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Patient characteristics and analgesic efficacy of antiviral therapy in postherpetic neuralgia

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ABSTRACT

Postherpetic neuralgia (PHN) is the most common complication of shingles caused by reactivation of varicella zoster virus (VZV). Management of PHN is often suboptimal while using current conventional treatments. Antiviral therapy was used to reduce PHN-associated pain in two small trials which showed conflicting results. We hypothesize the analgesic efficacy of antiviral therapy on PHN is affected by patient characteristics including pathophysiology of the participants and serum vitamin D levels. Pathophysiology of PHN includes neuronal excitability and chronic VZV ganglionitis (persistent active VZV infection in ganglions). VZV-DNA positivity or a positive IgG coupled with a positive IgM indicates recent or current VZV infection. Positive VZV-DNA or IgG/IgM tests are used to confirm whether the patients experience chronic VZV ganglionitis. Antiviral therapy decreases pain in PHN patients with chronic VZV ganglionitis; whereas, antiviral therapy shows no effects in PHN patients with negative VZV-DNA or IgM. Vitamin D is a natural antiviral mediator. Studies show a high prevalence of vitamin D deficiency in hepatitis B/C virus-infected patients. Serum vitamin D levels and vitamin D supplementation are factors which affect the antiviral efficacy on hepatitis B/C virus infection. Serum 25-OHD levels of hospitalized patients with shingles were significantly lower compared to healthy controls. Accordingly, PHN patient may have a high prevalence of vitamin D deficiency which negatively affects the antiviral efficacy. Vitamin D supplementation may improve the antiviral efficacy on PHN. Future trials regarding antiviral therapy on PHN should consider patient characteristics and should be conducted among different subgroups of PHN patients.

Herpes zoster and postherpetic neuralgia

Herpes zoster (HZ, shingles) is a viral disease caused by reactivation of the varicella zoster virus (VZV). Pain is the most common symptom of HZ. In a large population-based study with medical record confirmation of HZ diagnosis from America, more than 65% of the adult HZ patients were prescribed pain medication for relieving acute herpetic pain [1]. Although many patients suffer from prolonged herpetic pain referred to as postherpetic neuralgia (PHN), there is no a clear definition of PHN [2–4]. PHN is generally defined as herpetic pain that was rated as 3 or more on a scale ranging from 0 (“no pain”) to 10 (“pain as bad as you can imagine”) [2], persisting more than 90 days after the onset of rash [1,5]. PHN is the most common complication of HZ. PHN can interfere with basic and essential activities of daily living including general activity, work, sleep and enjoyment of life. As a result, PHN can have a serious impact on quality of life and functional ability.

In large population-based studies from UK and America, the prevalence of PHN (3-month definition) increased from 5 to 8% in those younger than 60 years to 20% more in those aged 80 years or older [1,6]. The incidence of PHN increased with age [1,6]. There are several topical Treatment (lidocaine patch, capsaicin cream/patch) and systemic treatment (gabapentinoids, tricyclic antidepressants, opioids) for PHN management. Gabapentinoids (gabapentin and pregabalin) are first-line drugs for PHN. However, 15–50% of PHN patients have inadequate therapeutic response due to adverse effects when treated with gabapentinoids [4,7]. Management of PHN is still challenging while

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using current clinical management strategies. Intriguingly, heterogeneous patterns of PHN suggest multiple pathophysiologic mechanisms [8]. Individualized treatment based on the pathophysiologic mechanisms is required for decreasing pain effectively in PHN.

Pathogenesis of postherpetic neuralgia

The pathophysiology of chronic pain in PHN is multifactorial. There are two non-mutual theory of PHN[2] including nerve injury-induced neuronal excitability and chronic VZV ganglionitis (neuroinflammation [9] caused by persistent VZV infection [10–12]).

