Neuropathic Pain in the Orofacial Region: Clinical and Research Challenges

Gary J. Bennett, PhD
Canada Research Chair
Department of Anesthesia, Faculty of Dentistry, and Centre for Research on Pain
McGill University
Montreal, Quebec, Canada

Correspondence to:
Dr Gary J. Bennett
Anesthesia Research Unit (McIntyre 1202)
3655 Promenade Sir William Osler
Montreal, Quebec H3G 1Y6
Canada
Fax: +514 398 8241
E-mail: gary.bennett@mcgill.ca

Neuropathic pain in the orofacial region poses a difficult challenge to the treating physician. In some cases diagnosis is far from easy. Common causes of orofacial neuropathic pain are reviewed here, with a focus on the 2 most common: postherpetic neuralgia and posttraumatic painful peripheral neuropathy. In addition, the discussion includes idiopathic trigeminal neuralgia (tic douloureux), a neuropathic pain syndrome that is nearly unique to the trigeminal distribution (very rarely, it has also been reported in the glossopharyngeal region). Brief summaries of major research problems and successes are also provided. J OROFAC PAIN 2004;18:281–286

Key words: postherpetic neuralgia, trigeminal neuralgia

Damage to somatosensory peripheral nerves may produce a loss of sensation, with the amount of loss corresponding approximately to the severity of the nerve damage. This is what usually occurs, but in some cases nerve injury produces positive symptoms, and these almost always include dysesthetic sensations or 1 or more types of pain.[1] Itch may also appear as a symptom, but this appears to be rare.[2] The abnormal pain experienced after nerve injury is called neuropathic pain. Neuropathic pain is a chronic, difficult-to-treat condition that is assumed to be due to dysfunction of the pain-processing neurons in the peripheral nervous system and central nervous system (CNS). Neuropathic pain is seen with injury to all somatic nerves, including the trigeminal nerve and the nerves arising from the upper cervical spinal segments that innervate the rest of the face and head. Neuropathic pain is also sometimes seen after injury to the somatosensory processing regions of the spinal cord, brain stem, and higher levels of the CNS. For example, such "central pain" can occur in the orofacial region after a brainstem infarct that damages the trigeminothalamic pathway. Such central pain manifested in the orofacial region is not considered here.

Nerve damage leading to neuropathic pain has many causes, only some of which are prevalent in the orofacial region. For example, painful diabetic neuropathy is a common condition that produces pain felt in the feet, hands, and midline thorax, but it rarely affects orofacial dermatomes. However, other causes of neuropathic pain

commonly affect orofacial structures. The discussions below focus on what I believe are the 2 most common: postherpetic neuralgia and posttraumatic painful peripheral neuropathy. In addition, the discussion includes idiopathic trigeminal neuralgia (tic douloureux), a neuropathic pain syndrome that is nearly unique to the trigeminal distribution (and, very rarely, has been reported in the glossopharyngeal distribution).

Postherpetic Neuralgia

A childhood infection with varicella virus (chicken pox) results in a lifelong latent infection in the cells of the dorsal root ganglia and trigeminal ganglion. The viral genome is stably integrated in the genome of the ganglionic cells (either the somatosensory neuronal cell bodies or the cell bodies of the satellite glia cells that invest them, or both). Expression of the viral genome is either extremely low or nonexistent until some point, usually in the late decades of life, when it suddenly reactivates with a very high level of viral expression, ie, an attack of shingles. Shingles was originally ascribed to the herpes zoster virus; it was not until 1955 that it became clear that zoster was identical to varicella. The cause(s) of the viral reactivation are incompletely understood, but decreased immune memory (ie, the gradual loss of clonal B-cells that "remember" viral antigens), a natural consequence of aging, and impaired immune function generally (as in the AIDS or immunosuppressed transplant patient), are known factors.[1,3]

