

POSTHERPETIC NEURALGIA: WHAT DO WE KNOW AND WHERE ARE WE HEADING?

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Postherpetic neuralgia (PHN) remains a difficult pain problem for patients and physicians alike. This review describes the epidemiology and pathophysiology of PHN and discusses proposed mechanisms of pain generation and the various treatments currently available.

Evidence is scant for the value of surgical and procedural interventions in general, although there are numerous small studies supporting the use of specific interventions such as nerve blocks, neurosurgical procedures and neuroaugmentation.

Medical interventions, particularly the use of antidepressants and anticonvulsants remain the best-documented therapies for treating pain associated with PHN. There is good evidence that amitriptyline and gabapentin reduce pain with PHN. Topical local anesthetics, such as lidocaine, may also be helpful. The decision to use a particular agent or intervention may depend on whether there is spontaneous pain, burning or lancinating pain or numbness. Interventions with low risk, such as TENS are appropriate.

Although prevention of postherpetic

neuralgia appears to be an appropriate strategy, there is little evidence to support the position that medical or interventional approaches (nerve blocks) will prevent PHN after a patient develops acute herpes zoster (HZ). Although antivirals are appropriate for acute HZ, and the use of neural blockade and sympathetic blockade may be helpful in reducing pain in selected patients with HZ, there is little evidence that these interventions will reduce the likelihood of developing PHN.

Keywords: Postherpetic neuralgia, acute herpes zoster, interventional pain management

Ancient chronicles contain accurate descriptions of herpes zoster (HZ). An impressive series of epidemiological, laboratory, and clinical investigations lead to the conclusion that varicella and HZ are the same virus (1, 2). According to Hope-Simpson's review (2), Ingrassi was the first to describe the features of varicella in 1553, the segmental nerve distribution of HZ lesions were noted by Bright in 1831 and in 1875 Steiner demonstrated the infectious nature of varicella by transmitting the disease with vesicular fluid. The Hungarian pediatrician Bokai was the first to recognize that varicella and HZ were manifestations of the same infectious agent (1).

The segmental distribution of HZ and post-herpetic neuralgia (PHN) has puzzled researchers for more than 150 years (2). Over the past 60 years, intense effort has been devoted to coping with the

disruptive primary lesion, reducing the frequency of relapsing attacks and searching for methods of actively treating PHN. And yet, the challenge remains urgent and acute since we are still largely unable to prevent or treat the disease in spite of the promise of the new up-to-date knowledge and new information that has appeared about every aspect of PHN.

The pain of acute HZ usually subsides within 3 weeks. Whenever the primary pain of HZ lasts for more than four to six weeks PHN is suspected. Acute HZ pain often is accompanied by decreased quality of life. Severe acute pain interferes with patients' abilities to carry out normal activities of daily living and is associated with greater use of analgesic medications (3).

Pain persists in a chronic form in 10-15% of patients following acute HZ infection (4, 5). The incidence of HZ ranges between 1.3 to 4.8 per 1,000, depending on several predisposing factors; the most important is the age of the patient (2, 6-11). Herpes zoster is most prevalent in the 50 to 70-year-old age group (2, 6). Age also influences the severity of the illness. It has been hypothesized that older patients have more severe herpes zoster infections (12), but the results of several studies have not provided uniform sup-

port for this prediction. The results of these studies suggest that older age is not consistently associated with either greater acute pain severity or longer acute pain duration (13, 14). Moreover, older age is not consistently associated with either greater rash severity or longer rash duration (15).

The incidence of HZ is also higher in cancer patients and in immunosuppressive states (16-22). In the older patient the active phase tends to be more severe, with more intense pain and the incidence of PHN is greater than in the younger patient (4, 11, 23). In one study only 4.2% of young people developed PHN, however, the incidence increased to 47.5% at the age of 70 (23). Patients with diabetes mellitus have a higher incidence of PHN (24, 25). In addition PHN is more frequent after ophthalmic herpes than after the spinal segment type. The prevalence of PHN shows no seasonal variation and no predilection for a particular sex or race (2, 4, 6, 7, 11).

There is some evidence that the incidence of zoster has increased in recent decades. It is likely that PHN will become more prevalent, not only because of this increased incidence of zoster but also because PHN is more likely to develop in the older individuals, whose numbers are in-

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creasing (26).

