

## POST-HERPETIC NEURALGIA

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Following the initial infection the chicken pox virus may lie in the dorsal horn of the spinal cord for decades before its unwelcome presence becomes evident when it is activated to cause an acute attack of shingles. Typically, this presents as a burning, tingling pain with occasional stabbing components that may precede the onset of small cutaneous vesicles in the distribution of a cutaneous nerve or nerves by as much as two or three days. In turn, this may lead to the unpleasant persistence of pain in the form of post-herpetic neuralgia (PHN). PHN is defined as pain arising or persisting in areas affected by herpes zoster at least three months after the healing of the skin lesions. The early recognition and treatment of herpes zoster prevents viral replication, relieves the acute pain and may reduce the complications of the disease of which PHN is the most feared. However, while it is important to emphasise that treatment may help PHN, there remains a core of patients who are incredibly difficult to treat successfully even in the most optimum circumstances.

### Incidence

The incidence of PHN is between 9 and 14% one month after the herpes zoster eruption. There is a definite tendency for PHN to improve with time and as few as 3% of patients may be left with severe PHN after one year. There is no way of predicting who will recover and some series report that as many as 40% of patients with PHN will continue to have long-term problems because of incomplete or no pain relief from our best treatments.

There is no difference between the incidence in males and females, but the incidence is directly related to age; with PHN becoming much more common and more incapacitating as the patient gets older. There is no seasonal incidence and the areas affected tend to be on the chest and abdomen and the ophthalmic division of the trigeminal nerve. One study has shown that black patients have a significantly lower risk of developing herpes zoster than whites. There is an increase in the incidence of herpes zoster with lymphoproliferative disorders (leukaemia / lymphoma) and severe disease and aggressive treatment seem to

increase the likelihood of severe PHN. Herpes zoster seems to be more common in any condition with a change in immune status and is not uncommon in patients with HIV.

### Pathology

It is thought that the varicella virus passes to the dorsal root ganglion via the skin during the initial infection (chicken pox) and lies dormant. The latent virus becomes reactivated when immune mechanisms are impaired and the revived activity of the virus is manifest by the rash and the pain. Some cases of pain in PHN may be due to persistent inflammation in the dorsal root ganglion and this may be the reason that anti-inflammatory or antiviral agents can be useful in some individuals. Evidence exists that the small pain fibre activity begins to predominate as the disease advances and that there is increased sensitivity to mechanical stimuli, alpha-adrenergic agonists and to sympathetic efferent activity. These mechanisms suggest that the success of antidepressants in treating PHN may be related to their serotonergic and nor-adrenergic effects.

### Clinical considerations

Herpes zoster usually starts with pain, paresthesiae (numbness / tingling) and dysaesthesiae (unpleasant sensations) in the affected dermatomes, followed a few days later by the rash. The pain is usually severe and particularly so in the elderly. The characteristic vesicles usually scab within a week and heal in a month. Generalised zoster is rare but may occur in immunocompromised patients. Infection in the sacral segments can occasionally give rise to urinary retention and there are rare cases of motor nerve involvement, usually in the facial nerve. No evidence exists to support the view that PHN occurs more frequently in the presence of an occult malignancy.

About 5% of patients develop a systemic response to herpes zoster, with fever, stiff neck, headache and nausea. This does not lead to a higher incidence of PHN. Ophthalmic shingles may jeopardise vision and early and aggressive management is advised. Recurrent attacks of herpes zoster are uncommon but

may be associated with immunosuppression or malignant disease.

The scarred areas are at least less sensitive, and often anaesthetic. Paradoxically the skin may exhibit marked superficial pain with light touch (allodynia) or an increased sensitivity to noxious stimulation (hyperesthesia). There may be two types of pain: one a steady burning or aching, the other a paroxysmal, lancinating (stabbing) pain. Both may occur spontaneously and may be aggravated by even the lightest contact with the involved skin. Curiously, firm pressure may lead to pain relief whereas light brushing may be unbearable. Severe pain also may be provoked by physical activity, temperature change, emotional upsets or, in rare cases, by stimuli as trivial as noise from the street or light breezes.