Evidence that PHN may be caused by chronic low-grade VZV infection has come from VZV DNA positivity in blood MNCs of some PHN patients [4,12] and from the favorable response of PHN patients to antiviral treatment [10,11]. The detection of VZV DNA by the polymerase chain reaction test was performed in blood mononuclear cells (MNCs) from PHN patients, zoster patients without PHN and elderly individuals without a history of HZ. VZV-DNA positivity was only found in PHN patients [12]. In an immunocompetent elderly woman with PHN, her blood MNCs contained VZV-DNA. She experienced pain relief after famciclovir treatment and negative virological tests for VZV-DNA. She discontinued famciclovir five times over an 11-year period. Pain always reoccurred within 1 week and blood MNCs contained VZV-DNA again [10]. Thus, pain in certain PHN patients is supposed to be caused by persistent active VZV infection in ganglia (chronic active VZV ganglionitis) [10–12]. Recently, Francesca Pica et al. demonstrated that 10% of PHN patients had VZV-DNA positivity in a one-year follow-up of PHN patients [4].

Laboratory tests for herpes zoster – testing VZV-DNA or immunoglobulins

HZ can be easily diagnosed by clinical manifestations including painful skin blisters and rash along the dermatomes in most cases. Laboratory tests for confirming VZV infection are required in patients with atypical symptoms or zoster sine herpete defined as dermatomal distribution pain without rash caused by VZV [13]. In addition, laboratory tests are needed for differential diagnosis of HZ from other skin diseases, such as zosteriform herpes simplex [14].

Laboratory tests include the virological test for VZV-DNA and the serological tests for VZV immunoglobulin (Ig) - IgG and IgM antibodies. Detection and quantification of VZV-DNA can be performed by sampling VZV-DNA from the skin lesion or blood MNCs via the polymerase chain reaction test [4].

Serological tests of VZV IgM/IgG can be done by enzyme-linked immunosorbent assay (ELISA) [14,15]. IgG and IgM antibodies are detected 2–5 days later and show the highest titers at 2–3 weeks after VZV skin rash appears. The IgG antibody titers gradually decline and remain positive for several years. The VZV IgM antibody titers rapidly decrease and are undetected at 1 year after HZ outbreak. The positive rate of VZV IgM antibody ranges from 10% to 70% in HZ patients [14], but it is unknown in PHN. Interestingly, high titers of serum VZV IgM in HZ have been found to be associated with the severity of skin lesions and the presence of PHN [16–18].

Compared to the methods of separating the virus from the skin lesion or blood MNCs, ELISA tests for VZV IgM/IgG is simple, high sensitive/specific and cost-effective for the diagnosis of current HZ infection [14,15]. A positive IgG result coupled with a positive IgM result indicates recent or current VZV infection. A positive IgG result coupled with a negative IgM result suggests previous VZV vaccination or infection [13]. Accordingly, a PHN patient with VZV IgM-positivity means that the patient experiences chronic active VZV ganglionitis.

Analgesic efficacy of antiviral therapy

In a prospective, open-label clinical trial, 15 patients with moderate to severe PHN received intravenous acyclovir for 14 days followed by oral valacyclovir for 1 month. As a result, eight out of fifteen PHN patients reported effective pain relief by a decrease of 2 or more on the 11-point Numeric Pain Rating Scale [11]. In the other randomized, double-blind, placebo-controlled trial, ten patients who had experienced at least 6 months of severe herpetic pain received intravenous acyclovir for 14 days, followed by oral acyclovir for 42 days. Only one of ten subjects reported improvement in postherpetic pain. The authors concluded that acyclovir therapy did not reduce pain in PHN patients [19]. Overall, the therapeutic outcomes in the two clinical trials showed conflicting.

Taking a closer look at the two trials, questions were raised. First, there are several pathophysiologic mechanisms of PHN patients [8,20]. Pain in certain PHN patients is caused by persistent active VZV infection in ganglia [10–12]; whereas, pain in the rest of PHN patients may be not associated with chronic VZV ganglionitis [2,10–12,21]. The underlying pathophysiology of PHN patients may affect therapeutic outcomes drastically. Second, a one-year follow-up study of PHN patients [4] revealed that PHN patients with positive VZV-DNA was 10%. The finding indicates only 10% of PHN patients suffered from chronic VZV ganglionitis. Third, fifteen patients were enrolled in one trial and only ten patients were enrolled in the other trial. The case numbers in the two trials were small. It is not possible for a small clinical trial to include all subgroups of PHN patients. Moreover, both trials did not examine patient characteristics including VZV-DNA or serum VZV IgG/IgM titers. Thus, we question whether the conflicting findings were associated with the participants whose pain was associated with different pathophysiologic mechanisms.