Because PHN patients suffer from physical and social disability and psychological distress and have greatly increased health care utilization as a result of chronic pain, this increase in the prevalence of PHN will have a major impact on public health (27).

DESCRIPTION OF THE SYNDROME

The *syndrome of PHN* is defined as the onset of persistent pain following an attack of HZ. The transition from the one condition to the other can be difficult to define. Thus, the choice of the appropriate therapy and the interpretation of treatment results can be problematic. The time interval between "crusting" of the HZ blisters and the onset of PHN differs according to different studies. It has been defined as four weeks (11), six weeks (22), eight weeks (28), and even as long as six months (29).

Although postherpetic neuralgia has been defined in different ways, recent data support the distinction between acute herpetic neuralgia (within 30 days of rash onset), subacute herpetic neuralgia (30-120 days after rash onset), and postherpetic neuralgia (defined as pain lasting at least 120 days from rash onset (30-32)). The most well established risk factors for PHN are older age, greater severity of acute pain during zoster, more severe rash, and a prodrome of dermatomal pain before onset of the rash (33). Patients with all of these risk factors may have as much as a 50-75% risk of persisting pain six months after rash onset.

The distress of the patient with PHN is the result of both pain and dysesthesias. The pain is generally described as burning and continuous in nature. There may be lancinating pain. In rare cases the pain is described as throbbing or cramping. The pain characteristically spreads along a single dermatome from the central dorsal line in a ventral direction. Often, the actual pain remains confined to a single dermatome even though there has been cutaneous spread beyond the originally affected dermatome. Later, the patient may suffer from hyperpathia related in part to a fall in the threshold to pain. Dysesthesia is the intermittent occurrence of abnormal sensations that are unpleasant and sometimes described as pain. Light touch may be intolerable to these patients. The affected area shows changes in the form of pigmentation and scarring where the ves-

icles have healed. Hypalgesia, paresthesia and hyperesthesia can be noted.

PATHOLOGY

Acute HZ is characterized by necrosis and scarring of the mixed dorsal root ganglion (DRG) leading to degeneration and destruction of the emerging motor and sensory fibers (34-37). Inflammatory processes can involve the anterior and posterior horns of the spinal cord (34, 35). A mononeuritis characterized by axonal damage and even myelin disruption (38) extends peripherally from the DRG (34). The number of nerve endings originating from the skin around the lesion decreases (39).

Pathological changes include the presence of "ghost cells" in the DRG of patients with PHN (37). Deterioration of large myelinated fibers has also been demonstrated. One study analyzing autopsies of patients with PHN found characteristic atrophy of the dorsal horn to be present in PHN (40).

Despite the descriptive pathological changes noted in PHN and HZ the exact mechanism(s) of how pain is generated is unclear. In HZ, activation of nociceptive primary afferents by direct viral attack and inflammatory changes in skin, peripheral nerves, nerve roots, posterior root ganglion, and spinal cord can explain pain in most patients. The pathophysiology of PHN may involve both peripheral and central mechanisms. In PHN there is a preferential loss of large caliber neurons. This results in a selective deficiency of large diameter neurons which can cause impairment of the segmental pain modulation system (41). According to the gate-control theory of pain (42), decreased activity of large nerves may allow increased rates of pain impulses reaching the dorsal horn of the spinal cord (42). In this respect, PHN may be regarded as a form of deafferentation pain.

It has also been postulated that dysesthetic pain in peripheral nerve lesions may be due to damaged or regenerating nociceptive afferent fibers (43). The existence of central mechanisms as a source of pain in PHN may account for the usual failure of attempts at curing pain through deafferenting procedures such as neurectomy, and spinothalamic tractotomy (44, 45).

Various investigators have attempted to correlate the pathology of PHN with symptoms. Morris et al (46) inves-

tigated the role of primary afferent fibers with polymodal nociceptors in the various pain symptoms and signs associated with PHN. Forty-four patients with PHN affecting thoracic dermatomes were examined clinically for evidence of sensory disturbance to touch and pinprick and compared to controls (14 normal subjects and nine subjects with evidence of past HZ infection but no pain). The patients were then divided into three groups on the basis of their clinical symptoms and signs; those with steady, burning discomfort only; those with burning discomfort, allodynia and hyperalgesia to pinprick; and those with burning discomfort, allodynia and hypalgesia to pinprick. Indirect measurements of primary afferent fiber function was performed by measuring the neurogenic axon reflex flare to topical capsaicin using Doppler flowmetry in the five clinical groups.

