Treatment and Recent Topics of Postherpetic Neuralgia

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Abstract
Postherpetic neuralgia (PHN), the most common sequela of herpes zoster (HZ), occurs in about 10% of patients with HZ. It is a condition with neuropathic pain arising from the degeneration of the relevant nerves as a result of neuritis caused by the reactivation of the varicella-zoster virus (VZV). The hypofunction of the descending inhibition system is considered to be the entity causing pain. Although several therapies have been attempted to treat PHN, none has been proved decisively effective. The most important strategy at present is the complete control of symptoms of HZ that trigger PHN. PHN tends to develop in elderly patients, resulting in significant deterioration of their quality of life (QOL). This disorder is an important issue in Japan in the face of the serious aging of the population. It should not be left unchecked merely because it is not life threatening. It is necessary to consider the use of varicella vaccine to prevent HZ within the national healthcare policy.

Key words  Herpes zoster (HZ), Postherpetic neuralgia (PHN), Neuropathic pain, Varicella vaccine

Introduction
Herpes zoster (HZ) is a disorder characterized by the sudden onset of skin eruption and severe pain caused by the reactivation of the varicella-zoster virus (VZV) occurring latently in ganglia after initial infection.

Pain along the course of the nerves develops simultaneously with the onset of HZ or before the appearance of skin eruption. This is the acute-phase pain of HZ. Pain of a different nature from the acute-phase pain may develop gradually in some cases. This pain is generally referred to as postherpetic neuralgia (PHN).

Common complications of HZ include motor nerve paralysis and ocular complications. Rare complications include myelitis and encephalitis. Among these conditions, PHN is a neurological complication observed in an overwhelming majority of patients. This condition is extremely important in an aging society.

Clinical Features of PHN
The pain of PHN is characterized by the fact that the skin surface of the affected part always presents hyposensitivity such as hypesthesia or anesthesia including pain sensation, accompanied by single or combined complaints of burning pain, aching pain, shooting pain, lancinating pain, tight pain, etc. Allodynia may be remarkable in some cases or absent in others.

The International Association for the Study of Pain defines PHN as “chronic pain with skin changes in a dermatomal distribution subsequent to acute herpes zoster”,1 without mentioning the timing of symptom onset.

With respect to the time from skin eruption due to HZ to the transition to PHN, different authors have used different definitions, requiring that the period after the onset of skin eruption be at least 1 month, 6 weeks, 2 months, 9 weeks, 3 months, or 6 months. Some others consider...
that PHN refers to the pain remaining after the healing of skin eruption. There is no established definition or consensus in this respect.\textsuperscript{2–6} When we observe the pain during the acute phase of HZ, we encounter many cases in which the nature of the pain changes irrespective of the presence or absence of skin eruption. It is also common that a patient who initially had skin eruption without pain later starts to complain of pain. These changes should be considered to mark the onset of PHN, and the length of time after the onset of skin eruption is not an important factor in defining PHN. This means that some patients that were conventionally considered to have the pain of acute-phase HZ might actually have PHN. On the other hand, some patients considered to have PHN might actually have continuation of acute-phase pain. The report showing the effectiveness of subarachnoidal injection of steroids for PHN\textsuperscript{7} indicates that the study subjects, considered to have PHN based on time, included cases of protracted inflammation. The reported incidence of PHN ranges widely. While a study reported pain remaining in 3\% of patients 6 months after the onset of skin eruption,\textsuperscript{10} another reported the rate of more than 20\% after 1 year.\textsuperscript{5} On average, PHN seems to develop in about 10\% of patients after 6 months.\textsuperscript{11,12}

**PHN is Surely Neuropathic Pain**

**Hypothesis on the formation of PHN** (Fig. 1)

The features of PHN closely resemble those of so-called neuropathic pain, which is the symptom cluster of pain arising from neuropathy due to various causes.\textsuperscript{13} In this respect, PHN deserves much attention as a form of pain derived from neuropathy caused by the disease.

