

Plenary Session on Headache

Comparison of trigeminal with postherpetic neuralgia

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Although postherpetic neuralgia and trigeminal neuralgia (tic douloureux) are common causes of facial pain, they have very little in common aside from lancinating pain (other qualities of pain in each disorder are different). Each disorder affects different areas of the face and the treatment of each is quite dissimilar. The pathogenesis of these two disorders quite likely involves different mechanisms. This report reviews aspects of these two difficult pain problems, particularly with reference to the work of the late Gerhard Fromm, to whom this is dedicated.

Key Words: *Facial pain, Postherpetic neuralgia, Trigeminal neuralgia*

Comparaison de la névralgie essentielle du trijumeau avec la névralgie postherpétique

RÉSUMÉ : Bien que la névralgie postherpétique et la névralgie essentielle du trijumeau (tic douloureux) soient des causes courantes de douleur faciale, elles ont très peu en commun si ce n'est une douleur lancinante (les autres types de douleur associés à chacune des affections diffèrent). Ces dernières touchent des endroits différents du visage et, par conséquent, requièrent un traitement différent. Leur pathogenèse implique probablement des mécanismes d'action différents. Le présent article passe en revue les caractéristiques de ces deux affections douloureuses complexes, en faisant particulièrement référence aux travaux du défunt Gerhard Fromm, à qui cet article est dédié.

The focus of this report is to compare two of the most common and most treatable types of facial pain: trigeminal neuralgia and postherpetic neuralgia. Doing this raises more questions than answers, but the questions are intriguing. Trigeminal neuralgia has been recognized for centuries; it is a stereotypical facial pain with a well worked out therapy. It is of particular interest because it appears (along with other, rarer cranial neuralgias such as glossopharyngeal neuralgia) to be unique to the face and head area, as are, for example, migraine and cluster headache. Postherpetic neuralgia is much more like nerve injury pain elsewhere in the body, both clinically and in its pharmacological response. Although postherpetic neuralgia has its own idiosyncrasies, it provides a good clinical model both for the investigation of neuropathic pain generally, and in the search for better therapies,

eg, for painful diabetic neuropathy, causalgia and some cases of the failed back syndrome. For comprehensive information on trigeminal neuralgia and postherpetic neuralgia, the reader is referred to recent books devoted to these conditions (1,2).

The differences between trigeminal neuralgia and postherpetic neuralgia are striking, particularly from a neuropharmacological point of view. These two disorders are the most easily treatable of facial neuropathic pain disorders, but by different means (surgical for trigeminal neuralgia and medical for postherpetic neuralgia). If we can find the reasons for these differences, we will come to a greater understanding of the trigeminal system, its disorders and their treatment.

Some trigeminal neuropathic pain syndromes are listed in Table 1. The really difficult problems are post-traumatic neural-

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TABLE 1
Some trigeminal neuropathic pain syndromes

Trigeminal neuralgia
Postherpetic neuralgia
Post-traumatic neuralgia
Anesthesia dolorosa
Atypical facial pain
Tumour, aneurysm

gia, anesthesia dolorosa and atypical facial pain. Although brain tumour and aneurysm can result in facial pain they are uncommon; however, they should be considered and relief may be provided by surgical decompression.

TRIGEMINAL NEURALGIA

Trigeminal neuralgia is unique to the head area. Its precise symptoms are not seen elsewhere in the body, and the marked success of carbamazepine and surgery is not seen in other neuropathic pain syndromes. The incidence of trigeminal neuralgia increases with age and is more common in females than males (3:2). It generally affects the lower face, ie, the face innervated by the second and third divisions of the trigeminal nerve. It is more right-sided than left-sided (2:1) and tends to be unilateral. The pain of trigeminal neuralgia is like an electric shock, is usually extremely severe and occurs in paroxysms with pain-free periods. It is classically triggered by very light tactile stimulation over a very small area of the skin (often around the nasolabial region). Because this intense pain is often accompanied by wincing, the French have called the disorder 'tic douloureux'. Sensory loss has been reported in trigeminal neuralgia by some authors (3-5). Patient selection in those studies has been questioned, and one study (6) found no such loss on quantitative sensory examination. Most cases do not have sensory loss on ordinary clinical examination, and its presence should encourage a thorough investigation for a structural lesion such as a neoplasm.