The two groups with allodynia had significantly decreased neurogenic flare responses compared to PHN subjects without allodynia and the two control groups. These results suggest that allodynia in patients with PHN may be a consequence of disrupted function of primary afferent fibers.

In contrast, in another investigation the peripheral nervous system was studied using classical electrophysiological methods in patients with PHN, and compared with the same parameters in 64 HZ patients without PHN (47). No disparity was found between the two groups in the mean percentage differences of the electrophysiological data for peripheral sensory fibers or between sides affected by HZ and healthy sides. The authors concluded that HZ is associated with sensory axonopathy, the severity of which is similar, on the whole, in the groups with and without PHN, and that damage to peripheral large-diameter sensory fibers is not the cause of PHN.

Rowbotham et al (48) performed sensory mapping and quantitative thermal sensory testing on 35 patients with established PHN. All subjects had pain in the torso or extremities and brush-evoked allodynia. The severity of allodynia was positively correlated with reported ongoing pain severity. As a group, subjects had a sensory deficit to thermal stimuli in PHN skin compared with unaffected mirror-image skin. However, the magnitude of the heat pain sensory deficit was inversely correlated with both pain inten-

sity and severity of allodynia. In fact, 12 subjects had heat hyperalgesia in their region of maximum pain. Compared with the 23 subjects with heat hypalgesia, the group of 12 heat-hyperalgesic subjects had significantly higher pain ratings and allodynia severity. The investigators concluded that there is no simple relationship between loss of peripheral nerve function and spontaneous or evoked pain. Rather, the preservation of several sensory modalities in their area of maximal pain suggests that in some PHN patients, activity in primary afferent nociceptors that remain connected to both their peripheral and central targets contributes significantly to ongoing pain.

A role for adrenergic receptor activation in PHN has also been postulated. Choi and Rowbotham (49) studied the effect of adrenergic receptor activation on PHN pain and sensory disturbances. Injection of saline or an adrenergic agonist in normal skin produced mild and transient pain without development of allodynia and without affecting overall PHN pain intensity. Injection of adrenergic agonist into PHN skin increases pain, probably through direct activation of C-nociceptors in the painful skin. Increased allodynia was thought to be mediated centrally and driven by the increase in C-nociceptor input. Other investigators do not agree that nociceptive C-fiber input has a role in the pain from PHN (50). They theorize that alterations in CNS processing recognize synaptic ties between central pain-signaling pathways and mechanoreceptive A beta-fibers, depending on afferent C-fiber degeneration rather than ongoing C-fiber input. Similarly, Baron et al (51) concluded that sensitized nociceptive C-fibers were not involved in signaling allodynia. They speculated that changes in CNS processing may occur after HZ infection that strengthen the synaptic ties between central pain signaling pathways and low threshold mechanoreceptors with A-beta fibers. Thus, an anatomical synaptic reorganization dependent on afferent C-fiber degeneration was thought to be more likely, particularly in advanced stages of PHN.

THERAPY

No definitive treatment for PHN is available. This may be attributed to the complex nature of the pathology. There are multiple therapies available, but each case responds in a different way and not

always in a manner at all convincing to the therapist. Until 1960, the literature on PHN contained large numbers of studies and descriptions of case reports of treatments that were not conducted under controlled conditions. These included both drug therapies and surgical procedures (8, 52-57). No definite conclusions can be drawn from these reports. Many of the therapies were highly imaginative and included such things as cobra venom, injections of posterior pituitary extract, and diphtheria antitoxin (8, 50-57).

In recent years treatment has mainly centered on psychotropic drugs and on anticonvulsant medications. Among the psychotropic drugs the most effective are the tricyclic antidepressants (58-60). Research in a small group demonstrated the efficacy of amitriptyline in 11 out of 14 patients (50). Desipramine has also been found to attenuate the pain of PHN (51). Taub (63) recommended treatment with a combination of fluphenazine and amitriptyline, which has proven to be beneficial (64). Watson et al (65) examined amitriptyline in a randomized double blind study using a placebo as a control in 24 patients suffering from PHN for more than 3 months. A marked improvement in pain ensued, without change of the fundamental lesion, using an average dosage of 75 mg amitriptyline. It was suggested that a therapeutic window exists and that the average dose was more effective than higher dosages. Some studies have confirmed these results (5, 66), others have refuted them (67). It is generally agreed that treatment with antidepressants should begin at low doses and be gradually titrated (67). Many other additional trials found evidence of improvement with tricyclic antidepressants (65, 66, 68-74). These improvements were achieved with tricyclic antidepressant medication alone (61, 70), or in combination with other therapies that included neuroleptic agents (64, 71) and acupuncture (72, 73).