The viral load during an attack of shingles is so high that it causes cells to burst.[3] The aggressive immune response that follows then causes secondary damage to nearby cells and microvascular hemorrhage. Moreover, the virus becomes incorporated onto the axoplasmic transport system, which transports it to the somatosensory neuron's terminal receptors in the skin. When the virus escapes from the neuronal terminals, the skin becomes infected, and the characteristic cutaneous lesions develop. While in transport, virus escapes from the axons into the endoneurial compartment. This also evokes an aggressive immune attack, and so the nerve itself becomes a site of cell damage and microvascular hemorrhage. It is reasonable to suppose that the axoplasmic transport of virus is both peripheral and central. Transport in the afferent neuron's central axon would be expected to produce an infection where those afferents terminate, in the spinal cord dorsal horn and trigeminal brainstem nuclei. There is surprisingly little evidence for such a CNS infection, although spinal cord dorsal horn atrophy (perhaps due to degeneration of the sensory innervation) has been demonstrated.[4]

The cutaneous lesions are so dramatic that there is a tendency to think of shingles as a dermatological disorder, but it is important to remember that the skin involvement is a secondary infection; the sensory ganglia and peripheral nerves bear the brunt of the damage. The secondary involvement of the skin is responsible for the typical mismatch between the onset of pain and the cutaneous lesions. Pain is felt days, weeks, or even months before the rash appears; such pain must thus be due to the ongoing damage in the ganglia and nerve. In rare cases, the skin lesions never appear, a condition known as zoster sine herpete. When the infection does invade the skin, the cause of pain must be compound—typical inflammatory pain from the skin in addition to neuropathic pain from viral-evoked injury to ganglia and nerve.[4] Indeed, an attack of shingles can be an extremely painful experience lasting for a month or more. Eventually, the virus re-enters its latent form, and the lesions in the skin, nerve, and ganglia heal. For the majority of patients, all that is left are insensate cutaneous scars (densely fibrous tissue does not accept regenerative innervation). However, in a minority of patients, the virus re-enters latency, the lesions heal, but the pain remains. This is postherpetic neuralgia (PHN), a type of neuropathic pain that may last for months, years, or even decades.[3,5] It is difficult to precisely separate acute shingles from PHN. A somewhat arbitrary but useful practice is to designate PHN as pain that persists for 3 to 6 months after the cutaneous eruptions crust over.

It is not known why only a minority of those with shingles develop PHN. Age is clearly a factor—if shingles occurs at the age of 65 or older, then the probability of developing PHN is about 50%.[3,6] Younger patients with shingles have a dramatically lower incidence of PHN. There is also data showing that a high level of pain during the acute infection predisposes to PHN. It can be confidently predicted that the incidence of PHN will continue to rise as the populations of developed countries continue to age, as the population of immunocompromised patients continues to grow because of the AIDS epidemic (and the steadily increasing life expectancy of the AIDS patient) and as the frequency of organ transplantation, a procedure requiring immunosuppression, increases.[6]

Chicken pox covers the whole body, and it thus seems likely that a latent infection is established in

all somatosensory ganglia. But shingles, and thus PHN, almost always appears in a single ganglion, and almost always on just 1 side. The cutaneous lesions thus usually appear in a single dermatome. Indeed, the correlation between records of the area of skin lesions with postmortem identification of scarred ganglia established the concept of dermatomal innervation.[7] Nonetheless, shingles and PHN may occur in any dermatome, but there are striking differences in incidence. Thoracic dermatomes are most commonly affected; orofacial dermatomes are the second most common. Shingles appears in the first division of the trigeminal nerve (V1) in about 10% of patients and in V2/V3 in about 2%.[3] The incidence of shingles is 125 per 100,000 patient years. The combined population of Canada and the United States is roughly 326 million. Thus, there are roughly 49,000 new cases of trigeminal shingles per year, of which about 30% will develop PHN. This is 14,700 new cases of trigeminal PHN per year. As PHN is chronic, there must be several tens of thousands of patients now living with trigeminal PHN.