Many disorders affect the trigeminal nerve root and may give rise to trigeminal neuralgia. Sometimes disorders affect the peripheral nerve distal to the ganglion, such as dental disease, but many conditions – and probably the most common cause of trigeminal neuralgia – involve compression of the nerve root. This may be one reason that the condition is unique. The varied causes include multiple sclerosis, which is classically associated with trigeminal neuralgia, and the phenomenon of vascular loops compressing the nerve root, which is thought by many (7-30) to be the cause of most trigeminal neuralgia. Relief of this compression is reported to have a high success rate. Other disorders, such as vascular anomalies, tumours and dental disease presumably injuring the peripheral nerve, can result in this syndrome. This has led to a hypothesis that the disorder has a peripheral cause and a central pathogenesis.

Treatment is quite standardized. The most successful treatment is carbamazepine, which relieves bouts of severe pain in upwards of 80% of patients and which can be introduced and

withdrawn according to the disorder's fluctuating natural history in order to control pain. Other drugs that have been suggested as useful are baclofen, phenytoin, clonazepam and valproic acid. Generally speaking, though, when carbamazepine fails, usually the condition is a problem to manage from a medical point of view. One can try combinations of carbamazepine with baclofen or phenytoin, or each drug alone.

Surgery has a high success rate for this disorder and ranges from simple procedures, such as radiofrequency lesions in the trigeminal ganglion and glycerol instillation in Meckel's cave, to larger procedures involving a craniotomy and decompression of the root of the fifth nerve. The peripheral simple procedures are useful in the elderly because they have low morbidity and mortality; however, there is a small risk of anesthesia dolorosa, which can be very difficult to treat, and this risk should be clearly explained to the patient. Decompression of the root of the fifth nerve is probably more suitable for younger patients who have a lower surgical risk because the morbidity and mortality is higher with this more extensive operation. All these procedures have a high success rate of probably 80% or greater. The trigeminal decompression operation seldom results in anesthesia dolorosa. Features that may make trigeminal neuralgia unique are that it often appears to be caused by minor injury and that its location is proximal to the gasserian ganglion.

POSTHERPETIC NEURALGIA

Postherpetic neuralgia begins with varicella (chickenpox), which is ubiquitous in the young and very contagious – nearly all children are exposed and infected by this virus. It can be very mild or very severe and tends to have a centripetal distribution, which may account for the fact that herpes zoster (following varicella) and postherpetic neuralgia most commonly affect the central areas of the body such as the forehead and midthoracic region. After varicella, the virus travels from the skin up sensory nerves and resides in the sensory ganglia where it remains dormant for many years until, with increasing age and presumably declining immune surveillance, it re-erupts. The organism then moves in a retrograde fashion down the nerve to re-erupt in a segmental distribution according to the dermatome supplied by the ganglion afflicted. It may also travel proximally into the spinal cord and cause an inflammatory myelopathy. The rash begins as vesicles that may coalesce on an erythematous base. They then become encrusted and pustular; the crusts fall off in three to four weeks, leaving shiny, reddened, scarred skin. The erythematous nature of this gradually fades and the scars may be pigmented, but in many cases they are very pale and can be difficult to see.

