

Pain Management: Trigeminal Neuralgia

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The International Association for the Study of Pain defines trigeminal neuralgia as sudden, recurrent, severe pain in the distribution of one or more of the branches of the fifth cranial nerve.¹

Although compression of the nerve root is the most common reported cause of the disorder, most cases are idiopathic. The pain can be triggered by talking, brushing teeth, touching the face, chewing, or swallowing. An episode generally lasts only a few seconds, but several episodes may follow each other in quick succession. Episodes can occur at various times throughout a given day and can occur relatively frequently for a period of days to months. However, pain-free periods may also last for several months or possibly years. This article reviews anatomic considerations relevant to the trigeminal nerve and characteristics of trigeminal neuralgia. The diagnosis and treatment of this disorder are also discussed.

HISTORICAL PERSPECTIVE

Trigeminal neuralgia has long been recognized in the medical literature; in fact, it was described as early as the first century AD in the writings of Aretaeus.² It was later discussed by Johannes Bausch in 1672.³ Nicolas Andre, in 1756, used the term *tic douloureux* ("painful spasm") to describe the disorder.³ Fothergill provided a vivid description of trigeminal neuralgia in 1773.³ Early treatments included bloodletting and the application of bandages containing arsenic, mercury, hemlock, cobra and bee venom, and other poisons.³

ANATOMIC AND FUNCTIONAL CONSIDERATIONS

The trigeminal nerve is the largest sensory cranial nerve. It also contains some motor fibers. There is a trigeminal nerve on either side of the head. The principal function of the nerve is to carry information relating to light touch, temperature, pain, and proprioception from the face and head to the brain.

Sensory Fibers

The sensory fibers arise from the gasserian ganglion (lying near the petrous part of the temporal bone in

the dura matter), pass backward, enter the pons, and divide into upper and lower roots. The upper roots end in the principal or superior sensory nucleus and locus caeruleus. The lower roots descend through the pons and medulla and terminate in the spinal tract nucleus, which consists of subnucleus caudalis, subnucleus interpolaris, and subnucleus oralis. The subnucleus caudalis serves as the principal brainstem relay site for orofacial pain, and the superior sensory nucleus and subnucleus oralis are sites relaying orofacial tactile information.

Cutaneous nociceptive neurons predominate in laminae I, II, V, and VI of the spinal cord. Electrophysiologic studies indicate that many of the nociceptive neurons in these laminae of the spinal dorsal horn have axons that project directly to the thalamus via the spinothalamic tract.⁴ Likewise, nociceptive neurons in each part of the trigeminal brainstem complex have axons that project directly or indirectly (via the reticular formation) to the thalamus. Neurons similar to the dorsal horn nociceptive neurons (ie, with axons extending to the thalamus) are found in the subnucleus caudalis; the subnucleus caudalis has many features in common with the spinal dorsal horn, including its layered appearance and cell types.

The response properties of cutaneous nociceptive neurons have been classified into 2 main groups: (1) high-threshold or nociceptive-specific neurons, which respond exclusively to noxious tactile stimuli such as a pinch or heat; and (2) wide dynamic-range neurons, which are excited by noxious and non-noxious tactile stimuli. Many nociceptive neurons in the subnucleus caudalis not only respond to noxious stimulation of the

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orofacial tissues (including tooth pulp) but also can be excited by noxious mechanical or chemical stimulation of the temporomandibular joint, dura mater, and afferent nerves of the jaw, tongue, and neck muscles.

Low-threshold mechanoreceptive neurons do not respond to noxious tactile stimuli; they are activated by light tactile stimuli applied to skin, mucosa, or teeth. These neurons are found mostly in laminae III and IV of the spinal cord and are similar to neurons in the superior sensory nucleus.

Motor Fibers

The motor fibers arise from superior and inferior nuclei. The motor fibers arising from the superior nucleus, also called *mesocephalic roots*, join with the motor fibers arising from the lower nucleus, and together they form the motor part of the trigeminal nerve. This part of the nerve joins with the sensory root as it emerges from the side of the pons.

Principal Divisions of the Trigeminal Nerve

There are 3 main branches to the trigeminal nerve. The ophthalmic nerve (V_1) is the smallest division, containing only sensory fibers. It supplies branches to the cornea, ciliary body, iris, lacrimal gland, conjunctiva, skin of the eyelid, eyebrows, forehead, and nose. The maxillary nerve (V_2) is intermediate in size and is also sensory in nature. It supplies branches to the side of the nose, upper eyelid, and upper lip. The mandibular nerve (V_3) is the largest branch and contains both sensory and motor fibers. It supplies branches to the teeth, gums, skin of the temporal region, lower lip, lower part of the face, and muscles of mastication.