Research on the cause of PHN pain has made dramatic progress in the last few years, mostly from observations in the clinical setting.[8–10] Animal research in this area has been hampered by the failure to establish and then reactivate a herpes zoster infection in animals. Recent work has modeled PHN, or perhaps more accurately, an acute attack of shingles, by injecting the virus into the rat's sciatic nerve. Animals so injected develop allodynia and hyperalgesia on the ipsilateral hind paw.[11,12]

At present, there is no reason to suppose that PHN pain in the trigeminal region is fundamentally different from PHN in any other dermatome, except for the obvious differences in the kinds of tissue available for infection (tooth pulp, cornea, etc).

Posttraumatic Painful Peripheral Neuropathy

Somatosensory nerves are damaged in all types of orofacial trauma, including dental procedures. Every pulpal extirpation and every third molar extraction is a blunt trauma to a dental nerve. These are certainly the most common nerve injuries of all; they must occur thousands of times a day, yet there is a question of how frequently they produce neuropathic pain, what symptoms they produce, and how they are to be diagnosed.[13–17]

The orofacial pain literature contains many descriptions, under different labels, that might qualify as posttraumatic painful peripheral neuropathy: atypical facial pain, atypical facial neuralgia, atypical odontalgia, dental causalgia, neuropathic orofacial pain, phantom orofacial pain, and phantom tooth pain.[13] Major questions for the field are to determine which, if any, of these are neuropathic pain, and to agree upon a nomenclature. This is not particularly difficult when *(1)* there is clear evidence of nerve injury, *(2)* ongoing pain is accompanied by hyperalgesia and allodynia, and *(3)* the pain is resistant to nonsteroidal anti-inflammatory drugs and opioids. The difficult cases are those in whom there is no definitive evidence of nerve injury. Injury to small nerves and partial injury to even large nerves can be difficult to prove. Quantitative sensory testing may be of help here.[14–16]

A second major challenge to the field is to determine the incidence of orofacial posttraumatic painful peripheral neuropathy. One gets the impression that these are very rare problems, especially when considered in the context of the large number of nerve injuries due to dental procedures. Only very limited epidemiological data are available. Retrospective studies of the incidence of painful phantom tooth suggest that at least 2% to 3% of endodontic surgery cases may be affected.[18,19] This is a surprisingly large percentage; if true, then dentistry is facing a much greater problem than is generally acknowledged.

Despite this caveat, the possibility must be considered that posttraumatic painful peripheral neuropathy is indeed relatively rare and that the response to trigeminal nerve injury is somehow different than the response to injury of other nerves. There are 3 factors that might be relevant. First, it is often noted that the trigeminal nerve innervates highly specialized tissues that participate in highly specialized functions (implying unique neural circuitry) that somehow render it relatively immune to the development of neuropathic pain. For example, the innervation of the tooth pulp and the tongue are certainly highly specialized, and the neural circuitry of the innervation of orofacial structures is functionally specialized for mastication and speech. However, I do not think that this argument is very persuasive. Other somatosensory nerves also innervate highly specialized tissues with highly specialized functions. For example, consider the innervation of the finger tips, genitalia, anal mucosa, and the nipples. The second factor that might render the trigeminal nerve relatively resistant to the development of neuropathic pain concerns 2 unique developmental events in the oral cavity. Only the trigeminal system has a biologically programmed pain event and a biologically

programmed denervation event-the eruption and loss of the primary teeth. Might these events in early life somehow offer protection against the consequences of later nerve injury? The third factor concerns dental surgery. Nearly all dental surgeries are performed under local anesthesia—no other type of surgery routinely blocks the innervation of the injured tissues. Consequently, in dental surgery the barrage of nerve impulses generated by the trauma does not gain access to the CNS. The injury-evoked impulse barrage, especially that from C-fiber nociceptors, is known to engage a process of central sensitization that may have relevance for the initiation of neuropathic pain.[17,20,21]

