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A Comprehensive Review of Trigeminal Neuralgia

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Abstract

Purpose of Review Trigeminal neuralgia (TN) is characterized by recurrent attacks of lancinating facial pain in the dermatomal distribution of the trigeminal nerve. TN is rare, affecting 4 to 13 people per 100,000.

Recent Findings Although there remains a debate surrounding the pathogenesis of TN, neurovascular compromise is the most currently accepted theory. Minimal stimulation caused by light touch, talking, or chewing can lead to debilitating pain and incapacitation of the patient. Pain may occur sporadically, though is primarily unilateral in onset. The diagnosis is typically determined clinically. Treatment options include medications, surgery, and complementary approaches.

Summary Anti-epileptic and tricyclic antidepressant medications are first-line treatments. Surgical management of patients with TN may be indicated in those who have either failed medical treatment with at least three medications, suffer from intolerable side-effects, or have non-remitting symptoms. Surgical treatment is categorized as either destructive or non-destructive. Deep brain and motor cortex neuro-modulatory stimulation are off label emerging techniques which may offer relief to TN that is otherwise refractory to pharmacological management and surgery. Still, sufficient data has yet to be obtained and more studies are needed.

Keywords Trigeminal neuralgia · Facial pain · Chronic pain · Neuropathic pain · Anti-convulsant · Microvascular decompression · Neuromodulation

Introduction

Trigeminal neuralgia (TN), or *tic douloureux*, is a chronic though uncommon syndrome characterized by recurrent bouts of lancinating facial pain occurring in the dermatome of the trigeminal nerve [1•]. The trigeminal nerve, or fifth cranial nerve (CN V), controls sensation and motor function of the face. The ophthalmic, maxillary, and mandibular nerves comprise the three subdivisions of CN V [2]. TN is neuropathic in nature and is associated with nerve injury or lesion. The International Headache Society (IHS) divides TN into two distinct categories: "classical" and "symptomatic." The typical or "classic" form of the disorder (Type 1, or TN1) causes a sporadic pain that is characterized as severe burning facial pain, with each episode lasting for up to two min. At times, onset of pain may occur in clusters that persist for several hours at a time [3]. The "atypical" form TN (Type 2, or TN2) in contrast is described as constant, characteristically burning and stabbing, though of lesser severity than TN1 [4]. Clinical diagnosis of TN relies on the identification of a paroxysmal occurrence of each episode with clear demarcation between onset and termination. Often, patients with TN1 are unable to identify an inciting event to explain their pain. Symptomatic TN defines cases with identifiable vascular compression of the trigeminal nerve as can be caused by tumor, multiple sclerosis, or an arteriovenous malformation. A patient may experience both forms of the pain, sometimes simultaneously, with severity that can be debilitating both physically and mentally. Onset of pain

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can be triggered even by minimal stimulation such as talking, chewing, or light touch of the overlying skin. Though most often unilateral, the pain occurs sporadically and frequently repeats throughout the day. The diagnosis of TN is primarily clinical and made based on the exclusion of other diseases [3]. In contrast to other neuropathic diseases, in many cases, TN may spontaneously resolve in as many as 63% of patients with a total absence of symptoms for several years [5••]. TN is not fatal; however, even fear of an impending attack can be debilitating for patients.

Epidemiology

TN was first described in the writings of Galen, Aretaeus of Cappadocia, and Avicenna as early as the first century, although the first accurate descriptions were not officially documented until the 1700s [6]. In 1756, Nicholas André coined the term "tic douloureux" because of the distinctive facial spasms that accompany the attacks [7]. An English physician named John Fothergill is credited as the first to give a full and accurate description of the disorder in a submission to the Medical Society of London in 1773, titled "On a Painful Affliction of the Face." As such, the disease is also known as "Fothergill's Disease."

TN is rare, affecting an estimated 4 to 13 people per 100,000 annually, with an overall prevalence in the general population of 0.015% [1•, 8]. Despite the low incidence, among facial pain syndromes, TN is the most common. Advanced age is a risk factor for developing TN. The condition affects those over age 50 most commonly and has an incidence of 25.9 per 100,000 people per year in those over age 80 [1•]. It can occur at any age, including rare cases in children [9]. More women are affected than men, with male-to-female prevalence ratios ranging from 1:1.5 to 1:1.7 [8]. Most cases are sporadic, but rare familial inheritance has been reported [10]. Interestingly, TN is predominantly right sided though rarely may be bilateral as well [11]. This disease does not appear to have any racial predilections.

