Postherpetic Neuralgia: The Importance of Preventing This Intractable End-Stage Disorder

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An argument is presented here for postherpetic neuralgia as an intractable end-stage disorder for many patients. The exciting possibility of prevention of this disorder by early, aggressive treatment exists; however, the extent to which therapy can be effective is unknown. Early, aggressive treatment of the pain of herpes zoster is, nevertheless, urged, and the options for treatment are discussed. These options include antiviral therapy within the first 72 h, if possible, from the onset of rash or radicular pain and the use of analgesics, including opioids (if necessary), nerve blocks, and early antidepressant therapy. In addition, the extent to which vaccination of older adults will prevent postherpetic neuralgia is unknown but appears to hold promise.

The two most feared complications of herpes zoster are postherpetic neuralgia (PHN) and severe ocular involvement. This article focuses on PHN, which may reasonably be compared with other end-stage disorders in which damage to an organ occurs and that organ is unable or not fully able to repair itself and respond to treatment. Evidence for this position lies with epidemiologic, clinical, and pathologic information, which will be reviewed here. In my view, as many as half of the patients with established PHN are incompletely or totally refractory to the best therapies available. Because of this and of the possibility of preventing this disorder, our thoughts must turn to early, aggressive treatment even though the effect of this approach is unproven. Optimally, this approach to treatment should be studied in a scientific fashion, but pending the results from such a study, it appears reasonable to proceed with early treatment of herpes zoster and to also consider the possibility of prevention or attenuation of the disease by vaccination of older adults.

Epidemiology

Herpes zoster is the most common neurologic disease [1]. PHN is a painful disorder that occurs 1 month after herpes zoster infection in ~10% (overall incidence) of those with the infection [2–4]. The incidence of PHN, however, increases with age, affecting ~50% of herpes zoster patients by age 60, and the incidence rises steadily with increasing age [5]. The prognosis for patients with established PHN is poor, since at least half continue to suffer for many years—some even until death [6]. Of the 50% who seem to do reasonably well, many require continual pharmacotherapy, often with unpleasant side effects. These data are from a clinic that specializes in the treatment of PHN; patient outcome may be worse elsewhere.

Clinical Findings

Clinical findings indicate that the nervous system is altered by this disease such that there are areas of sensory loss and widespread areas of sensitive skin, which respond to the lightest touch with severe pain (figures 1, 2). There are three types of pain associated with PHN: steady, often burning pain; lancinating, shock-like pain; and pain on non-painful stimulation of the skin (allodynia). These are often all present in a single case. The allodynia suggests that central neurones have expanded their receptive fields and have lowered thresholds to sensory stimulation. There is no evidence that the sensory changes are reversible.

Table 1 summarizes controlled trials of antidepressant and opioid therapies in PHN. These data indicate that 30%–50% of the patients responded poorly or not at all to some antidepressants and to opioids, the most powerful analgesics [12]. Even with these drugs, responses are usually incomplete, with total relief unusual. Side effects occur in nearly all treated patients. For most, other treatments are ineffective and include a variety of trial-and-error approaches, which may benefit an occasional patient with differing pain mechanisms [13].

Pathology

The few pathologic studies of PHN cases indicate that there is extensive damage to the peripheral and central nervous system [14, 15]. The peripheral nerve, ganglion (figure 3), and sensory root are extensively scarred, leading to the loss of normal structures. Surviving nerve fibers appear to shift to the smaller fiber population, which may be predominantly excitatory and may fire spontaneously or in response to the lightest of tactile stimulation. Further, there is evidence of central nervous system damage in that the dorsal horn of the spinal cord...
not scientifically proven to prevent PHN, this treatment may do so, particularly in conjunction with other approaches.

Antidepressants have been repeatedly shown to have an analgesic action in PHN that is independent of an antidepressant effect [7–11]. It is suggested that this action is via inhibition of re-uptake of serotonin and noradrenaline in the central nervous system. These are inhibitory neurotransmitters for pain pathways. Only amitriptyline, nortriptyline, desipramine, and maprotiline have been shown to relieve established PHN [7–11]. It has also been suggested that early antidepressant therapy may help to prevent persistent pain [19]: Treatment may be instituted with low doses (10–25 mg, depending on the patient’s age) of amitriptyline. This dose can be titrated every few days by similar increments until relief occurs or side effects supervene, and then the dose can be slightly reduced and held steady [13].

These preventative measures need to be studied scientifically to see if they alter the long-term natural course of PHN [2–6]. However, used by experienced practitioners, these measures have minimal untoward effects; thus, it seems reasonable to

is infiltrated by inflammatory cells and later becomes atrophic because of the destruction of nerve fibers and neurones (figure 4). There is no evidence that any of these pathologic changes are reversible.

Discussion

It is not known whether vaccination of older adults will attenuate or prevent herpes zoster; however, on the basis of current concepts of the pathogenesis of the disorder (i.e., it is thought that declining cell-mediated immunity is an important factor in the eruption of zoster), it would seem reasonable to study this approach.

The other preventative avenue is to treat herpes zoster early and aggressively. This would require education of the general population so that patients would recognize the symptoms of zoster, contact a physician, and make arrangements to be seen promptly. Educational material regarding herpes zoster is available from the Varicella Zoster Research Foundation [16]. It is important that antiviral therapy with valacyclovir or famciclovir be initiated within 72 h from the onset of pain or rash in order to inhibit viral replication. It appears that there is a modest reduction in zoster-associated pain with this approach [17, 18].

Another measure that should be considered is the early, aggressive use of analgesics to prevent the development of sensitization of the nervous system. Opioids may be required, in which case, infectious disease specialists may wish to consult a pain management expert. There is evidence that regional anesthesia of the painful area (by an anesthesiologist expert in these techniques) may help to resolve acute pain, and although
Table 1. Number of postherpetic neuralgia patients responding poorly or not at all to treatment with antidepressants or opioids in controlled trials.

<table>
<thead>
<tr>
<th>Study, year [reference]</th>
<th>Agent</th>
<th>% of subjects responding to treatment with</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Opioid or antidepressant*</td>
</tr>
<tr>
<td>Watson et al., 1982 [7]</td>
<td>Amitriptyline</td>
<td>8/24, 33%</td>
</tr>
<tr>
<td>Max et al., 1988 [8]</td>
<td>Amitriptyline</td>
<td>21/41, 53%</td>
</tr>
<tr>
<td>Kishore-Kumar et al., 1990 [9]</td>
<td>Desipramine</td>
<td>14/26, 54%</td>
</tr>
<tr>
<td>Watson et al., 1992 [10]</td>
<td>Amitriptyline and/or maprotiline</td>
<td>17/32, 53%</td>
</tr>
<tr>
<td>Watson et al., 1998 [11]</td>
<td>Amitriptyline and/or nortriptyline</td>
<td>10/31, 32%</td>
</tr>
<tr>
<td>Watson and Babul, 1998 [12]</td>
<td>Oxycodone</td>
<td>17/38, 45%</td>
</tr>
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</table>

* Data are no. responding/no. treated, %.

Figure 3. Dorsal root ganglion in case of postherpetic neuralgia. Figure shows extensive fibrosis and loss of normal structures. Arrows indicate surviving ganglion cells.
make them part of the clinical treatment of herpes zoster until such studies are completed.

References

16. VZV Research Foundation, 40 East 72nd St., New York, NY 10021 (phone, 212-472-7148; fax, 212-861-7033).