Vitamin D – a natural antiviral mediator

Beyond classic effects in musculoskeletal health [22], vitamin D can inhibit neuroinflammation by reducing proinflammatory cytokines and increasing anti-inflammatory cytokines [23,24]. Vitamin D deficiency has been demonstrated to be associated with increased neuropathic pain in patients with diabetes mellitus [25]. Vitamin D can be an analgesic for diabetic patients with neuropathic pain [26].

There are high prevalences of vitamin D deficiency in hepatitis B virus (HBV)- and hepatitis C virus (HCV)-infected patients [27]. Low serum vitamin D levels are associated with high viral load in HBV/HCV-infected patients [28,29]. High rates of a sustained virological response, defined as an undetectable serum HCV-RNA level at the end of antiviral therapy, were observed in HBV/HCV -infected patients with vitamin D levels above 30 ng/mL or receiving vitamin D supplementation [30–32]. Although not conclusive proof, there are associations between vitamin D levels/vitamin D supplementation and the efficacy of antiviral treatment for HBV/HCV infection. Interestingly, serum25-OHD levels of hospitalized patients with HZ was found to be significantly lower than that of the healthy controls [33]. Vitamin D is a direct inducer of antimicrobial peptides (human cathelicidin (LL-37) and beta-defensin) [34]. In a skin-infection model, antimicrobial peptides including LL-37 and beta-defensin-2 can reduce viral replication in keratinocytes and B cells infected with VZV through different mechanisms of action [15]. Due to similar mechanisms among vitamin D deficiency, vitamin D supplementation and the efficacy of antiviral treatment on HBV/HCV infection, questions regarding vitamin D and PHN are raised. First, is there a high prevalence of vitamin D deficiency in PHN patients? Second, does vitamin D deficiency negatively influence the analgesic efficacy of antiviral therapy on PHN? Third, does vitamin D supplementation improve the analgesic efficacy of antiviral treatment on PHN [15,26,34]?

Hypothesis – analgesic efficacy of antiviral therapy on PHN is associated with patient characteristics including pathophysiology and serum vitamin D levels.

We hypothesize the analgesic efficacy of antiviral therapy on PHN is associated with patient characteristics including pathophysiology of the participants and serum vitamin D levels.

First, to identify pathophysiology of PHN patients whose pain is associated with chronic active VZV ganglionitis. PHN patients with chronic VZV ganglionitis are confirmed by positivity of VZV-DNA or VZV IgG/IgM tests. One group is those with VZV-DNA positivity or a positive IgG coupled with a positive IgM indicating a recent or current VZV infection [13,14]. The other group is those with negative VZV-DNA or a positive IgG result coupled with a negative IgM result suggesting previous VZV infection. PHN patients with positive VZV-DNA or IgM tests are considered to suffer from chronic active VZV ganglionitis [2,10–12,21]. Antiviral therapy helps decrease pain in PHN with VZV-DNA positivity or positive/high-titer VZV IgM. But, antiviral therapy shows no effects in PHN with negative VZV-DNA or negative/low-titer VZV IgM.

Second, to identify the associations between antiviral therapy response and vitamin D levels in PHN. The efficacy of antiviral therapy in PHN patients with vitamin D deficiency may be significantly lower than that in PHN patients with normal vitamin D levels. Vitamin D supplementation may improve the antiviral efficacy in PHN significantly.

Evaluation of the hypothesis

The hypothesis regarding patient characteristics and the analgesic efficacy of antiviral therapy on PHN can be evaluated by a prospective randomized, double-blind trial in patients and observers. Antiviral therapy is prescribed for PHN patients who have the virological test for VZV-DNA or serological tests of VZV IgM/IgG antibodies before and after antiviral therapy. All PHN patients are divided into two groups – one group is with positive VZV-DNA/IgM and the other group is with negative VZV-DNA/IgM. The effective rates are compared between groups. The effective rate of antiviral therapy in PHN with positive VZV-DNA/IgM may be significantly higher compared to that in PHN with negative VZV-DNA/IgM. In addition, the rate of vitamin D deficiency is evaluated in all PHN patients. Vitamin D deficiency may predict an unfavourable response to antiviral treatment.