Pathophysiology

The pathophysiology of pain caused by TN is derived from a complex interaction of neuromodulators and neurotransmitters leading to a convergence of nociceptive transmission onto the trigeminal neurons. The main theory for the pathophysiology of TN involves compression of the nerve root at the prepontine cistern [1•]. Neurovascular compression can either be primary or secondary to another pathology. Primary compression is visual compression of the nerve without a secondary cause. Secondary compression causes include brain tumors such as meningiomas and vestibular schwannomas, aneurysms, arteriovenous malformations, and even cysts [1•]. Certain conditions can also predispose patients to suffer from TN more often than the general population. Chronic sinusitis, multiple sclerosis, and diabetes are conditions associated with increased risk of trigeminal neuralgia [1•].

Brain imaging studies have led researchers to new insight into the pathophysiology of TN. Multiple brain tests such as MRI, diffusion tensor imaging, functional MRI, and three-dimensional time-of-flight MRA have been used to study disease functional pathology. Functional MRI has provided researchers with encouraging results as it can assess brain activity in response to activation of TN trigger zones [1•]. A study by Moisset et al. showed involvement in many different brain neural structures during both painful and nonpainful stimulation of trigger zones involved in TN [12]. After a patient suffers from this disease state, Moisset et al. study showed increased sensitization of trigeminal nociceptive systems that was maintained in responsive to a multitude of stimuli [12].

Disease Characteristics

TN can cause varying degrees of pain in varying distributions of the trigeminal nerve for patients. In general, patients usually experience intermittent, stabbing pain in at least one trigeminal nerve dermatome unilaterally. There have been rare cases involving patients who suffer from bilateral trigeminal neuralgia [13]. The pain disease process normally affects the V2 and V3 distributions of suffering patients. In contrast, a prospective study of 158 patients concluded that less than 5% of patients also have pain in the V1 distribution [14]. This study also found that autonomic symptoms occurred in 31% of patients with trigeminal neuralgia on the same side as the pain [14]. Autonomic symptoms include conjunctival injection or tearing, miosis, ptosis, sweating, and clogged nose that occurs unilaterally with the intermittent pain. Daily and routine activities have been found to incite the onset of trigeminal neuralgia. Most frequent triggering activities have been found to be mastication, brushing teeth, speaking, touching site of pain, and cold wind [14].

Diagnosis

Diagnosis of TN is largely clinical and is based on the International Classification of Headache Disorders, which further categorizes conditions as classical, secondary, or idiopathic trigeminal neuralgia [15]. TN can be diagnosed after three episodes of unilateral pain that fulfill the following two circumstances [16]: First, the pain must occur along at least one trigeminal nerve division, and this pain must not be associated with a neurologic deficit or radiate beyond the distribution of the trigeminal. Secondly, the characteristics of the pain must satisfy two of the following three criteria: (a) severe

intensity; (b) either sharp, electric, shock-like, or stabbing in quality; and (c) paroxysmal occurrences lasting from one s to up to but not exceeding two min. Another criterion for diagnosis is that the trigeminal pain can be provoked by an innocuous stimulus to the dermatomes on the unilateral side of the face involving the pain [16].

The classical diagnosis involves transient or paroxysmal episodes of pain caused by neurovascular compression without another cause for the pain. This diagnosis should have pain-free breaks between the pain episodes and should not be continuous. Imaging and special testing may be used to rule out alternative diagnoses such as herpes zoster, trigeminal nerve trauma, migraine, cluster headache, occipital or glossopharyngeal neuralgia, multiple sclerosis, temporomandibular joint pain and other dental problems, cerebral aneurysms, tumors, and intracranial hemorrhage [17]. Once the diagnosis of TN is suspected clinically, neuroimaging is recommended to help distinguish classic from symptomatic TN. This can be accomplished with magnetic resonance imaging (MRI) or computed tomography (CT). MRI with and without contrast is preferred for improved visualization of the trigeminal nerve and adjacent structures and can aid in diagnosing the neurovascular compression of the trigeminal nerve, which should not include a secondary cause for nerve compression [18]. The secondary TN diagnosis can be continuous or near continuous and is associated with a triggering pathology causing the pain. Most pain in this circumstance is caused by arteriovenous malformations, certain brain tumors, or multiple sclerosis [15, 16]. A third form, idiopathic trigeminal neuralgia, is diagnosed when symptoms occur but without a clear cause of neurovascular compression or secondary causes based off negative MRI and other neurophysiologic tests.