There are now several animal models of posttraumatic painful peripheral neuropathy, and the last 15 years have seen an explosion in our knowledge of potential pain-producing mechanisms. The majority of work has been done on the rat's sciatic nerve, but it is possible to use an experimental injury to a branch of the rat's trigeminal nerve. Analysis of the rat's behavior after trigeminal injury confirms the presence of a neuropathic pain syndrome.[21–24]

To date, there are 2 observations that hint that trigeminal posttraumatic painful peripheral neuropathy may have special features. First, cutting a somatosensory primary afferent's axon gives rise to spontaneous ectopic discharge that originates at the site of nerve injury and also in the injured neuron's cell body in the ganglion (for review, see Devor and Seltzer[25]). A direct comparison of the incidence of such ectopic discharge following transection of the rat's trigeminal and sciatic nerves suggested a significantly lower incidence after trigeminal injury.[26] However, there is a report of a high incidence of ectopic discharge following trigeminal nerve injury in the ferret,[17] which suggests the possibility of a significant interspecies difference for this phenomenon. Second, injury to the rat's sciatic nerve causes the sympathetic postganglionic afferents that normally innervate the ganglion's blood vessels to sprout. The sympathetic sprouts establish functional contacts onto the neuronal cell bodies in the ganglion. This de novo sympathetic-sensory connection may be relevant to sympathetically-maintained pain.[27] Sympathetic sprouting is observed reliably after sciatic injury, but it has not been observed after trigeminal nerve injury.[17]

It seems certain that trigeminal posttraumatic painful peripheral neuropathy will receive increasing attention from basic science researchers. At the least, the wealth of data from models using other nerves is likely to be partially relevant to the trigeminal case. The challenge here is mostly on the clinical side: Is this a common problem or not, what are its signs and symptoms, and what are we to call it?

Neuroimmune Interactions and the Genesis of Posttraumatic Painful Peripheral Neuropathy

Nerve damage activates those processes of the innate immune system that are involved in inflammation and healing. It is important to note that this occurs even with a completely sterile injury. An experimental inflammation of the rat's sciatic nerve (a neuritis) at mid-thigh level produces neuropathic pain sensations in the animal's hind paw. The inflammation does not produce axonal degeneration.[15] A similar syndrome is produced by creating an experimental inflammation of the rat's infraorbital nerve.[15] The pain is believed to be due to the activation of nociceptors coursing through the inflamed region by proinflammatory cytokines such as tumor necrosis factor-alpha.[28]

The clinical significance of this sort of neuritic pain is unclear. A persistent inflammatory process (due to occult infection, bone resorption, or mechanical irritation), even if it is at a relatively low level, might produce neuropathic painlike symptoms which would not necessarily be accompanied by any of the traditional signs of nerve damage.

Idiopathic Trigeminal Neuralgia

Tic douloureux has been a clear diagnostic entity since Andrè's original description in the mid-18th century; a careful history almost always allows a confident diagnosis.[29,30] The terminology for this condition still evokes much debate.[13] A pain syndrome that appears to be identical occurs with multiple sclerosis. Autopsies of multiple sclerosis patients with tic douloureux have found sclerotic plaque at the trigeminal root's entry zone.