Pain is usually referred to a main division of the trigeminal nerve, but in some cases, it may be felt over the distribution of more than one division. For example, pain associated with dental caries of the mandible may be felt in the ear. Pain associated with ulcers of the tongue may be experienced over the temporal fossa and ears.

EPIDEMIOLOGY

Trigeminal neuralgia is rare and thus statistical data regarding it scant. Early literature suggested a strong preponderance in women; however, current data indicate that only approximately 60% of patients with trigeminal neuralgia are female.³ The annual incidence for women is approximately 5.9 cases per 100,000 women; for men, it is approximately 3.4 cases per 100,000 men.⁵ Incidence increases with age. Although peak onset occurs between age 50 and 70 years, the disorder can also occur in children. The youngest child reported to have trigeminal

neuralgia was approximately age 12 months⁶; other children between age 3 and 11 years have also experienced the condition.⁶ No known racial or ethnic risk factors exist. Patients with multiple sclerosis may develop trigeminal neuralgia as a secondary symptom. However, this occurrence is relatively rare, involving only approximately 1% of patients with multiple sclerosis.⁷

ETIOLOGY

Although several hypotheses have been put forth, the causes of trigeminal neuralgia have not been fully explained in the literature. For most patients, the cause is unknown.^{8,9} The most common reported cause of trigeminal neuralgia is compression of the nerve root.^{10–12} Mechanical compression of the trigeminal nerve can occur as the nerve leaves the pons and traverses the subarachnoid space toward Meckel's cave. Most commonly, the nerve is compressed by a major artery, usually the superior cerebellar artery. When pain is felt in the second or third division of the trigeminal nerve, the usual finding is compression of the rostral and anterior portion of the nerve by the superior cerebellar artery; if the pain is felt in the distribution of the ophthalmic division, the usual finding is compression of the nerve by the anterior inferior cerebellar artery. Moreover, it has been postulated that compression of the trigeminal nerve by tumors and other blood vessels can lead to the disorder.^{13–16} However, tumors, veins, and arteriovenous malformations are rarely involved in compression.

Also, damage to the myelin sheath can cause trigeminal pain. This type of damage typically occurs in connection with multiple sclerosis.^{17,18} Normally, different nerves transmit different sensations (eg, pain, heat). The myelin sheath of the nerves isolates the nerves from each other. If the myelin sheath is damaged, different signals blend together, and thus, the brain may interpret the sensation caused by a light touch as pain. Because demyelination plaques are common findings on autopsy of patients with multiple sclerosis—even of those who did not have trigeminal neuralgia—questions have been raised as to whether damage to the myelin sheath is a cause or an incidental finding in patients with trigeminal neuralgia and multiple sclerosis.

Traumatic accidents, unsuccessful dental work, and various infections can damage the trigeminal nerve. It is hypothesized that trigeminal neuralgia is caused by foci of abscesses and bone resorption with irritation of the trigeminal nerve in the maxilla or mandible. The varicella virus, which causes herpes zoster, can sometimes also cause intense pain in the trigeminal area that is particularly difficult to treat.

PATHOGENESIS

Several theories exist explaining the pathogenesis of trigeminal neuralgia; however none of the theories explain the process completely. Theories regarding pathogenesis may ultimately be classified as either *central* or *peripheral*.³ Central theories are based on the similarity of trigeminal neuralgia to focal epilepsy and emphasize the role of deafferentation (secondary to compression of the trigeminal roots or ganglion) in the genesis of neural hyperactivity. Peripheral theories note that changes in peripheral axons and myelin may lead to altered nerve sensitivity to chemical and mechanical stimuli.

Calvin concluded that both central and peripheral mechanisms are required to produce clinical trigeminal neuralgia.¹⁹ For example, if compression occurs at the root entry zone (ie, the area where the nerve enters the pontine brain stem), the pressure on the nerve may cause a breakdown of myelin, resulting in abnormal depolarization, ectopic impulses, and pain. Fromm proposed that the process begins with a peripheral nerve lesion, which then leads to central synaptic changes; the response of the central synapses to altered peripheral events set the stage for trigeminal neuralgia.²⁰ Patients with multiple sclerosis who also have trigeminal neuralgia often have demyelination in the roots of the trigeminal nerve, as seen during surgery or at autopsy. Some of these patients may also have compression of the gasserian ganglion by small blood vessels.

CLINICAL FEATURES

With respect to classic trigeminal neuralgia, the pain occurs in short spasmodic episodes, often described as being similar to electric shocks. A typical attack lasts only a few seconds. However, subsequent attacks can follow within minutes.