An article by Cruccu et al. sought to improve the classification criteria in order to streamline patient treatment as well as triage for clinical trials [5••]. A patient's pain would only have to satisfy 3 simplistic characteristics for diagnosis: (1) unilateral, (2) paroxysmal, and (3) trigeminal distribution. The article argues for the need to initially order an MRI or other imaging studying in order to ensure correct diagnosis of classification type [5••]. An MRI showing changing in the trigeminal root and neurovascular compression would be classified as classical trigeminal neuralgia. An MRI that displays a secondary cause of nerve compression such as a brain tumor or an arteriovenous malformation impinging the nerve would be classified as secondary. A negative MRI would then be classified as idiopathic trigeminal neuralgia with appropriate symptoms and exam findings. Cruccu et al.'s main argument is for a simplified method to prevent misclassification of trigeminal neuralgia and ensure quick and proper treatment of diagnosed patients [5••]. In patients that cannot undergo MRI, trigeminal evoked potentials and neurophysiologic recordings of trigeminal reflexes should be used for proper classification [5••]. Correct identification of trigeminal neuralgia as well as its classification type can improve treatment strategies as well as patient satisfaction.

Treatment Strategies for Trigeminal Neuralgia

Treatment options include medications, surgery, and complementary approaches. The initial management of choice for TN is medical pharmacotherapy. Medications such as anticonvulsants and tricyclic antidepressants are the mainstays of treatment. Carbamazepine is the first-line therapy for TN; however, other drugs such as baclofen, gabapentin, lidocaine, and misoprostol have demonstrated efficacy in refractory cases [18, 19]. Most patients respond at least temporarily to treatment with anticonvulsant medications. Patients who do not tolerate or fail medical management may benefit from neurosurgical intervention [3, 20]. The major types of procedures are microvascular decompression of the trigeminal nerve root, and neuro-ablation via rhizotomy with radiofrequency thermocoagulation, mechanical balloon compression, and chemical neurectomy [19]. There is some evidence suggesting that botulinum toxin injections may be beneficial in medically refractory cases as well [21]. Neuromodulation and peripheral nerve field stimulation are promising alternative techniques for pain refractory to traditional methods and merit further exploration.

Medical Therapy

The medications used to treat TN are primarily used to treat other medical conditions, namely epilepsy. Carbamazepine, which stabilizes sodium channels in an inactive state, is the gold standard and has been shown to be most efficacious according to one high-quality meta-analysis [22]. Other studies have shown rates of 100% symptom relief in 70% of patients [20]. Common side effects include tiredness, dizziness, and poor concentration, while some serious complications include agranulocytosis, aplastic anemia, and drug-drug interactions through hepatic cytochrome P450 induction. Oxcarbazepine is an alternative first-line therapy shown to have similar efficacy with fewer side effects [23].

Second-line medications include baclofen, a $GABA_B$ receptor agonist, and lamotrigine, a sodium channel inhibitor. Baclofen acts by depressing excitatory neurotransmission and can be used alone or in conjunction with carbamazepine. Similar to carbamazepine, common side effects include sedation, faintness, fatigue, and nausea. Sudden discontinuation of this drug can lead to withdrawal consisting of seizures and hallucinations [24]. Lamotrigine is an anticonvulsant that is also used to treat bipolar disorder. This medication was shown to have a beneficial response in TN that was proportionate to plasma levels up to a maximum dose of 400 mg/day in an

open-label study of 15 patients [25]. Another small double-blind placebo controlled crossover trial showed that 400 mg lamotrigine therapy in conjunction with carbamazepine was more effective than placebo [26]. Similar to those of antiepileptics, side effects can include sleepiness, dizziness, headache, and vertigo. Skin rash may develop in 7–10% of patients and typically resolves with continued treatment, though 1 in 10,000 patients develop Stevens-Johnson syndrome in which the medication should be discontinued immediately [27].

Newer medications including levetiracetam, topiramate, gabapentin, pregabalin, and botulinum toxin A are used as third-line therapies [23]. A recent Cochrane systematic review, however, concluded that there is not enough evidence demonstrating significant benefit from non-anticonvulsants for treating TN [28]. Medical therapy used for the management of TN is summarized in (Table 1).