Patients usually experience both a steady, often burning, pain as well as lancinating, brief pain. Both these phenomena may be aggravated by light tactile contact with the skin. Most cases of postherpetic neuralgia are accompanied by scarring and by sensory loss, which usually involves the scarred areas, and by the curious paradox of anesthetic skin, which may be hyperesthetic, dysesthetic or may exhibit allodynia (pain from tactile stimulation of the skin) (Figure 1) (31). The allodynia may be over a much wider area than the scarring and may encompass several dermatomes above and below the scars. The scarred areas, although anesthetic, may be sensitive. This puzzling phenomenon

occurs because the allodynia is induced by stimuli that produce a summation effect, so that although stimulating a small area with a tactile stimulus or with a pin is anesthetic, by stroking the skin or picking it up between thumb and forefinger (the latter being, in the author's view, the best way of demonstrating this) a severe, usually steady pain will be provoked.

This allodynia is very different from the type seen in trigeminal neuralgia. The explanation for this phenomenon probably lies with changes in spinal second-order sensory neurones which have expanded their receptive fields by the activation of latent connections with other dermatomes above and below that level. With the summation of multiple stimuli, suddenly the threshold is exceeded and the neurone transmits pain in place of a non-noxious sensation, so that instead of going through a gradual progression from light touch or tickle and then pressure through discomfort to pain, there is either nothing or extreme pain experienced. The propensity for postherpetic neuralgia to affect the trigeminal dermatomes and thoracic area is inexplicable except to reflect perhaps the centripetal distribution of varicella. The frequent involvement of the forehead is also unexplained.

A widely used definition of postherpetic neuralgia is persistent neuropathic pain one month or more following herpes zoster in similar dermatomes. This is an arbitrary definition because it is not clear when the pain of acute herpes zoster becomes the pain of postherpetic neuralgia. If one is studying herpes zoster pain it is probably more useful to lump it together and call it zoster-associated pain. If one is studying postherpetic neuralgia, it is more helpful to choose an arbitrary period such as three to six months after the rash because the pain then is more stable and fewer patients are required for a controlled trial, particularly of a crossover type. This definition of postherpetic neuralgia also helps one to interpret the literature because there are many putative therapies, all of which, if they are uncontrolled, look very good because of the natural history of the condition (overall, 90% of individuals affected with herpes zoster are free from significant pain one month later). The pain of postherpetic neuralgia has three aspects: a constant, steady, usually burning pain; a paroxysmal, lancinating shock-like pain; and the aforementioned skin sensitivity. All these three types of pain should be addressed when taking a history. The incidence of postherpetic neuralgia increases with age so that if one is, for example, 60 years old the chance of severe pain one month after the rash rises to 50% and increases thereafter with each decade (32).

Knowledge about the pathology of postherpetic neuralgia is based on only a few cases (33,34). We know that the hemorrhagic inflammation of herpes zoster usually heals to form a scar in the sensory ganglion. Whether there are sensitive neurones with ectopic discharges in this location is unknown. The balance of nerve fibres in the peripheral nerve changes in this condition so that there becomes a preponderance of small myelinated and unmyelinated fibres and a loss of large myelinated fibres (33,34). This finding has some theoretical importance in terms of the gate control theory because small fibres are excitatory and large fibres are inhibitory to dorsal horn neurones. It is also known from several pathological cases that there is atrophy of the dorsal horn of the spinal cord on the affected side (33,34). One may hypothesize that hypersensitive, de-afferented neurones with expanded