There are characteristic features of tic douloureux that are clearly different from other neuropathic pains. First, paroxysmal electric shock–like pains with intervening pain-free intervals are pathognomonic for tic douloureux. The paroxysms may be followed by a lingering soreness, but absence of pain in the absence of paroxysms is usually a very clear feature of the disease. Paroxysmal pain is sometimes seen in PHN patients, but in this case the patients also have a more or less continuous background pain that they describe as burning or aching. Second, at least some tic

douloureux patients have a refractory period, ie, an interval of seconds to minutes after a paroxysm or brief series of paroxysms during which triggering stimuli fail to launch another paroxysm.[31] The refractory period seems similar to the postictal refractory seen in stimulus-evocable epilepsies. To my knowledge, a postictal refractory period has never been described for any other type of neuropathic pain. Third, at least some tic douloureux patients have referred paroxysmal pain, ie, triggering stimulation in 1 location evokes pain in a distant location, with no pain felt in the intervening region.[31] This has never been described for any other kind of neuropathic pain. Fourth, tic douloureux sometimes remits for weeks, months, or years. This never occurs with any other kind of neuropathic pain. Fifth and finally, many tic douloureux patients obtain excellent pain relief with carbamazepine (Tegretol).[29] Carbamazepine is rarely very effective in other kinds of neuropathic pain.

The success of decompression surgery in the treatment of tic douloureux leads considerable credence to the idea that the nerve injury occurs because of mechanical irritation where the nerve exits the skull. A recent electron microscopic study of trigeminal root biopsies taken during decompression surgery has supported this hypothesis, although the absence of normal tissue for comparison makes interpretation difficult.[32] The presence of demyelination, abnormal myelination, axonal debris, and excess collagen in the biopsies are what would be expected of an accumulating injury burden from repetitive mechanical irritation. Demyelinated and axotomized afferent neurons would be expected to be hyperexcitable, such that they would discharge in an epileptiform way when the ionic composition of their microenvironment was disturbed by the passage of normal nerve impulse traffic. This possibility has been referred to as the "ignition" hypothesis.[33] If applicable to neurons, it could account for many of the unique characteristics of tic douloureux.

There is no animal model of tic douloureux. Although it is technically feasible to create a demyelinating lesion of the rat's trigeminal root, it is not obvious how one would recognize paroxysmal pain in an animal. It seems likely therefore that improvements in our understanding of this condition will rely heavily on clinical observations.

References

1. Bennett GJ. Neuropathic pain. In: Wall PD, Melzack R (eds). Textbook of Pain, ed 3. Edinburgh: Churchill Livingstone, 1994:201–224.
2. Oaklander AL, Cohen SP, Raju SV. Intractable postherpetic itch and cutaneous deafferentation after facial shingles. Pain 2002;96:9–12.
3. Watson CPN. Herpes Zoster and Postherpetic Neuralgia. Amsterdam: Elsevier, 1993.
4. Watson CP, Morshead C, Van der Kooy D, Deck J, Evans RJ. Post-herpetic neuralgia: Postmortem analysis of a case. Pain 1988;34:129–138.
5. Bennett GJ. Hypotheses on the pathogenesis of herpes zoster-associated pain. Ann Neurol 1994;35(suppl):S38–S41.
6. Dworkin RH, Portenoy RK. Pain and its persistence in herpes zoster. Pain 1996;67:241–251.
7. Head H, Campbell AW. The pathology of herpes zoster and its bearing on sensory location. Brain 1900;22: 353–529.
8. Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. Neurobiol Dis 1998;5:209–227.
9. Oaklander AL, Romans K, Horasek S, Stocks A, Hauer P, Meyer RA. Unilateral postherpetic neuralgia is associated with bilateral sensory neuron damage. Ann Neurol 1998; 44:789–795.
10. Pappagallo M, Oaklander AL, Quatrano-Piacentini AL, Clark MR, Raja SN. Heterogenous patterns of sensory dysfunction in postherpetic neuralgia suggest multiple pathophysiologic mechanisms. Anesthesiology 2000;92: 691–698.
11. Kress M, Fickenscher H. Infection by human varicella-zoster virus confers norepinephrine sensitivity to sensory neurons from rat dorsal root ganglia. FASEB J 2001; 15:1037–1043.
12. Fleetwood-Walker SM, Quinn JP, Wallace C, et al. Behavioral changes in the rat following infection with varicella-zoster virus. J Gen Virol 1999;80:2433–2436.
13. Zakrzewska JM. Classification issues related to neuropathic trigeminal pain. J Orofac Pain 2004;18:325–331.
14. Jääaskeläinen SK. The utility of clinical neurophysiological and quantitative sensory testing for trigeminal neuropathy. J Orofac Pain 2004;18:355–359.
15. Eliav E, Gracely RH, Nahlieli O, Benoliel R. Quantitative sensory testing in trigeminal nerve damage assessment. J Orofac Pain 2004;18:339–344.
16. Essick GK. Psychophical assessment of patients with post-traumatic neuropathic trigeminal pain. J Orofac Pain 2004;18:345–354.
17. Robinson PP, Boissonade FM, Loescher AR, et al. Peripheral mechanisms for the initiation of pain following trigeminal nerve injury. J Orofac Pain 2004;18:287–292.
18. Marbach JJ, Hulbrock J, Hohn C, Segal AG. Incidence of phantom tooth pain: An atypical facial neuralgia. Oral Surg Oral Med Oral Pathol 1982;53:190–193.
19. Jacobs R, De Geyseler C, Van Loven K, De Laat A. Appearance of painful or non-painful phantom tooth after tooth extraction [abstract]. J Dent Res 1998;77:1008.
20. Dubner R, Ren K. Brainstem mechanisms of persistent pain following injury. J Orofac Pain 2004;18:299–305.
21. Iwata K, Tsuboi Y, Shima A, et al. Central neuronal changes after nerve injury: Neuroplastic influences of injury and aging. J Orofac Pain 2004;18: 293–298.