When HZ has developed as a result of reactivation of VZV, the patient should be regarded as having undergone or being in the process of nerve degeneration triggering PHN. In extreme cases, nerve degeneration may be present when pain is observed several days or weeks before the appearance of skin eruption. The patient in this stage should be considered to be in the process of developing PHN.\textsuperscript{14}

In fact, it has been reported that autopsy of a patient with myeloma who developed HZ in the first division of the trigeminal nerve and died while presenting acute-phase pain demonstrated...
uneven but strong nerve degeneration.\textsuperscript{15}

**Histopathological facts**

Although there have been only a limited number of reports of the histopathological examination of patients with PHN, some remarkable facts have been reported. Inflammation of the sensory nerve ganglia, destruction of the nerve cells, and degeneration and fibrosis of the sensory nerve ganglia have been observed.\textsuperscript{16,17} It has also been noted that peripheral nerve fibers in the affected parts of patients with PHN show a significant decrease in thick myelinated nerve fibers compared with thin unmyelinated nerve fibers.\textsuperscript{18}

In addition, comparison between cases of HZ with pain and those without pain demonstrated no difference in terms of nerve degeneration, suggesting a lack of association between nerve degeneration and the development of PHN.\textsuperscript{19} However, it is a well-known fact that neuropathic pain does not occur in all patients with nerve degeneration. Neuropathic pain is caused by some unknown mechanism in addition to nerve degeneration.

**Mechanism for pain in PHN** (Fig. 2)

We consider that PHN is clearly a form of neuropathic pain on the basis of the aforementioned histopathological changes in nerve fibers and ganglion cells, as well as clinical symptoms such as the loss of pain sensation and tactile sensation in the skin.

Pain of this type, whether it is caused by disease or injury, is a result of neuropathy, and is considered to arise from the dysfunction of either the ascending systems or the descending inhibition system involved in pain transmission from the peripheral to the central systems.

Since PHN is characterized by deafferentation pain, it is considered to arise from the hypo-function of the descending inhibition system. The normal body has a system called the descending inhibition system, which inhibits the transmission of noxious stimuli to the central system. When only myelinated nerve fibers are damaged and unmyelinated nerve fibers are not damaged among afferent fibers, the descending inhibition system does not work normally and pain is generated.

The histopathological changes...
observed in nerve fibers and ganglia in PHN support pain generation through this mechanism.

We sometimes encounter cases in which all symptoms of neuropathic pain are present without a clear sign of nerve impairment and the pain is eliminated by sympathetic nerve block. This condition, called sympathetically maintained pain, is assumed to involve the result of abnormal activity of sympathetic nerve functions and the continuous excitation of wide-dynamic-range neurons occurring in the spinal cord dorsal horn.  

Some cases of PHN respond well to sympathetic nerve block, similarly to these cases of pain. The presence of meningitis and other complications also suggest the involvement of impairment of higher-level neurons. These observations illustrate the very complex nature of PHN.

Treatment of PHN

If PHN is a result of nerve degeneration, all methods attempted for the treatment of neuropathic pain may be indicated for PHN. Although many attempts have been made in this direction, none has been proved decisively effective.

Importance of treatment of acute-phase pain

The most important goals of treatment at present are pain reduction and the prevention of transition from HZ to PHN.

The pain during the acute phase of HZ is caused by inflammation. Therefore, the use of nonsteroidal anti-inflammatory drugs and the use of antiviral agents to remove the pathogens are essential. However, the treatment of HZ normally begins when skin symptoms are confirmed, and there is a possibility that nerve degeneration has already occurred or is going to occur at this point.

Since this disease is nowadays considered to develop in parallel with the alteration of cellular immunity, it is reasonable to consider the use of various immunostimulation therapies, as well as immunosuppressive therapies and steroids. However, no definitive results have been obtained.

The use of opioid analgesics and similar agents against intense pain is an issue requiring future examination. If neuropathic pain is already going to develop in the acute phase of HZ, early administration of an antidepressant drug to high-risk patients may be an effective treatment.

While persistence of pain is considered to establish a vicious cycle of pain, appropriate nerve block is greatly effective in stopping this cycle, and should be encouraged as a treatment for acute-phase pain. While blocking sensory nerves provides sufficient analgesia, blocking sympathetic nerves is considered to help prevention of nerve degeneration because it increases local blood flow.

Frequent warm bathing and thermotherapy are recommended as methods of pain relief, although these are not suitable for patients with broken blisters and infection.