Anticonvulsant agents were found helpful in patients with a lancinating pain component (74-77). Neuroleptic drugs such as fluphenazine and flupinedol have been tried together with anticonvulsant medications for treatment of PHN, but since there has been no report on the isolated use of each agent it is difficult to reach any conclusion as to their individual efficacy (63, 64). The same applies to studies that claim benefit from valproic

acid when given in combination with amitriptyline (73), therefore their efficacy remains undetermined (77).

More recently, gabapentin has been proven superior to placebo in PHN with 43% of patients reporting at least moderate improvement (versus 12% with placebo). Because it appears to have fewer side effects than antidepressants, it has been suggested as a first-line treatment for this condition. A dose of 3500 mg/day was the target dosage in the trial above, and many patients reached that dose (78, 79).

Gabapentin appears to be effective and well tolerated for the short-term treatment of PHN. However, future controlled studies are needed to determine whether the effectiveness of gabapentin for PHN is maintained for more than 2 months and to establish the optimal dose of gabapentin with that of other pharmacologic agents used for the treatment of PHN (80, 81).

An alternative approach using pregabalin was studied recently. It was reported that the treatment was safe and efficacious in relieving PHN pain and sleep interference (82). It was also noted that the global improvement was greater than a treatment with placebo.

Niv et al (77) attempted to find a correlation between the management of PHN and the characteristics of the PHN pain. They suggested that a burning type of pain, which appears in approximately 70% of the patients, would react effectively to amitriptyline treatment. In contrast pain with lancinating or stabbing/pinprick characteristics would be managed effectively with anticonvulsant drugs such as carbamazepine or clonazepam. Dysesthetic sensations were reduced with the use of phenothiazine such as fluphenazine.

Vitamin therapies also have been proposed. An encouraging anecdotal account of success with systemic administration of vitamin E, a potent antioxidant was reported (83), however, this treatment has since been abandoned.

It is possible to treat the acute pain of HZ by local or regional anesthesia; although blocking the somatic nerve supply temporarily alleviates PHN, there is little evidence of any lasting benefit from a somatic or sympathetic nerve block for treatment PHN (84). Furthermore, there are just not enough adequately controlled studies to warrant approbation of any one of these procedures. Sympathetic block

has been evaluated for treatment of PHN in large groups but provided relief in less than 50% of the participants (85-87). Injection of steroids into the epidural space or intrathecally, both with or without local anesthetic supplement gave temporary relief to a minority of patients (77, 88). Local injection of these substances was only partially palliative in up to 70% of those treated (89-91).

Various topical treatments for PHN have been studied. These include: capsaicin, EMLA cream, lidocaine patch, and aspirin/diethyl ether mixture (92-98). Capsaicin, a neuropeptide extracted from hot pepper, has been shown to reduce and eliminate the accumulation of substance P, and possibly other neurotransmitters in peripheral sensory nerves (99, 100). Capsaicin ointment must be rubbed in four to five times daily for at least a month, even if no signs of improvement are seen, prior to determining that the treatment is a failure (92, 101). Topical capsaicin is not associated with any severe systemic adverse effects. However, stinging and burning, particularly during the first week of therapy, is reported by many patients (92).

Watson and coworkers reported on capsaicin treatment of 33 patients (101). Twenty-four patients completed the course of four weeks; of these, 55% showed good to excellent results. Side effects of the treatment included an unbearable burning sensation that caused nine patients in the study to withdraw within the first three days. EMLA cream is an acronym for eutectic mixture of local anesthetics. It contains lidocaine and prilocaine in an optimized mixture that enhances dermal uptake of both agents. EMLA penetrates the dermis after an application period of one to two hours. Several studies demonstrated that EMLA is beneficial in some patients with PHN (93, 102).

