Review Article

Trigeminal Neuralgia

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Abstract

Trigeminal neuralgia (TN) is a recognized complication associated with trigeminal nerve. This case report describes a patient with classical unilateral TN. TN or tic douloureux is an idiopathic disorder and the most common cause of unilateral facial pain. There is no specific test to make a diagnosis of TN, and a clinical examination including assessment of cranial nerve function is mandatory. Magnetic resonance imaging can be useful in examining patients with neurological abnormalities. The various hypothesis on the pathogenesis of TN is discussed in the report. The current opinion is now in favor of a "neurovascular conflict:" an artery, most often a loop of the superior or anteroinferior cerebellar artery, has an offending contact with the trigeminal nerve root, which results in localized demyelination and ectopic triggering of neuronal discharges. This hypothesis is in agreement with the relief provided by antiepileptic drugs and is supported by recent neuroimaging data. Medical treatment (particularly carbamazepine) in these patients is very effective in controlling pain symptoms. For patients with continued pain, in spite of adequate medical treatment surgical options can be considered.

Keywords: *Magnetic resonance, neurovascular conflict, tic douloureux, trigeminal neuralgia*

Received: September, 2017.
Accepted: September, 2017.

Introduction

Classical trigeminal neuralgia (TN) is a chronic pain condition that was clinically recognized centuries ago. Nevertheless, the pathological mechanism(s) involved in the development of classical TN is still largely based on the theory of peripheral versus central nervous system origin. Limitations of both hypotheses are discussed.

Many TN patients suffer pain attacks for months or years before the condition is finally diagnosed.[1] This is unfortunate because the severe pain attacks in TN can have a devastating impact on patients.[2-4] A timely accurate diagnosis of TN is particularly important because a variety of specific treatments can greatly reduce – or totally eliminate – TN pain symptoms in most patients.[5,6] The dental medicine clinician is often the first to be consulted when patients experience these pain attacks and should be familiar with the syndrome to make an accurate diagnosis and initiate treatment.

TN, or "tic douloureux," is most easily recognized in medical practice as "a sudden, usually unilateral, brief stabbing recurrent pain in the distribution of one or more branches of the fifth cranial nerve."[7] TN may have no apparent cause (idiopathic, essential, or classic TN) or be secondary to major neurological disease (symptomatic TN). Symptomatic TN can be related to slowly growing tumors such as cholesteatomas, meningiomas, or neurinomas of the VIII nerve that compress the trigeminal nerve root near the dorsal root entry zone (REZ), or multiple sclerosis (MS), which is typically associated with TN.[8-10] Many investigators refute the term "idiopathic TN" because they support the view that, when no lesion affecting the trigeminal system can be demonstrated, TN is due to a vascular compression of the trigeminal nerve root by tortuous or aberrant vessels. Microsurgical interventions in the posterior fossa always find a compressing vessel, most often the superior cerebellar artery. Further support for this view comes from magnetic resonance imaging (MRI) studies reporting a frequent contact between vessels and the trigeminal root.[11]

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Access this article online

Quick Response Code:

Website: www.ijofb.org

DOI: 10.4103/ijofb.ijofb_13_17

How to cite this article: Taltia AA. Trigeminal neuralgia. Int J Orofac Biol 2017;1:48-52.

Diagnosis of trigeminal neuralgia

TN diagnosis is based primarily on the person's history and description of symptoms, along with results from physical and neurological examinations. Other disorders that cause facial pain should be ruled out before TN is diagnosed. Some disorders that cause facial pain include postherpetic neuralgia (nerve pain following an outbreak of shingles), cluster headaches, and temporomandibular joint disorder (which causes pain and dysfunction in the jaw joint and muscles that control jaw movement). Because of overlapping symptoms and the large number of conditions that can cause facial pain, obtaining a correct diagnosis is difficult, but finding the cause of the pain is important as the treatments for different types of pain may differ.