In the next prospective randomized, double-blind, placebo-controlled trial, PHN patients with positive VZV-DNA/high-titer VZV IgM and vitamin D deficiency are enrolled. Serum levels of vitamin D are measured in all patients before and after antiviral therapy. Antiviral therapy combined with vitamin D supplements or antiviral therapy combined with placebo is tested. The effective rate is predicted to be significantly higher in patients receiving antiviral therapy combined with vitamin D. In addition, there is significance improvement in serum vitamin D levels after the antiviral therapy combined with vitamin D supplements.

Consequences of the hypothesis

Many PHN patients remain refractory to current conventional therapeutics. More effective therapies are needed for PHN treatment. If the research results support antiviral therapy as a therapeutic option for certain PHN patients, the virological test or serological tests of VZV IgM/IgG by ELISA [14,15] are suggested for PHN patients. Antiviral therapy can be prescribed in PHN patients with positive VZV-DNA or IgM. Vitamin D, a natural antiviral mediator [15,34], may act as a potential adjuvant in treatment of HZ infections. Vitamin D deficiency may negatively influence on the antiviral efficacy. Serum vitamin D survey is suggested for PHN patients. Antiviral therapy combined with vitamin D supplementation is indicated for PHN patients with positive VZV-DNA or IgM, in particular vitamin D deficiency. Future trials regarding antiviral therapy on PHN should consider patient characteristics and should be conducted among different subgroups of PHN patients. Importantly, the new treatment strategy based on VZV virological/serological tests and serum vitamin D levels provides an evidence-based alternative for the pain management of PHN patients.

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Declaration of Competing Interest

None.

References

[1] Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc 2007;82(11):1341–9.
[2] Tontodonati M, Ursini T, Polilli E, et al. Post-herpetic neuralgia. Int J Gen Med 2012;5:861–71.
[3] Yawn BP. Post-shingles neuralgia by any definition is painful, but is it PHN? Mayo Clin Proc 2011;86(12):1141–2.
[4] Pica F, Gatti A, Divizia M, et al. One-year follow-up of patients with long-lasting post-herpetic neuralgia. BMC Infect Dis 2014;14:556.
[5] Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352(22):2271–84.
[6] Gauthier A, Breuer J, Carrington D, Martin M, Remy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiol Infect 2009;137(1):38–47.
[7] Massengill JS, Kittredge JL. Practical considerations in the pharmacological treatment of postherpetic neuralgia for the primary care provider. J Pain Res 2014;7:125–32.
[8] Pappagallo M, Oaklander AL, Quatrano-Piacentini AL, Clark MR, Raja SN. Heterogenous patterns of sensory dysfunction in postherpetic neuralgia suggest multiple pathophysiologic mechanisms. Anesthesiology 2000;92(3):691–8.
[9] Ellis A, Bennett DL. Neuroinflammation and the generation of neuropathic pain. Br J Anaesth 2013;111(1):26–37.
[10] Gilden DH, Cohrs RJ, Hayward AR, Wellish M, Mahalingam R. Chronic varicella-zoster virus ganglionitis–a possible cause of postherpetic neuralgia. J Neurovirol 2003;9(3):404–7.
[11] Quan D, Hammack BN, Kittelson J, Gilden DH. Improvement of postherpetic neuralgia after treatment with intravenous acyclovir followed by oral valacyclovir. Arch Neurol 2006;63(7):940–2.
[12] Vafai A, Wellish M, Gilden DH. Expression of varicella-zoster virus in blood mononuclear cells of patients with postherpetic neuralgia. Proc Natl Acad Sci USA 1988;85(8):2767–70.
[13] Nagel MA, Gilden D. The challenging patient with varicella-zoster virus disease. Neurol Clin Pract 2013;3(2):109–17.
[14] Min SW, Kim YS, Nahm FS, et al. The positive duration of varicella zoster immunoglobulin M antibody test in herpes zoster. Medicine (Baltimore) 2016;95(33):e4616.
[15] Crack LR, Jones L, Malavige GN, Patel V, Ogg GS. Human antimicrobial peptides LL-37 and human beta-defensin-2 reduce viral replication in keratinocytes infected with varicella zoster virus. Clin Exp Dermatol 2012;37(5):534–43.
[16] Volpi A, Gatti A, Pica F, Bellino S, Marsella LT, Sabato AF. Clinical and psychosocial correlates of post-herpetic neuralgia. J Med Virol 2008;80(9):1646–52.
[17] Higa K, Dan K, Manabe H, Noda B. Factors influencing the duration of treatment of acute herpetic pain with sympathetic nerve block: importance of severity of herpes zoster assessed by the maximum antibody titers to varicella-zoster virus in otherwise healthy patients. Pain 1988;32(2):147–57.
[18] Kim Young Gyun, Kim Joung Soo, Yu Hee Joon. Clinical significance of serum varicella zoster virus immunoglobulin M and G in varicella and herpes zoster. Korean J Dermatol 2015;53(6):441–8.
[19] Acosta EP, Balfour Jr. HH. Acyclovir for treatment of postherpetic neuralgia: efficacy and pharmacokinetics. Antimicrob Agents Chemother 2001;45(10):2771–4.
[20] Helfert SM, Reimer M, Hoper J, Baron R. Individualized pharmacological treatment of neuropathic pain. Clin Pharmacol Ther 2015;97(2):135–42.
[21] Mahalingam R, Wellish M, Brucklier J, Gilden DH. Persistence of varicella-zoster virus DNA in elderly patients with postherpetic neuralgia. J Neurovirol 1995;1(1):130–3.
[22] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357(3):266–81.
[23] Griffin MD, Lutz W, Phan VA, Bachman LA, McKean DJ, Kumar R. Dendritic cell modulation by 1alpha,25 dihydroxyvitamin D3 and its analogs: a vitamin D receptor-dependent pathway that promotes a persistent state of immaturity in vitro and in vivo. Proc Natl Acad Sci USA 2001;98(12):6800–5.
[24] Piemonti L, Monti P, Sironi M, et al. Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. J Immunol 2000;164(9):4443–51.