Rowbotham et al (97) investigated 5% lidocaine gel or vehicle applied simultaneously to both the area of pain due to PHN and to the contralateral mirror-image unaffected skin. Patients with cranial PHN and those with torso or limb PHN favored local drug application. Remote lidocaine application to mirror-image skin was no different from placebo. No systemic adverse effects were reported and blood levels did not exceed 0.6 microgram/ml. In a second study topically applied 5% lidocaine in the form of a non-woven polyethylene adhesive patch was used to cover

the painful area (98). All subjects had allodynia on examination. Patches, covering a maximum of 42 cm² were applied to cover the area of greatest pain as fully as possible. Lidocaine containing patches significantly reduced pain intensity. The highest blood lidocaine level measured was 0.1 micrograms/ml, indicating minimal systemic absorption of lidocaine. Patch application was without systemic side effect and well tolerated when applied on allodynic skin.

In another trial the efficacy of topical aspirin/diethyl ether mixture in the treatment of HZ and PHN was evaluated in a double-blind crossover placebo-controlled study as compared with indomethacin and diclofenac drug/ether mixtures (95). The study included 37 patients (15 with HZ and 22 with PHN). Comparative treatment results showed that only aspirin (but not indomethacin and diclofenac) was beneficial in both groups. Good-to-excellent results were achieved by 87% of HZ patients and by 82% of PHN patients treated with the aspirin/diethyl ether mixture. Similar results were noted with aspirin in chloroform (103). The mechanism responsible for the analgesic properties of aspirin is probably not the same as that responsible for its anti-inflammatory properties.

Other experimental modalities for treatment of PHN have been reported. Low energy laser therapy was investigated as a primary treatment during the acute pain phase of HZ to reduce incidence of PHN and in the treatment of PHN itself (104, 105). The authors reported improvement in approximately 60% of the patients with PHN. Sympathetic ganglion block (using alcohol) on PHN left untreated for more than six months was evaluated in a retrospective study (106). One year following the onset, the disease was nearly or completely cured in nine of 37 patients (24%) treated with sympathetic ganglion block with alcohol and in six of 34 (17.6%) without the treatment. The difference may not be clinically significant, and further research is needed before recommending either of these modalities.

Several novel methods of treating PHN have emerged. Interest in the role of the *N*-methyl-D-aspartate (NMDA) receptor has led to the use of NMDA antagonists for treating PHN. The effect of continuous subcutaneous infusions of ketamine on nerve injury pain was exam-

ined in patients with PHN (107). Ketamine was administered continuously in increasing doses using a portable infusion pump for a total of seven days and nights. Relief of continuous pain, as evaluated daily by visual analogue scales, was observed at the infusion rate of 0.05 mg/kg/hr, but was most marked during infusion of 0.15 mg/kg/h. All patients reported that ketamine reduced the severity of continuous pain as well as reduced the severity and number of attacks of spontaneous pain. Allodynia was maximally reduced 59-100% after one week infusion of 0.15 mg/kg/h. Common side effects were itching, fatigue and dizziness.

In a further trial of ketamine, pain and sensory thresholds were tested before and after intravenous administration of ketamine (0.15 mg/kg), morphine (0.075 mg/kg) or saline in 8 patients with PHN (108). Neither ketamine nor morphine significantly changed the thresholds for warm, cold, heat pain or tactile sensation. However, ketamine normalized abnormal heat pain sensation in four patients, possibly due to a central effect. Ketamine, but not morphine, produced significant relief of pain. Allodynia was inhibited by ketamine as well as by morphine. Wind-up-like pain (pain evoked by repeatedly pricking the affected skin area) was significantly inhibited by ketamine, but significantly aggravated by morphine. Side effects were observed in all the eight patients after injection of ketamine and in 6 patients after injection of morphine.

Suzuki et al (109) reported the use of dextromethorphan, a non-selective NMDA receptor antagonist, in 25 patients with PHN. A decrease in pain intensity and alleviation of allodynia were observed in nine patients (36%). Side effects with no severe cases occurred in eight patients (32%), and these were mainly digestive symptoms.

Various forms of stimulation have been used to treat PHN. These include: counter irritation, transcutaneous electrical nerve stimulation (TENS), acupuncture, spinal cord stimulation, and deep brain stimulation. Taverner (110) found counter irritation effective as a method of pain relief in 12 out of 16 patients with PHN using repeated spraying of the affected skin with ethyl chloride.