Most people with TN eventually will undergo an MRI scan to rule out a tumor or MS as the cause of their pain. This scan may or may not clearly show a blood vessel compressing the nerve. Special MRI imaging procedures can reveal the presence and severity of compression of the nerve by a blood vessel.

A diagnosis of classic TN may be supported by an individual's positive response to a short course of an anti-seizure medication. Diagnosis of TN 2 is more complex and difficult, but tends to be supported by a positive response to low doses of tricyclic antidepressant medications (such as amitriptyline and nortriptyline), similar to other neuropathic pain diagnoses.

Clinical features

TN is more common in females than males with a female to male ratio of 1.74:1 and the most common from age 50–69 years with preponderance for the right side of the face.[12,13] The attacks can occur during the day or night but rarely during sleep.[14] Pain distribution is unilateral (bilateral TN sometimes occurs in MS) and follows the sensory distribution of the trigeminal divisions, typically radiating to the maxillary (V2) or mandibular (V3) territories. Ophthalmic (V1) pain is less common and was previously considered indicative of symptomatic TN.

According to the international headache society criteria for TN is V1 alone - 4%, V2 alone - 17%, V3 alone - 32%, V1 + V2 - 14%, and V1 + V2 + V3 - 17%.

The right side of the face is involved more frequently than the left, and the disorder is more common in women than in men (3:2). Pain, usually referred to as stabbing or electric shock-like, is brief and paroxysmal, lasting a few seconds, with no pain between paroxysms. However, there is sometimes an after pain described as slowly fading away. Pain may be provoked by stimulating cutaneous or mucous trigeminal territories (trigger zones). Gently touching the face, washing, shaving, talking, brushing the teeth, chewing, swallowing, or even a slight breeze can trigger the paroxysms. Pain provokes brief muscle spasms of the facial muscles, thus producing the "tic." Especially, in the early years of the condition, there can be long pain-free periods; however, these remission periods gradually become shorter and shorter. Classic TN occurs more often in the sixth or seventh decade of life and is stereotyped in each individual. Pain in the tongue is rarely affected in classical TN. The pain is never felt in the teeth.[15]

Pathogenesis of classical trigeminal neuralgia

Aretaeus de Cappadocia was the first to attempt to describe TN. In 1773, John Fothergill provided an accurate clinical description of this painful syndrome. Even though it is a recognized condition for centuries, there is no consensus about the pathological mechanism(s), leading to the most common neuralgia observed. All theories proposed to date are susceptible to criticism since flaws exist when it comes to explain all the features of TN.

Peripheral origin of trigeminal pain

TN has been identified as a peripheral neuropathy since the neurovascular conflict theory was proposed by Jannetta in 1967.[16] Since then, this has been the most accepted theory explaining the origin of trigeminal pain. Dandy made the initial observations of vascular impingement into the trigeminal nerve in 1925.[17]

The REZ of the trigeminal nerve lies about 2–3 mm away from the surface of the pons. It is characterized by the transition between the central myelin produced by the oligodendrocytes and the peripheral myelin produced by the Schwann cells. The latter is known to be significantly more resistant to injuries, including repetitive vascular pulsation at the myelin sheet, which provides insulation of the trigeminal nerve. Damage to the most sensitive portion of the myelin (central myelin) is the most accepted source for classical TN.[9,18] Frequently, vascular conflicts are observed where there is a contact of the superior cerebellar artery at the REZ of the trigeminal nerve.[16,19] However, the neurovascular conflict theory is not justified in all cases. Some patients present with a clear neurovascular conflict, but on the opposite side of their pain. There are vascular compressions noticed in thin-cut MRI scans, which do not necessarily correlate with a clinical diagnosis of trigeminal pain. And lastly, there are cases where a neurovascular conflict cannot be diagnosed in the MRI scan. Barker *et al*.[19] described cases where the MRI was negative, but a tiny vein compressing the nerve was observed intraoperatively. Recently, specific MRI sequences such as three-dimensional (3D) constructive

interference in steady state or 3D fast imaging employing steady-state acquisition and 1-mm slice thickness cuts provide exquisite visualization of the trigeminal pathway.[20]