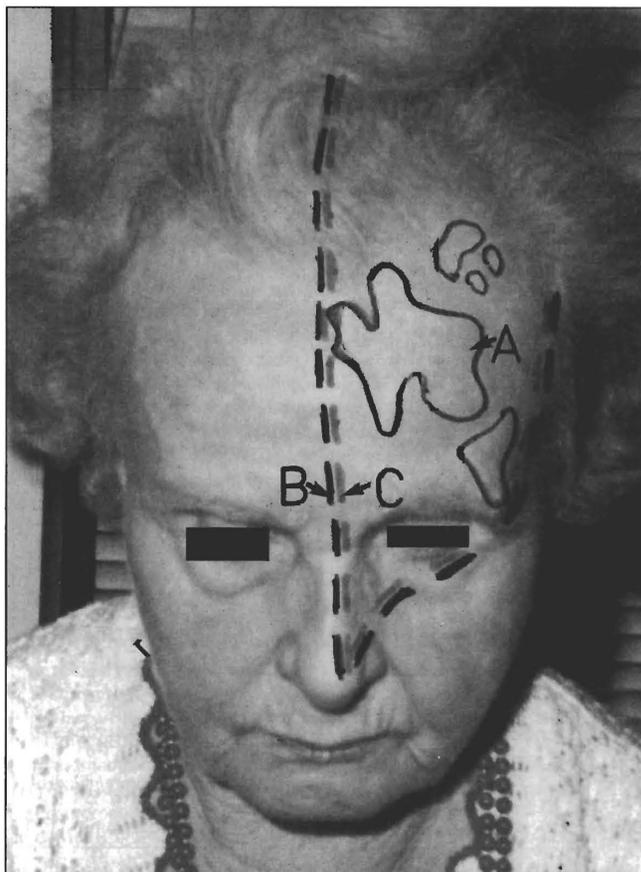


Figure 1) Photograph showing key regions in postherpetic neuralgia. **A** Scarred areas; **B** Area of sensory loss; **C** Area of allodynia

receptive fields are in this area. Following from there, the pathogenesis of postherpetic neuralgia may be seen as a change in the peripheral input from a shift to a larger proportion of excitatory input and loss of inhibition with possibly ectopic generators, to a disordered, damaged spinal cord where there may be hypersensitive, de-afferented neurones with expanded receptive fields and raised thresholds. Some pathological cases of long-standing pain (of one year) have ongoing inflammation, and postherpetic neuralgia seems to follow a progressive course in about 20% of patients, which raises the possibility that there may be an ongoing progressive inflammatory disorder in some cases (34). This has therapeutic implications and further studies are needed.

It is very important to understand the concept of antidepressant analgesia in postherpetic neuralgia treatment because antidepressants are the standard therapy for this condition. Controlled trials in a variety of conditions, such as headache, arthritis, fibrositis, diabetic neuropathy and postherpetic neuralgia, have shown that the older antidepressant drugs have an independent analgesic action that is separate from the antidepressant effect (35). This effect occurs at low doses and involves antidepressants that potentiate both serotonin and noradrenaline (amitriptyline), and the selective noradrenergic ones (nortriptyline, desipramine, maprotiline). The selective serotonergic drugs do not seem effective for most patients. As mentioned, about 30% of patients with postherpetic neuralgia are completely refractory to treatment; one solution may be prevention of postherpetic neuralgia through

TABLE 2
Differences between postherpetic neuralgia and trigeminal neuralgia

	Postherpetic neuralgia	Trigeminal neuralgia
Clinical	Major injury V1	Minor injury V2, V3
	Non-noxious (tactile) trigger in painful area	Localized tactile trigger areas in or out of pain area
	Shock-like pain, steady pain, skin sensitivity	Shock-like pain
	Hyperesthesia, dysesthesia, allodynia	
	Allodynia is steady pain	Allodynia is shock-like pain
	Sensory loss	No or little sensory loss (?25-40%)*
	No pain-free intervals	Pain-free intervals
Pathology	Damage to dorsal horn, nerve root, nerve and spinal cord	Demyelination at nerve root
Surgery	Some relief in up to 50% of patients with DREZ lesions	1) Decompression of vessel loops 2) Radiofrequency/glycerol
Drugs	Amitriptyline, capsaicin	Carbamazepine

*Based on references 3 and 5. DREZ Dorsal root entry zone lesions

vaccination of children and the elderly to boost immune surveillance and prevent varicella and herpes zoster. Early aggressive treatment of herpes zoster with antiviral agents (such as acyclovir), analgesics (involving narcotics if necessary), possibly early antidepressant therapy and nerve blocks may also be important. All these treatments are relatively unproven except for a modest effect from antiviral agents. The newer antiviral agents famciclovir and valacyclovir may prove more effective in preventing this condition.