Further experience in this field was gained using TENS. Niv et al (77) reported a 60% success rate in decreasing pain with TENS patients whose skin sensation

was normal to pinprick, but only a 30% success rate in patients with numbness of the skin. In previous studies a 30% success rate was reported, however, patients were not stratified according to skin sensation (111). The analgesic effect of TENS maintained itself for several hours after the treatment. Other investigators have also had positive results with TENS (44, 112, 113). However, randomized studies comparing TENS with clomipramine and carbamazepine reported no advantage with TENS (114). Other stimulation treatments have met with little success.

Peripheral treatment by ultrasound was not beneficial (115); and, similarly, no difference could be found between acupuncture and placebo (116). Spinal cord stimulation has been reported as helpful, however, the majority of the studies are lacking detail or poorly designed. In a study of long-term results in 70 patients, only two showed objective signs of improvement while 14 reported subjective improvement (117). There is very little published information concerning attempts at deep brain stimulation for PHN. Stimulation of the ventro-posteromedial nucleus has been reported as beneficial in 30% of treated PHN sufferers (118,119). At present, this method should be regarded as experimental.

A wide variety of surgical interventions have been tried as treatment for PHN but no single operational procedure design stands out as a solution to the problem. Most reports mention a small number of patients. Numerous papers on these procedures have been presented and most report a minute benefit (44, 120, 121). Surgical lesioning has been attempted and tried at multiple levels, starting from the periphery, with procedures such as undermining of the skin (success rate of 30%) (122) and surgical skin shaving (success rate of 25%) (123).

Browder and Deveer (54) reviewed the disappointing results of cordotomy, rhizotomy and sympathectomy for PHN, but were in favor of excision of the whole affected area. Other approaches to brain stem structures have been attempted including: trigeminal tractotomy, mesencephalotomy, retrogasserian rhizotomy, avulsion of the supraorbital nerve and greater superficial petrosal neurectomy (44, 121). Such radical surgery has brought relief to a number of isolated cases in which the surgical procedure was undertaken as a last desperate effort. Recog-

nizing the rate of recurrence and the potentially extreme morbidity, resorting to surgical operations of these dimensions must be limited to the severest cases, having the poorest quality of life due to pain.

A method of chemically lesioning the peripheral nerve was reported through the use of adriamycin (124). Adriamycin, an anthracycline antineoplastic agent, can swiftly be transported to the sensory or somatic motor neurons by way of axoplasmic transport when injected into the subepineurium of the trigeminal nerve or sciatic nerve in experimental animals. It is consequently able to induce degeneration of the neurons without any systemic side effects. Intraneural injection of this agent was carried out for the treatment of a total of 22 patients presenting with intractable neural dysfunction (including seven with PHN). The nerve that innervated the affected site was exposed under local anesthesia and Adriamycin was injected into the subepineurium. Results of the treatment after average follow-up periods of 21.5 months demonstrated that of 12 patients with neuralgia, good or fair results were obtained in 67.7%. There were no changes in symptoms in four cases (33.3%). No major complications were encountered during these procedures and once symptoms had disappeared after the treatment, no recurrence of symptoms was experienced. Further research is required before this method should be recommended.

Dorsal root entry zone lesions (DREZ operation) have been utilized with varying results and severe complications in the treatment of PHN. Friedman and Nashold reported immediate analgesia after this procedure in 17 cases of refractory PHN; however, pain recurred within two months in three instances. In the remainder, good analgesia lasted between six to 25 months (125). More recently, Gorecki and Nashold (126) reported the results of 101 DREZ operations performed since 1982. Between 1982 and 1988, radiofrequency lesions were made using a straight electrode in the trigeminal nucleus extending from the C2 root to the obex. Complications included ipsilateral arm ataxia due to spinocerebellar tract injury and ipsilateral lower limb weakness from the pyramidal tract. The former occurred at least transiently in 90% of cases. The electrode employed from 1988 to 1989 had proximal insulation protecting the spinocerebellar tract. Since 1989, a 90-de-

gree bend was added to the electrode to allow better placement. The newest electrodes were used in 46 procedures; with these ataxia was seen in 39%. In PHN, 71% of the patients stated excellent or good relief. In contrast, Rath and coworkers (127) performed 12 procedures on patients with PHN and reported continuous marked improvement after DREZ lesions in only two out of ten patients (mean follow up: 52 months). The authors noted that DREZ lesions appeared to be an effective procedure in patients with pain related to root avulsion and paraplegia. In contrast, it was less successful for painful states due to PHN.