Central origin of trigeminal pain

In 1756, Nicolas Andre coined the term tic douloureux to define TN, which is a direct allusion to the similarities between the pain attacks and a seizure. Episodic recurrence of pain attacks in the absence of neurological deficits reinforced the resemblance with epilepsy. There are certain features of the trigeminal pain attacks that challenge the validity of a pure peripheral pathophysiological mechanism for the genesis of TN.[9,21,22] These factors are as follows: (a) delay between the trigger point stimulation and the trigeminal pain attack; (b) pain attack is self-sustained, its magnitude is larger and outlasts the duration of the starting sensory trigger stimuli; and (c) refractoriness following the pain attack, which consists of absolutely no response to stimulation or to a milder pain attack. Moreover, demyelination by itself is not enough to generate the pain attacks. Myelinated axons composing the trigeminal nerve are related to thermal and touch inflow, not pain. Partial myelin damage should generate patches of numbness in the hemiface rather than pain, which is sometimes accompanied by hyperesthesia. Experimental studies evaluating the effect of carbamazepine (CBZ), phenytoin, and baclofen injections in the subnucleus oralis of the spinal trigeminal nucleus revealed a dual mechanism of action: facilitation of segmental inhibition and decrease of excitatory stimuli coming from the periphery.[23-25] The corroboration between the central nervous system mechanism of action observed in animal studies and the clinical efficacy of the drugs used to treat TN suggests that a central mechanism is also a part of the process to develop classical TN. Even though the initial process triggering TN may have a peripheral origin, it is necessary to have a central component to actually lead to the self-outlasting pain attack paroxysms in the absence of major sensory deficits. The common use of MRI in the modern era reveals vascular conflict in the REZ of the TN in the absence of pain or any other symptoms, corroborating the hypothesis of centrally generated TN.

Hypotheses of trigeminal neuralgia pathogenesis

A conciliatory theory proposing peripheral and central nervous system events that would ultimately lead to TN has been suggested.[9,22] In addition to increased generation of stimuli, mechanisms involved in suppressing afferent stimuli should be somewhat impaired (i.e., the dorsal root reflex). Presynaptic inhibition occurs through axo-axonic GABAergic synapses in the trigeminal nuclei.[26] The peripheral nerve damage would disrupt the dorsal root reflex, therefore allowing the excessive peripheral sensory information to reach trigeminal nuclei relays above the brainstem level.

However, not all experts refute the sole peripheral origin of TN. For instance, the ignition hypothesis[9] aims to explain the self-duration of the pain attacks and their spread beyond the area of the original stimuli. It has been shown that few dorsal root ganglia neurons of peripheral nerves can act as active pacemakers and sustain continuous discharges.[27] This phenomenon has also been observed in areas of demyelination of sensory ganglia neurons, independently from the tactile stimuli originating the depolarization. Ephaptic transmission between axons would facilitate the recruitment of an increasingly larger population of neurons, which would in turn amplify sensory input to the trigeminal nucleus. Analysis of surgical specimens of patients with TN showed the lack or decrease of the insulation between the nerve fibers, providing the substrate for electrical axon-to-axon crosstalk.[9,18] The spontaneous pacemaker areas could also explain the occurrence of pain attacks in the absence of stimulation in the trigger points. The authors also comment on the crossed after discharge mechanism which is nonsynaptic and nonephaptic coupling.[21] Neurotransmitters and potassium ions are released in the interstitial space after an excitatory discharge of some sensory neurons. Other neurons are excited by diffusion of these mediators. This type of spread of excitatory stimuli would set the stage for transmission from Aß-fibers to C-fibers (nociceptive). The refractoriness period could be explained by the release of potassium ions due to activation of potassium channels by calcium, leading to neuronal hyperpolarization. Partial remyelination and normalization of membrane channels would account for the periods of remission.[9,21]

Treatment

As the mechanism leading to paroxysmal pain begins in demyelinated fibers that become hyperexcitable and generate high-frequency discharges, the ideal drugs are those that reduce neuronal excitability and in particular, those able to limit the discharge frequency, i.e., sodium-channel blockers. Some local anesthetics (lidocaine) and antiepileptic drugs (phenytoin, CBZ, oxcarbazepine [OXC], and lamotrigine) belong to this category.