At its worst, the pain is completely paralyzing. It usually seems very localized within the area of the trigeminal nerve and does not radiate into other areas. The pain almost always affects only one side of the face. The area of the face affected reflects the branch of the trigeminal nerve that is involved.

Trigger points, or areas of the face that with light pressure will trigger a pain attack, are a characteristic feature of trigeminal neuralgia. Such points may be located on the lips, on the side of the jaw, underneath the eye, in the eyelid, or anywhere the trigeminal nerve reaches. There are several activities that can trigger an attack. Eating can become almost impossible, and loss of weight is common among those with the disorder. Shaving, applying make-up, and even talking can become difficult. In some cases, even a gust of wind can be enough to start an attack. An attack can also start without provocation.

Even without treatment, there can be periods of remission when pain is completely absent. These periods—which can last days, weeks, months, or even years—are unpredictable. However, without medical treatment, the pain usually returns.

Many patients with trigeminal neuralgia have symptoms that do not conform to those of classic trigeminal neuralgia. In addition to stabbing, shock-like pain, many patients experience pain that they describe as throbbing, burning, crushing, or pulsating. For some, there is no remission from the pain. These atypical forms of trigeminal neuralgia are often very difficult to treat.

DIAGNOSIS

No medical test exists that can be used to clearly diagnose all cases of trigeminal neuralgia.²¹ However, establishing the diagnosis is usually not difficult, especially in cases of classic trigeminal neuralgia in which the symptoms are clear and distinct. A thorough medical examination should be performed, and a history of symptoms should be obtained.

Medical tests should be performed to rule out any serious medical problems; these tests can include computed tomographic (CT) and magnetic resonance imaging (MRI) scans. Conventional MRI scans used to rule out the presence of a brain tumor or multiple sclerosis as a cause of a patient's facial pain are not, however, adequate to observe the trigeminal nerve or an associated blood vessel. Fortunately, an improved form of magnetic resonance neuroimaging now makes it possible to observe both the nerve and associated blood vessels. The technique, called *3-D volume acquisition*, is performed with contrast injection and uses thin cuts (ie, 0.8 mm) without gaps. This technique is similar to MRI angiography and venography.²² The trigeminal nerve is easily observed in the axial plane when the MRI series is centered at the midpoint of the fourth ventricle. To ensure adequate evaluation, the nerve should be observed on 3 adjacent cuts. Early studies indicate that when an offending vessel is present, it will be detected 80% of the time²; with continued technologic improvements, this percentage should increase.

TREATMENT

Initially, administration of anticonvulsant drugs was the treatment of choice for trigeminal neuralgia. There are now a variety of other effective treatments, both pharmacologic and surgical. However, none of them is a cure. In our experience, there are several factors that can affect a treatment plan, including the patient's age (child vs adult), life expectancy, associated medical and psychiatric conditions, compliance with medical therapy,

Table 1. Pharmacologic Treatments for Trigeminal Neuralgia

| Medication | Mechanisms of Action | Dosage | Common Adverse Effects |
|---------------|--|--|---|
| Carbamazepine | Slows recovery rate of voltage-gated sodium channels, modulates activated calcium channel activity, and activates descending inhibitory modulation system | 200 to 1200 mg daily in 2 divided doses | Nausea, drowsiness, fatigue, dizziness, memory problems, diplopia, nystagmus, liver dysfunction, and hematosuppression (rare) |
| Phenytoin | Possibly promotes sodium efflux from neurons | 300 to 500 mg daily | Nystagmus, ataxia, slurred speech, decreased coordination, mental confusion |
| Oxcarbazepine | Same as carbamazepine | 300 to 1800 mg daily in 2 divided doses | Decreased blood sodium level, dizziness, fatigue, headache, tremors, drowsiness, diminished concentration, diplopia, and stammering |
| Lamotrigine | Decreases repetitive firing of sodium channels by slowing the recovery rate of voltage-gated channels | 100 to 150 mg daily in 2 divided doses; starting dosage, 25 mg every other day for 6 to 8 days, with the dosage increased 25 to 50 mg every 1 to 2 weeks | Sleepiness, dizziness, headache, vertigo, rash, Stevens-Johnson syndrome |
| Gabapentin | Mechanism unknown but possibly includes blockage of voltage-gated calcium channels by binding to α_2/Δ subunit | 1200 to 3600 mg daily in 3 or 4 divided doses | Fatigue, somnolence, dizziness, ataxia, nystagmus, and tremor |
| Topiramate | Voltage-gated sodium channel blockage; potentiation of γ -aminobutyric acid activation receptor by nonbenzodiazepine, nonbarbiturate mechanisms; blockage of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate glutamate receptors; inhibition of high-voltage activated calcium channels; and inhibition of types II and IV carbonic anhydrase | 200 to 300 mg daily in 2 divided doses | Fatigue, nervousness, tremor, weight loss, and difficulty with concentration/attention |