[25] Soderstrom LH, Johnson SP, Diaz VA, Mainous 3rd. AG. Association between vitamin D and diabetic neuropathy in a nationally representative sample: results from 2001–2004 NHANES. Diabet Med 2012;29(1):50–5.
[26] Lee P, Chen R. Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain. Arch Intern Med 2008;168(7):771–2.
[27] Berkan-Kawinska A, Koslinska-Berkan E, Piekarska A. The prevalence and severity of 25-(OH)-vitamin D insufficiency in HCV infected and in HBV infected patients: a prospective study. Clin Exp Hepatol 2015;1(1):5–11.
[28] Farnik H, Bojunga J, Berger A, et al. Low vitamin D serum concentration is associated with high levels of hepatitis B virus replication in chronically infected patients. Hepatology 2013;58(4):1270–6.
[29] Bitetto D, Fattovich G, Fabris C, et al. Complementary role of vitamin D deficiency and the interleukin-28B rs12979860 C/T polymorphism in predicting antiviral response in chronic hepatitis C. Hepatology 2011;53(4):1118–26.
[30] Villar LM, Del Campo JA, Ranchal I, Lampe E, Romero-Gomez M. Association between vitamin D and hepatitis C virus infection: a meta-analysis. World J Gastroenterol 2013;19(35):5917–24.
[31] Bitetto D, Fabris C, Fornasiere E, et al. Vitamin D supplementation improves response to antiviral treatment for recurrent hepatitis C. Transpl Int 2011;24(1):43–50.
[32] Hoan NX, Tong HV, Song LH, Meyer CG, Velavan TP. Vitamin D deficiency and hepatitis viruses-associated liver diseases: a literature review. World J Gastroenterol 2018;24(4):445–60.
[33] Gyeong-Yoon Han Y-AC, Lee Kyung-Shik, Park Young-Kyu, Cho Sung-Min, Shim Minji, Kim Byungkook, Kim So-Youn. The comparison of the blood level of 25-hydroxyvitamin D3 in healthy adult and patients with herpes zoster. Korean J Fam Pract 2016;6(4):288–92.
[34] Wang TT, Nestel FP, Bourdeau V, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol 2004;173(5):2909–12.