Treatment of PHN

The treatment of neuropathic pain is extremely difficult. Various therapies have been devised, attempted, and sought. The situation is similar to the treatment of PHN. No definitive method has been established, and all possible means of pain treatment are attempted at present.

(1) Nerve block

While about 20 different methods of nerve block are used for the treatment of pain, those frequently used for PHN include sympathetic nerve block (such as stellate ganglion block), epidural block, trigeminal nerve block, and spinal nerve block.

Nerve block is usually performed under local anesthesia. The use of neurolytic agents or thermocoagulation techniques is selected in some cases.

(2) Pharmacotherapy

Antidepressants and anticonvulsants, such as amitriptyline and carbamazepine, are still frequently used.

With the progress of recent efforts to clarify the mechanisms leading to neuropathic pain, studies are conducted to evaluate the effectiveness of substances such as Na channel blocker, NMDA receptor antagonist, Ca channel blocker, GABA receptor activator, opioid analgesics, α2-adrenoceptors, serotonin antagonist, capsaicin, gabapentin, selective serotonin reuptake inhibitor, and selective noradrenaline reuptake inhibitor.

Nonsteroidal analgesic drugs, exerting an analgesic effect through the suppression of local inflammation, are still used widely for PHN. However, such use is not rational because the pathogenesis of PHN suggests that inflammation no longer exists in PHN.
(3) Other therapies
Various methods are being attempted, including transcutaneous electrical nerve stimulation, spinal colon electrical stimulation, deep brain electrical stimulation, electrical convulsive therapy, laser beam therapy, dry ice therapy, iontophoresis, lidocaine ointment, and capsaicin ointment.

Is HZ Prevention Possible?

A logical strategy for preventing the development of PHN is to prevent the development of HZ, which precedes PHN. In fact, varicella vaccine is expected to be effective in preventing the onset of HZ and to have a better chance of limiting the severity of HZ symptoms when vaccinated individuals develop HZ.27

It is an unquestionable fact that reactivation of latent VZV in the body causes the development of HZ, and some form of nerve degeneration resulting from this process triggers PHN. The reactivation of latent VZV requires a change in the internal environment of the host. Crudely speaking, this change means weakening the immunocompetence of the host, as indicated by the fact that patients with factors such as malignant tumors, autoimmune disease, HIV infection, and immunosuppressive therapy are liable to contract HZ and its progression to severe conditions.28,29

A considerably high percentage of HZ patients in the general population are elderly patients, probably reflecting the decline in cellular immunity. A study examining patients within 7 days after the onset of HZ using tuberculin reaction as an index for general cellular immunity and intradermal reaction to varicella as an index for specific immunity demonstrated that these patients had decreased specific immunity against VZV rather than a decrease in cellular immunity in general.30 Such a decrease in specific immunity has also been reported in patients with ocular herpes.31

A study using VZV-specific lymphoproliferation tests (SI) in middle-aged and elderly persons, normal adults, and pediatricians demonstrated that the SI in middle-aged and elderly persons was significantly lower than that in other groups, and that it decreased with age. In addition, the SI in normal adults was significantly lower than that in pediatricians.32 This result suggests that specific immunity decreases in persons with fewer opportunities for re-infection of VZV. Therefore, it is considered possible to enhance VZV-specific immunity by using varicella vaccine to induce re-infection before the decline in specific immunity.

It has been reported that the use of varicella vaccine in elderly persons clearly enhanced the specific immunity against VZV, although a half of this booster effect disappeared within 6 years.33 Symptoms remained very mild in the patients who developed HZ during this period.34 In addition, the use of varicella vaccine in elderly persons provided the same degree of VZV-specific immunity as in the elderly patients who developed HZ.35 These results support the effectiveness of HZ prevention using varicella vaccine. A number of practical questions remain to be examined in the future, including when vaccination should be performed, how many inoculations are required for the acquisition of sufficient specific immunity, and how long the acquired immunity persists.

Conclusion

HZ frequently develops in elderly persons, and the likelihood of permanent sequelae increases with age. Treatment of PHN, as well as the treatment of HZ to prevent the transition from HZ to PHN, is an important issue, considering the aging of the population in Japan. However, treatment of PHN, which is a form of neuropathic pain, is extremely difficult and no definitive method has been established. On the other hand, the use of varicella vaccine is expected to inhibit the development of HZ and prevent progression to PHN.

References