Examination of the affected, scarred skin may reveal that there is a loss of sensation to pinprick, pain and temperature over a far wider area than the scars and in addition, that the area of sensitive or painful skin is even wider still. This phenomenon is thought to be due to the damaged central neurons becoming sensitive to stimuli from a wider area.

#### **Treatment of the acute infection**

The acute pain can be treated topically and systemically. Covering the lesions with calamine lotion, petroleum jelly, local anaesthetic creams or an occlusive bandage may give some symptomatic relief. Non-steroidal anti-inflammatory drugs and paracetamol (acetaminophen) with or without codeine or other opioids, may be indicated because of the severity of the pain. There is every justification for using stronger opioids in cases with severe pain that is not relieved by other methods. It makes sense to treat the acute infection as well as possible as this may prevent alterations in the central nervous system that may be responsible for the development of PHN.

It has been suggested that the use of antiviral agents within the first 72 hours may prevent viral replication and thus reduce the severity of the acute eruption and prevent PHN. There is now some evidence to support the use of these agents in this fashion. The use of low dose (10- 50 mg) of amitriptyline at night may reduce the onset of PHN in anyone developing shingles. Use of corticosteroids has been suggested but results of clinical trials have been confusing and their use cannot

be recommended as a method of preventing PHN. The initial infection seems to clear up earlier but there was no effect upon the incidence of PHN. Regional anaesthesia has been the subject of several uncontrolled trials, but no clear answer has been achieved. Suffice it to say that the pain of acute shingles can be relieved by appropriate somatic or sympathetic blockade, or both, and that sometimes this is the only way of getting symptomatic relief in difficult cases.

#### **Treatment of established PHN**

- **Antidepressants** have been shown to be effective in the treatment of PHN in a number of well-designed trials. The gold standard for treatment is the tricyclic drug amitriptyline, and this was originally used in 1965 to treat patients with PHN who were thought to be depressed. Good pain relief was noted over almost a year in some patients and it is now known that the effects of amitriptyline on PHN are independent of any action upon depression. The pain relief usually occurs at dosages that are lower than those needed for the effective treatment of depression (50 mg median for PHN 125mg median for depression). Good relief can be expected in over half the patients treated but relief is rarely complete and amitriptyline has significant limitations in the long term because of side effects. These range from annoying (dry mouth, drowsiness, constipation, urinary hesitancy and weight gain) to potentially significant (cardiac conduction defects, memory impairment and hypotension).

As one of the effects of amitriptyline is to potentiate serotonin and noradrenaline in the central nervous system, subsequent research has explored whether agents that work selectively on these neurotransmitters might be more effective and have fewer side effects. Experience with serotonergic agents such as clomipramine, trazodone, and fluoxetine) has been disappointing. However, use of nor-adrenergic agents has been more successful. Desipramine, nortriptyline and maprotiline have all been shown to relieve PHN, at least to some degree. The mixed serotonin- reuptake inhibitor venlafaxine also appears to be effective, but only at the top end of the dose range when it is working like a tricyclic.

- **Neuroleptics.** There is no evidence to support the use of this group of drugs for the treatment of PHN despite reports of success in some small early trials.

- **Anticonvulsants.** It is difficult to be certain about the effects of anticonvulsants in the treatment of PHN. Trials of carbamazepine, phenytoin and sodium valproate have been either unconvincing or the results have been clouded by the concomitant use of antidepressants. The use of carbamazepine for paroxysmal lancinating pain is well established and there may be a small effect upon this sort of pain but there is no apparent effect on continuous pain. Overall, there simply isn't any evidence to support its use in the treatment of PHN.

More recently, gabapentin has been shown to relieve the pain of PHN. The mechanism of action of this agent is not known; the most recent suggestion being that it works via calcium channels. There seems little question that gabapentin is effective in the treatment of PHN in doses ranging between 600 to 3600 mg daily in divided doses. It has a lower side effects profile than amitriptyline but is vastly more expensive.

- **Local anaesthetic drugs** such as lignocaine or mexiletine block voltage sensitive sodium channels to produce membrane stabilization. An infusion of 3 mg/kg of lignocaine given over 30 minutes (monitoring electrocardiogram and blood pressure for signs of systemic toxicity), may predict the response to systemic mexiletine. Dramatic relief of PHN with this therapy is rare.

