is used [7]. Indeed, selenium status was monitored carefully in our case and the result of this case supported that adequate selenium supplementation within physiological concentration attenuates neuropathic pain [1, 15].

Gabapentinoids attenuate neuropathic pain through inhibiting NMDA receptors, reducing iNOS/NO and binding to the $alpha_2$-delta subunit of T-type calcium channels to alter the function of calcium channels. Selenium treatment reverses neuropathy via modulating NMDA receptors, reducing iNOS/NO, restoring mitochondrial function, and decreasing ROS production [15]. These mechanisms provide the molecular basis for selenium supplements alone or the combined therapy of pregabalin and selenium.

Selenium might be used as a modulator of neuropathic pain based on the molecular mechanisms of selenium. To our knowledge, no studies reported the analgesic effects of selenium on PHN. Based on the case, it is not possible to recommend that all PNH patients need to examine selenium levels and receive selenium supplements. More studies are required to determine the selenium status in PHN patients and whether selenium therapy alone or as an adjuvant to

gabapentinoids is beneficial in PHN patients with low selenium levels.

Patient Consent Statement

Written patient consent was obtained for this case report.

Conflicts of Interests

None. All authors declared no conflict of interest.

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