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Is peptic ulcer disease a risk factor of postherpetic neuralgia in patients with herpes zoster?

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ABSTRACT

Postherpetic neuralgia is the most common complication of herpes zoster which is caused by a reactivation of latent varicella zoster virus. The pathogenesis of postherpetic neuralgia may involve peripheral and central mechanisms. Reported risk factors for postherpetic neuralgia include female gender, old age, diminished cell-mediated immunity and nutritional deficiencies. Based on our clinical observation which revealed that peptic ulcer disease (PUD) is one of the common comorbidities in patients with postherpetic neuralgia, we hypothesize that herpes zoster patients with PUD may be at a greater risk for the development of postherpetic neuralgia due to their impaired cellular immunity and depressed nutritional status. Major causes of PUD include *Helicobacter pylori* infection and usage of ulcerogenic medications. Patients with *H. pylori* infection may develop T cell dysfunctions and nutritional deficiencies including vitamin C, iron, cobalamin, carotenes and alpha-tocopherol. Ulcerogenic medications such as nonsteroidal anti-inflammatory drugs and steroids have been found not only to be ulcerogenic but also immunosuppressive to T cells. In addition, usage of steroids and nonsteroidal anti-inflammatory drugs may cause deficiencies of alpha-tocopherol, carotenes, cobalamin, iron, zinc and vitamin C. Vitamin C, carotenes and alpha-tocopherol are anti-inflammatory and the major oxidant scavengers in the aqua phase and biomembranes. Deficiencies of these nutrients may induce dysregulated inflammation and oxidative damage leading to neuropathic pain in patients with herpes zoster. Furthermore, nutrient deficiencies including zinc, iron, cobalamin and vitamin C are associated with dysregulation of Ca(v)3.2 T-channels and N-methyl-D-aspartate receptors, upregulation of nitric oxide synthase, the increase of nitric oxide formation and dysfunction of central norepinephrine inhibitory pain pathway. Prospective cohort studies are suggested to test the hypothesis. We further propose that a follow-up study that contains two groups of herpes zoster patients, i.e., with or without gastroendoscopy-proven PUD, be conducted to determine their incidence of postherpetic neuralgia. In addition, despite of the high proportion of zoster patients having been treated with antiviral therapies, prevention and treatment of postherpetic neuralgia remain challenging in clinical practice. The potential risk of postherpetic neuralgia in zoster patients with PUD could mean that physicians need to pay more attention to the comorbidity - PUD in patients with herpes zoster and treat PUD earlier in order to prevent the development of postherpetic neuralgia.

Background

Herpes zoster, caused by a reactivation of varicella zoster virus (VZV), leads to acute herpetic pain and usually spontaneously subsides within 2–4 weeks. Patients with herpes zoster may suffer from prolonged herpetic pain which lasts 90 days or longer. This prolonged herpetic pain is termed postherpetic neuralgia which is the most common complication of herpes zoster. Postherpetic

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neuralgia can be long-term and disabling, leading to a profoundly negative impact on the quality of a patient's life. The risks of postherpetic neuralgia increase significantly with old age. Among patients aged 60 years and older, the risk of postherpetic neuralgia might be as high as 60–70%. As the elderly population grows, the prevalence of postherpetic neuralgia is expected to increase and become a substantial burden on the health care system [1].

Three antiviral drugs — acyclovir (Zovirax), valacyclovir (Valtrex) and famciclovir (Famvir) — are approved for the treatment of herpes zoster. Antiviral therapy reduces the severity and duration of herpes zoster but does not prevent the development of postherpetic neuralgia. Postherpetic neuralgia may persist for years and is difficult to treat in some patients [2]. It is therefore crucial that physicians identify those patients who are most likely to develop long-term pain and treat them accordingly.

Pathogenesis of postherpetic neuralgia

Clinically, patients with postherpetic neuralgia may suffer diverse neuropathic pain including spontaneous pain and stimulus-evoked pain. Spontaneous pain in patients with postherpetic neuralgia is described as burning, throbbing, lancinating, or electric-shock-like pain. Spontaneous pain can be intermittent or continuous. Patients with postherpetic neuralgia may develop allodynia or hyperesthesia (stimulus-evoked pain) which is classified into chemical, thermal or mechanical categories. The pathogenesis of postherpetic neuralgia may involve peripheral and central mechanisms. Traditional pain research mainly focuses on neurons and the transmission of pain signals. One pain theory concerning postherpetic neuralgia is that changes of dorsal root or spinal cord neurons caused by VZV in the acute herpetic phase lead to prolonged pathological pain. Injured neurons contribute to neuropathic pain by any of the following mechanisms including upregulations of nitric oxide synthase, the increase of nitric oxide formation, dysregulations of sodium channels, T-type calcium channels and N-methyl-D-aspartate (NMDA) receptors as well as dysfunction of the central norepinephrine inhibitory pain pathway [3–9]. Another theory of postherpetic neuralgia has been proposed based on the fact that herpes zoster is a result of declining VZV-specific cellular immunity. Owing to immunological dysfunctions in the hosts, low-grade productive virus infection in ganglia persists. Persisting VZV-induced ganglionitis leads to postherpetic neuralgia [10]. This concept is supported by the detection of VZV DNA and proteins in blood mononuclear cells and blood from patients with postherpetic neuralgia [11,12] and an autopsy reporting chronic ganglionitis with VZV antigens in sensory ganglia from three donors [13]. Recent studies emphasize that the development of neuropathic pain involves neurons, immune cells, glia cells and their receptors [14]. Glia cells including astrocytes and microglia are key players of the immune responses in the nervous system. Glia cells respond to peripheral and central infection, injuries and various stress signals in the nervous system. The immune responses triggered by glia cells include the release of proinflammatory mediators such as cytokines, reactive oxygen species and nitric oxide (NO). An efficient immune response is required for the defense against invading pathogens; however, a dysregulated inflammatory response in the nervous system may be a driving force of pathological pain. In particular, dysfunctional activated glia and glial proinflammatory mediators may enhance the likelihood of developing neuropathic pain [14,15].