- **Topical agents.** A variety of topical agents have been tried in PHN (Capsaicin, aspirin and local anaesthetics). Capsaicin, the active ingredient in red peppers and other plants, acts by depleting the neurotransmitter substance P in small primary afferent fibres. Any clinical effect is small and this drug may be best used in conjunction with other treatments. The burning sensation induced by the application of capsaicin may be unpleasant and limit its use clinically. Care must be taken when using this agent to avoid contact with mucous membranes around the eyes and mouth.

Uncontrolled studies have suggested a role for aspirin in a variety of vehicles such as chloroform, ether and Vaseline ointment. Similarly, local anaesthetic creams such as lidocaine and EMLA (a prilocaine based eutectic mixture of local anaesthetics) applied under occlusive dressings may be useful but the effect is small and the expense may be large.

- **Peripherally acting drugs.** As there may still be a residual inflammatory component to some cases of prolonged PHN it makes sense to try the effect of NSAIDs and paracetamol (acetaminophen) in normal clinical doses.

- **Opioids.** There has always been a prejudice against the use of opioids to treat any kind of non-malignant pain but the fact remains that these drugs work effectively in many kinds of severe pain. There is no doubt that the pain of nerve injury, such as is seen with PHN, will respond to opioids. In view of the severity of the pain that may be encountered with PHN there can be no justification for withholding opioids if these are available. Common sense dictates that the dose should be titrated against effect starting with weak opioids, and then escalating strength and dose of opioid to achieve a clinical effect. If side effects supervene without any pain relief, the pain is not opioid sensitive and the drug can be stopped. Studies have shown benefit with the use of tramadol (which has opioid and non-opioid analgesic properties), oxycodone, levorphanol and morphine.

- **Clonidine.** The high density of alpha-2 adrenoreceptors in the dorsal horn of the spinal cord suggests that there should be a role for clonidine in the treatment of PHN. Pain reduction has been reported after this drug has been used epidurally and orally, but there are no properly constructed controlled trials to show benefit is anything more than a theoretical possibility.

- **N-methyl-D-aspartate (NMDA) antagonists.** Ketamine and dextromethorphan are NMDA antagonists that have been tried in the treatment of PHN. It is thought that tricyclics may have NMDA antagonist activity too. Ketamine has helped selected cases when given orally or by injection but there are no controlled studies of the drug given by either method to suggest anything other than occasional help in isolated cases.

- **Miscellaneous therapies.** There seems to be no end to the number of treatment that have been tried to relieve this dreadful problem. These range from vitamin B to snake venom and include serial somatic or sympathetic nerve blocks with local anaesthetic (with and without steroids), serial local anaesthetic infiltrations, prolonged courses of subarachnoid or epidural steroids, hypertonic saline injections,

transcutaneous electrical nerve stimulation, acupuncture, use of hand held vibrators, coolant sprays (such as ethyl chloride) and occlusive dressings such as cling film and cryotherapy.

The surgical treatment of PHN has developed an extensive folklore but it can be stated categorically that no proven surgical cure exists for PHN. Almost any operation can be shown to work a few times but none helps consistently or frequently enough to be worth the effort. Among the surgical treatments shown to be ineffective are local excision, nerve avulsion, cordotomy, rhizotomy and sympathectomy. Theoretically dorsal root entry zone (DREZ) lesioning may be effective but there is insufficient experience anywhere in the world to be able to recommend this approach even in the most severe cases. DREZ lesioning for the treatment of PHN is not advocated by the American Association of Neurosurgeons due to limited efficacy, and the high rate of morbidity. The

use of central electrical stimulation is subject to the same strictures.

### **Conclusions**

Initial treatment of the acute infection should be symptomatic and tailored to the needs of the individual as described earlier. Treatment of persistent PHN should be systematic and begin with simple measures such as an occlusive dressing, simple analgesics and amitriptyline. It is rare for patients to respond to monotherapy and drug combinations up to and including opioids will be the most likely to give success. Each agent should be tried at an adequate dosage and for an adequate time before it can be said to have failed. Drugs that are ineffective or which lead to unacceptable side effects should be replaced by another drug until effective relief is obtained. The eventual combination will be dependent upon what is available and what is affordable.