PREVENTION

Perhaps, the optimal approach to PHN should be prevention, the thought being that appropriate treatment in the acute phase of HZ might circumvent the chronic pain associated with PHN. Various treatments have met with mixed results. Antiviral drugs, while ameliorating the acute pain of HZ prevented chronic pain in some studies but not others (23, 128-132). Similar mixed results were found in studies of steroid therapy (28, 133-135). It appears that the effectiveness of treatment increases if the patients are treated early after the onset of acute symptoms of HZ, while the problem is still localized to the periphery of the damaged nerve. This impression is supported by recent theories which claim that the interruption of the nociceptive impulses, which travel along the nerve, is not only a symptomatic cure, but also can help prevent transformation to a chronic pain state (136).

Winnie and Hartwell (137) examined the relationship between time of treatment of HZ with sympathetic blockade and prevention of PHN in a retrospective review of 122 patients treated at variable intervals after the onset of HZ. Data tabulated included the duration of symptoms at the time of treatment, the number of sympathetic blocks required to provide relief and the efficacy of the sympathetic blockade in terminating the acute phase of HZ and then preventing the development of PHN. The authors determined that sympathetic blocks terminated the pain of acute herpes zoster and prevented or relieved PHN in more than 80% of patients treated within two months of the onset of the acute phase of the disease, after which time the success rate decreased

drastically. The benefit was hypothesized to be due to a restoration of intraneural blood flow, thus preventing the death of large fibers and avoiding the development of PHN. If sympathetic blocks were to be carried out after two months, the damage to the large fibers would be irreversible and this therapeutic modality would not be able to prevent the development of PHN.

Not all investigators agree that sympathetic ganglion block can prevent PHN. A recent literature review (138) examined the role of sympathetic block in the prevention of PHN. A total of 84 references were reviewed. The opinion of the medical community is divided on the role of sympathetic block in preventing PHN because of the lack of controlled trials and the conflicting retrospective reports as to its effectiveness. While many reports promote the early use of sympathetic blocks during HZ to prevent PHN, others deny their value. Despite this degree of uncertainty, the seriousness of PHN may indicate early sympathetic block in addition to treatment with antiviral agents during HZ. This choice to provide sympathetic block remains a clinical decision; large controlled trials are needed to provide the necessary scientific evidence.

Pre-emptive analgesia has been investigated as a method of avoiding central sensitization in acute pain states (139, 140). Pain of peripheral origin is amplified by central sensitization, and this amplification appears to be maintained for as long as the peripheral source is present. Possibly, the aspect of central sensitization in HZ that leads to the development of PHN could be avoided through the administration of a prolonged, continuous somatic nerve block. Alternatively, the development of techniques for blocking the central sensitization process itself (e.g., NMDA-channel antagonists) may provide a new tool in the future. The ultimate importance of this approach, however, depends on the degree of amplification caused by central sensitization. This parameter remains unknown.

CONCLUSION

Clearly, we still have much to learn. Studies investigating the pathophysiology of HZ and PHN may prove to be beneficial in developing better treatments. Antiviral agents are useful in acute HZ and may help prevent PHN. Sympathetic blocks also appear to be warranted in the prevention

of PHN in some cases, but this remains a clinical decision, as there is little scientific evidence to support the procedure. Local treatments like capsaicin and EMLA have been demonstrated to be helpful in some patients with PHN. Tricyclic antidepressants and anticonvulsant drugs, particularly gabapentin, have been demonstrated to be helpful in scientific studies and remain first line therapy for PHN.

Although monotherapy is commonly applied, no single best treatment for PHN has been identified. Nevertheless, appropriate therapy includes attention to psychosocial factors as well as medical treatment with gabapentin and recently pregabalin (anticonvulsants) and transdermal lidocaine (topical local anesthetics).

In 1796 the French writer Se'bastien-Roch Nicolas de Chamfort wrote: "Philosophy, like medicine, has plenty of drugs, few good remedies, and hardly any specific cures." To date, we do not have a panacea. Hopefully, we have made some progress.

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