and tolerability of adverse effects of drugs. Invasive procedures are usually reserved for those patients who are unable to obtain relief with medical management or who experience unacceptable adverse effects from the use of pharmacologic agents. **Table 1** lists several pharmacologic treatments and their mechanisms of action, dosages, and adverse effects.

Pharmacologic Treatments

Carbamazepine. Traditionally, carbamazepine, an anticonvulsant medication, has been used as a first-line drug for the treatment of trigeminal neuralgia.²³ In fact, some clinicians believe that if orofacial pain does not

respond to carbamazepine, then it is not trigeminal neuralgia pain. (We, however, do not endorse this concept.)

Carbamazepine use can lead to intolerable adverse effects involving the central nervous system. Adverse effects can include drowsiness, fatigue or extreme exhaustion, dizziness, nausea, and nystagmus. Problems with memory, vision (eg, diplopia), and other mental activities may occur. Also, patients taking the medication may develop liver dysfunction and, rarely, hematosuppression.²⁴ The nausea can often be partly controlled by taking the drug at mealtime. Diplopia and dizziness can be minimized with the use of a long-acting formulation of the drug (eg, Carbatrol, Tegretol XR).

Phenytoin. Phenytoin is the second treatment of choice for trigeminal neuralgia. If pain relief is not obtained after reaching adequate serum levels for 3 weeks, the drug should be discontinued because higher doses may lead to toxicity. The short-term efficacy rate is 60%; the efficacy rate decreases to 30% after 2 years.

Phenytoin is difficult to dose at high levels (eg, a single loading dose of 1000 mg) because the zero-order kinetics are reached at these high concentrations. Even a small increase beyond the dose at which zero-order kinetics are achieved may result in a large increase in serum drug concentration. The usual dose is 300 to 500 mg per day.

Oxcarbazepine. Oxcarbazepine is also an anticonvulsant drug. It is a 10-keto analogue of carbamazepine and is at least as effective. It has fewer drug interactions and causes the release of fewer catabolic enzymes than does carbamazepine. Only drug molecules free of catabolic enzymes will have therapeutic effects.

Lamotrigine. Lamotrigine is a relatively new anticonvulsant drug used in the treatment of partial and generalized seizures. Recent studies show lamotrigine treatment provided pain relief in patients with otherwise treatment-resistant trigeminal neuralgia, especially in those whose pain was not controlled by or who could not tolerate carbamazepine.^{25,26} Lamotrigine appears to have few serious adverse effects; the most common adverse effects are sleepiness, dizziness, headache, vertigo, and rash. Stevens-Johnson syndrome can occur in 1 in 10,000 patients taking lamotrigine.²⁷ Long-term studies have not yet been performed.

Gabapentin. Gabapentin is becoming increasingly popular as a treatment option for trigeminal neuralgia and has a relatively benign adverse-effect profile. In one study, 6 of 7 patients with multiple sclerosis and trigeminal neuralgia became free of pain, and the other patient experienced substantial relief. These effects were maintained for the year the patients were studied.²⁸

In another study, low-dose gabapentin proved effective when used as an adjunct to lamotrigine or carbamazepine in 11 patients with multiple sclerosis and trigeminal neuralgia.²⁹ The usual dose is 1200 to 3600 mg daily.

Topiramate. Topiramate is the newest drug to be evaluated for the treatment of trigeminal neuralgia. In one study, patients with multiple sclerosis and trigeminal neuralgia that was refractory to combination therapy with a variety of conventional treatments all became free of pain with topiramate therapy.³⁰ Doses ranged from 200 to 300 mg per day. One patient continued concomitant treatment with carbamazepine, but the other 4 patients were able to discontinue all other medications

taken for trigeminal neuralgia. Pain relief was maintained at the 6-month follow-up period.³⁰

Surgical Treatments

Surgical procedures are aimed at either destroying parts of nerve fibers or decompressing the trigeminal nerve to relieve pain. Percutaneous radiofrequency thermocoagulation of the gasserian ganglion involves using a high-frequency current to precisely heat tissue, so that A-delta and C-fiber nociceptors are preferentially destroyed. Under fluoroscopic guidance, an insulated needle is passed through the foramen ovale next to the gasserian ganglion, and the technique is then performed.^{31,32} The initial efficacy is approximately 90%, with 80% of tested patients remaining free of pain at 1 year and 50% remaining pain free at 5 years.³²

Risks include numbness, paresthesia, and anesthesia dolorosa. Corneal anesthesia may develop after lesioning of the ophthalmic division. Percutaneous destructive procedures are appropriate for the elderly and for those with poor medical conditions.