22. Vos BP, Hans G, Adriaensen H. Behavioral assessment of facial pain in rats: face grooming patterns after painful and non-painful sensory disturbances in the territory of the rat's infraorbital nerve. Pain 1998;76:173–178.
23. Vos BP, Strassman AM, Maciewicz RJ. Behavioral evidence of trigeminal neuropathic pain following chronic constriction injury to the rat's infraorbital nerve. J Neurosci 1994;14:2708–2723.
24. Imamura Y, Kawamoto H, Nakanishi O. Characterization of heat-hyperalgesia in an experimental trigeminal neuropathy in rats. Exp Brain Res 1997;116:97–103.
25. Devor M, Seltzer Z. Pathophysiology of damaged nerves in relation to chronic pain. In: Wall PD, Melzack R (eds). Textbook of Pain, ed 4. Edinburgh: Churchill Livingstone, 1999:129–164.
26. Tal M, Devor M. Ectopic discharge in injured nerves: Comparison of trigeminal and somatic afferents. Brain Res 1992;579:148–151.
27. Jänig W. CRPS-I and CRPS-II: A strategic view. In: Harden RN, Baron R, Jänig W (eds). Complex Regional Pain Syndrome. Seattle: IASP Press, 2001:3–15.
28. Watkins LR, Maier SF. Beyond neurons: Evidence that immune and glial cells contribute to pathological pain states. Physiol Rev 2002;82:981–1011.
29. Watson CPN. Management issues of nerve damage and neuropathic trigeminal pain from a medical perspective. J Orofac Pain 2004;18:366–373.
30. Stookey B, Ransohoff J. Trigeminal neuralgia: Its history and treatment. Springfield, IL: Charles C. Thomas, 1959.
31. Dubner R, Sharav Y, Gracely RH, Price DD. Idiopathic trigeminal neuralgia: Sensory features and pain mechanisms. Pain 1987;31:23–33.
32. Devor M, Govrin-Lippmann R, Rappaport ZH. Mechanism of trigeminal neuralgia: An ultrastructural analysis of trigeminal root specimens obtained during microvascular decompression surgery. J Neurosurg 2002;96:532–543.
33. Devor M, Amir R, Rappaport ZH. Pathophysiology of trigeminal neuralgia: The ignition hypothesis. Clin J Pain 2002;18:4–13.