According to recent guidelines,[28,29] the two first-line drugs for TN are CBZ 400–1000 mg and OXC 900–1800 mg daily. Both drugs are very efficacious, reducing the number of attacks by more than 50% in more than 80% of patients, a proportion far higher than the 30%–40% of

responders achieved by any drug in other neuropathic pain conditions.[29,30] The problems may come with the side effects on the central nervous system, such as drowsiness and unsteadiness. Besides these relatively common side effects, CBZ can occasionally induce leukopenia and thrombocytopenia. Although there are uncontrolled case series reporting the efficacy of several new drugs, only baclofen and lamotrigine are the second-line drugs. Baclofen 18 has the advantage of a synergistic action with CBZ, but probably due to its frequent – and sometimes severe – side effects it is rarely prescribed. Oral phenytoin (historically the first antiepileptic drug used for the treatment of TN) is effective in only 25% of patients, and its chronic administration has serious adverse effects. Thirty, however, phenytoin can be administrated intravenously, and thus, it is useful in an emergency, when extremely frequent TN paroxysms preclude taking anything orally.[31]

Several surgical procedures proved to be efficacious in TN. Percutaneous procedures on the gasserian ganglion, microvascular decompression, and gamma-knife radiosurgery have proved effective.

The percutaneous procedures on the gasserian ganglion (which are also called percutaneous rhizotomies) involve penetration of the foramen ovale with a cannula and then controlled lesion of the trigeminal ganglion or root by various means: thermal (radiofrequency thermocoagulation), chemical (injection of glycerol), or mechanical (compression by a balloon inflated into Meckel's cave). About 90% of patients attain pain relief from these procedures. At 4 years, around 50% of patients are still pain-free. Sensory loss after these percutaneous procedures is present in about 50% of patients. Fewer than 6% develop troublesome dysesthesias, and 4% develop anesthesia dolorosa. Corneal numbness, with the risk of keratitis, occurs in 4% of patients. Up to 50% of patients undergoing balloon compression experience transitory masticatory weakness. Mortality is extremely low.[32-35]

Gamma-knife surgery is the only noninvasive technique. It aims a focused beam of radiation at the trigeminal root in the posterior fossa. At 1 year after gamma-knife therapy, complete pain relief with no medication occurs in almost 70% of patients. This falls to 50% at 3 years. Pain relief can be delayed for a mean of 1 month. Sensory complications average 6%, while anesthesia dolorosa is practically absent. No complications outside the trigeminal nerve have been reported. Quality of life improves and 88% are satisfied with outcome.[36-38]

Microvascular decompression is a major neurosurgical procedure that entails craniotomy to reach the trigeminal nerve in the posterior fossa. Vessels compressing the nerve are identified and moved out of contact. The procedure aims to preserve trigeminal nerve function. About 90% of patients obtain pain relief. Over 80% will still be pain-free at 1 year and 73% at 5 years. The average mortality associated with the operation is 0.2%, although this may rise to 0.5% in some reports. Postoperative morbidity is lower in high-volume units.[39] Up to 4% of patients incur major problems such as cerebrospinal fluid leaks, infarcts, or hematomas. Aseptic meningitis and ipsilateral hearing loss are the most common complications (about 10%). Diplopia is usually transient and facial palsy is rare. Sensory loss occurs in 7% of patients.[20,40-42]

Other surgical treatments include balloon compression, gangliolysis, glycerol gangliolysis, stereotactic radiosurgery, peripheral neurectomy, cryotherapy, and alcohol block.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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