Risk factors for postherpetic neuralgia

Reported risk factors for postherpetic neuralgia include female gender, old age, diminished cell-mediated immunity and nutritional deficiencies [16,17]. In 1965, Dr. Hope-Simpson proposed that immunity to VZV plays a pivotal role in the pathogenesis of herpes zoster. Supporting evidence shows that the increased incidence and severity of herpes zoster and postherpetic neuralgia are noted among older adults and immunosuppressed patients. Declining specific-VZV cell-mediated immune responses in hosts occur naturally as a result of aging or are induced by medical treatments or immunosuppressive illnesses [1,18]. Recently, nutrient deficiencies have been discovered to increase the risk of herpes zoster and postherpetic neuralgia [17,19–22].

Our previous prospective observational study revealed that peptic ulcer disease (PUD) is one of the common comorbidities in patients with postherpetic neuralgia [17]. PUD has been linked to immunological dysfunctions [23,24] and nutritional deficiencies [25,26], both of which are risk factors of postherpetic neuralgia. Based on our clinical observation, we propose a hypothesis that herpes zoster patients with PUD are at greater risk of developing postherpetic neuralgia (Fig. 1).

The hypothesis: peptic ulcer disease as a risk factor of postherpetic neuralgia in patients with herpes zoster

How could PUD increase the risk of developing postherpetic neuralgia in patients with herpes zoster? It is well-known that the two major causes of PUD are *Helicobacter pylori* infection and the usage of ulcerogenic medications including nonsteroidal anti-inflammatory drugs (NSAIDs), steroids and aspirin. In the United States, *H. pylori* infection and the use of NSAIDs account for 48% and 24% of PUD cases, respectively [27]. *Helicobacter pylori* infection has been linked to immunological dysfunctions [23,24]. In experimental studies, a secreted low-molecular-weight protein from *H. pylori* has been found to induce cell-cycle arrest of T lymphocytes. In peripheral blood of *H. pylori* infection-infected patients, the percentage of CD8(+) T cells is significantly lower when compared to control subjects. Furthermore, patients with *H. pylori* infection may develop several nutritional deficiencies including vitamin C, iron, cobalamin, beta-carotene and alpha-tocopherol. The severity of nutritional deficiency ranges from subtle sub-clinical deficiencies to severe clinical disorders [28]. Recently, NSAIDs and steroids have been found not only to be ulcerogenic but also harbor additional immunomodulatory properties [29–31]. In viral infections, dendritic cells are the professional antigen-presenting cells. NSAIDs and steroids inhibit the intracellular processing of the phagocytized antigen as well as antigen presenting functions in dendritic cells [30,31]. Importantly, NSAIDs suppress T cell proliferation and activation by inhibition of the MAPK pathway and specifically p38 activation [29]. In addition, usage of steroids and NSAIDs may cause deficiencies of alpha-tocopherol, carotenes, vitamin C, cobalamin, iron and zinc [25,26,32,33]. Consequently, nutritional deficiencies may result in the impairment of cell-mediated immunity [34].

Since *H. pylori* infection and the usage of ulcerogenic agents may induce deficiencies of many nutrients, how do these nutrients play their roles in causing postherpetic neuralgia? It has been proven that vitamin C, alpha-tocopherol and carotenes possess anti-inflammatory effects. Vitamin C is mainly responsible for scavenging free radicals in the aqueous phase and plasma; whereas, alpha-tocopherol and carotenes are the oxidant scavengers in biomembranes. Deficiencies of these anti-inflammatory and anti-oxidative nutrients may lead to dysregulated inflammation and oxidative damage in the hosts when suffering from VZV infection [28]. Furthermore, nutrient deficiencies including zinc, iron, cobalamin and vitamin C are associated with upregulations of nitric oxide synthase, the increase of NO formation, dysregulations