Microvascular decompression (MVD) of the posterior fossa is performed to relieve compression of the trigeminal nerve. The junction of the trigeminal nerve with the pons is explored during the procedure.^{33–35} Using microscopic techniques, blood vessels and tumors are identified and removed from direct contact with the nerve. The superior cerebellar, posterior inferior cerebellar, vertebral, and anterior inferior cerebellar arteries (or their small branches) are separated from the trigeminal nerve by a piece of Dacron fabric. Efficacy is reported to be 85% initially, and 80% at 5 years.³⁶ A review of the literature shows that the risk for perioperative mortality, serious morbidity (eg, stroke, hemorrhage, venous occlusion, myocardial infarction, hydrocephalus), permanent hearing loss, and facial palsy is higher after MVD than after percutaneous procedures.³⁷ The risks for these complications are higher still in patients who have an ecstasic (atherosclerotic) and a tortuous vertebrobasilar arterial tree. Although MVD is highly successful in treating the pain of trigeminal neuralgia and carries a relatively low risk of pain recurrence, dyesthesia, corneal analgesia, and trigeminal motor weakness, one should not overlook the perioperative risks associated with this or any surgical procedure, especially in the elderly.

Percutaneous microcompression of the gasserian ganglion involves passing a fine balloon catheter through the foramen ovale. Inflation of the balloon produces an ischemic or mechanical destruction of cells in the ganglion.³⁸ Of the surgical techniques, balloon compression is associated with the highest risk for postoperative motor trigeminal weakness. Balloon compression is the best

choice for patients who have ophthalmic nerve pain and who are not candidates for MVD.

In gamma knife irradiation, the radiation is aimed at the proximal nerve and root entry zone in the pons.^{39,40} The gamma knife projects 201 very fine beams of gamma rays (generated by radioactive cobalt) through the skull and brain. The dose of radiation along any one beam is too small to effect any change by itself, but when all 201 beams intersect, a very high dose of radiation can be administered with little or no radiation to surrounding tissue.⁴¹ Gamma knife irradiation has been shown to affect abnormal ephaptic transmission but not normal axonal conduction.

Other surgical techniques include glycerol injection behind the ganglion, which destroys small and large myelinated and unmyelinated fibers. Under fluoroscopic guidance, glycerol is injected into the cistern of Meckle's cave.

All available surgical procedures for trigeminal neuralgia have advantages and disadvantages. Unfortunately, although surgical treatment may initially be successful, trigeminal neuralgia may recur. When this happens, it is advisable to retry medical therapy, because drugs that were previously ineffective may become effective later.

Alternative Treatments

Proparacaine is a local anesthetic agent that anesthetizes the eye and possibly the nerves around it. Some uncontrolled studies have shown that anesthetic eye drops containing proparacaine can give short-term relief from some instances of trigeminal neuralgia pain.⁴² The treatment is usually effective if the pain is in the distribution of the ophthalmic division of the trigeminal nerve. Another study suggests that the treatment is almost certainly ineffective for the pain of classic trigeminal neuralgia.⁴³ Although otherwise relatively harmless, proparacaine can damage the eye if used extensively; thus, it cannot be considered a long-term treatment.

Capsaicin is not considered a standard treatment for trigeminal neuralgia; however, one article indicated that it may be effective for this condition.⁴⁴ The article alleges that using capsaicin to treat traumatic injury to the trigeminal nerve can result in significant, long-term pain reduction.

Laser treatment has also been used experimentally for trigeminal neuralgia. In a study, human subjects received irradiation of the skin overlying peripheral nerves with a helium-neon laser for 20 seconds to each selected site. This treatment was accompanied by irradiation of the skin overlying painful facial areas for 30 to 90 seconds. Control subjects received placebo treat-

ment. Laser or placebo therapy was repeated 3 times weekly for 10 weeks. Subjects in the experimental group exhibited a statistically significant reduction in the intensity and frequency of painful episodes.⁴⁵

CONCLUSION

Trigeminal neuralgia has long been recognized by medical professionals. However, it is still an enigmatic disorder, and its management remains controversial. Future multicenter, randomized, controlled trials may help establish curative therapies. **HP**

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