DIFFERENCES AND SIMILARITIES BETWEEN TRIGEMINAL AND POSTHERPETIC NEURALGIA

There are far more differences (Table 2) than similarities between trigeminal and postherpetic neuralgia. Certainly the pain is shock-like in trigeminal neuralgia and electric shock-like pain is often a component of postherpetic neuralgia, but these pains are really not similar, as will be discussed below. The key similarity is that both disorders occur with increasing frequency with increasing age (36), which may be due to the decline in inhibitory axo-axonic synapses that occurs with increasing age (1).

The differences between trigeminal and postherpetic neuralgia are much more striking (Table 2). Postherpetic neuralgia occurs with major injury to ganglion, nerve, nerve root and spinal cord. Trigeminal neuralgia occurs with presumed minor injury to the nerve root. Postherpetic neuralgia affects the first division of the trigeminal nerve while trigeminal neuralgia affects the lower

face. The difference in the allodynia of the two conditions has already been discussed. In postherpetic neuralgia non-noxious stimulation certainly produces pain, but the stimulation has to be over a wider area and it usually produces a steady burning pain. Very localized areas in trigeminal neuralgia trigger pain with very light tactile stimulation producing a shock-like pain. Sensory loss is present in postherpetic neuralgia but is usually absent in trigeminal neuralgia, probably reflecting the more minor nature of the injury. There are no pain-free intervals in postherpetic neuralgia whereas they occur in trigeminal neuralgia. The pathology is much more extensive in postherpetic neuralgia and may consist of just demyelination of the nerve root in trigeminal neuralgia.

Surgery has generally been abandoned for postherpetic neuralgia whereas it plays a major role in refractory cases of trigeminal neuralgia. Pharmacological treatment of each disorder is very different, with amitriptyline being the standard therapy for postherpetic neuralgia and carbamazepine for trigeminal neuralgia. Overall, about 80% or more of trigeminal neuralgia patients find relief with carbamazepine whereas there is no effect from opioids or amitriptyline. About 60% of postherpetic neuralgia patients respond to amitriptyline and there is a modest opioid effect. Trigeminal neuralgia seems to be completely resistant to narcotics, but postherpetic neuralgia is only partially resistant to these agents and some patients only obtain relief by their use.

These pharmacological differences led Gerhard Fromm to study the effect of these drugs, and because he found that amitriptyline inhibited wide-dynamic range neurones in the nucleus caudalis of the trigeminal system, he postulated that postherpetic neuralgia was a disorder affecting excessive excitation of these neurones (36). He found that carbamazepine reduced the excitation of low threshold mechanoreceptive neurones in the nucleus oralis of the trigeminal system and enhanced its segmental inhibition. He, therefore, postulated that trigeminal neuralgia was a disorder of low threshold mechanoreceptive neurones in this area, which led secondarily to excessive excitation of the wide-dynamic range neurones.

CONCLUSIONS

Trigeminal neuralgia and postherpetic neuralgia may occupy opposite ends of the spectrum of neuropathic facial pain, and the different syndromes may depend upon the different location and severity of the insult to the nerve. Probably both disorders result in reduced inhibition and excess excitation to hyperactive, damaged, central neurones in the nucleus of the trigeminal nerve. Clinical and pharmacological differences point to different pain mechanisms and require further elucidation. For more information about trigeminal neuralgia and postherpetic neuralgia, the interested reader is referred to the books referenced (1,2).

DEDICATION: This paper is dedicated to the memory of Gerhard Fromm, Professor of Neurology at the University of Pittsburgh, who died prematurely in late 1993. Dr Kim Burchiel has said of him, "Much basic investigation (of trigeminal neuralgia) has come from Dr Fromm's work. He should be congratulated for his contributions and his continued efforts to bring basic science to bear on clinical practice in this important area."

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