Surgical Therapy

Surgical management for TN patients should be reserved for those who have either failed medical treatment with at least 3 medications, suffer intolerable side-effects, or have suffered relapse of symptoms. It has been estimated that up to 50% of this patient population will require surgery at some point [29, 30]. Surgical options consist of destructive and non-destructive (microvascular decompression) modalities. Microvascular decompression (MVD) is the most invasive surgical option though most successful for permanent treatment of pain. It has a low risk of sensory loss and is a good option for otherwise healthy patients and those who have failed less invasive treatments. Long-term studies have shown that this method provides lasting pain relief in more than 70% of patients [31, 32]. This procedure also provides the highest long-term patient satisfaction and lowest rate of pain recurrence in comparison to other surgical treatments [33, 34]. Significant risks associated with MVD occur at rates of less than 2% and include stroke, meningitis, and death [35].

Percutaneous rhizotomy is a surgical technique that involves the selective destruction of A-delta and C pain nerve fibers with intent to preserve A-alpha and beta sensory nerve fibers. The three types of rhizotomy include mechanical (balloon compression of the Gasserian ganglion), chemical (glycerol injection of the trigeminal cistern), and radiofrequency thermal (application of heat to damage the trigeminal nerve ganglion). Access to the trigeminal ganglion for these techniques is gained by threading of a cannula through the foramen ovale [1•]. Balloon compression offers immediate pain relief in 80–90% of patients and time free from medications from 2 to 3 years [36, 37]. Glycerol rhizotomy has a similarly high short-term success rate, with over 90% of patients obtaining initial relief and over 50% of patients remaining pain free at three years [38, 39]. Thermocoagulation rhizotomy also provides a high initial success rate of 90%, though recurrence occurs in 25% of cases [40, 41]. Though less invasive than microvascular neuralgia, these percutaneous procedures have the risk of sensory loss in the trigeminal distribution (50%), dysthesias (6%), anesthesia dolorosa (4%—a feared complication consisting of numbness and pain in the targeted dermatome), corneal numbness leading to keratitis (4%), aseptic meningitis (0.2%), and very small risk of mortality [18, 42].

Gamma knife radiosurgery (GKRS) is used in treatment centers as a surgical alternative for poor surgical candidates or those refusing more invasive therapy [1•]. This is a stereotactic, outpatient procedure that utilizes high doses (70–80 Gy) of submillimeter radiation beams focused at the trigeminal root entry zone which causes necrosis over time and thus decreases pain signals [43]. A systematic review demonstrated a 69% success rate at 1 year and 52% at 3 years after surgery [23].

Table 1 Summary of medical therapies for the treatment of trigeminal neuralgia [24]

	Medication	Dose	Features
First line	Carbamazepine	200–300 mg/day	Gold standard treatment. As with most anticonvulsants, the most common side-effects include drowsiness, dizziness, and nausea
	Oxcarbazepine	1200–2400 mg/day	Another first-line treatment typically used if carbamazepine is not tolerated
Second line	Baclofen	60–80 mg/day	Sudden discontinuation can cause seizures and hallucinations
	Lamotrigine	200–400 mg/day	Associated with skin rash if titrated too quickly and 1:10,000 chance to develop Steven-Johnsons syndrome
Third line	Levetiracetam	1000–4000 mg/day	Advantages include no need for routine blood tests and less drug interactions
	Topiramate	100–400 mg/day	Binds to non-benzodiazepine GABA receptors and blocks voltage-gated calcium channels
	Gabapentin	300–1800 mg/day	Advantages include no known drug interactions, no known skin reactions, and a mild side-effect profile
	Pregabalin	150–600 mg/day	Analog of GABA that is structurally related to gabapentin
	Botulinum toxin A	20–75 U	Causes local release of anti-nociceptive neuropeptides

Emerging Therapy

Neuromodulation via motor cortex stimulation (MCS) and deep brain stimulation (DBS), though currently off label, have been described in literature as possible treatments for refractory cases [1•]. Use of MCS has been documented to bring effective pain relief in 75–100% of patients undergoing treatment for neuropathic pain syndrome [44, 45]. However, the patients studied were mostly those with complex regional pain syndrome and only a few had classic TN. DBS has also been practiced as treatment for pain refractory to medical and surgical methods since 1997 [46]. The posterior hypothalamus has been hypothesized to act as a switchboard for the neuropsychological circuits of pain behavior and the neurovegetative system; thus, it has been the target of DBS treatment for pain [47]. As of yet, no evidence has been shown for DBS as sole therapy for refractory TN.

While peripheral nerve/field stimulation is used to treat chronic, neuropathic, and refractory pain for a wide variety of conditions, literature involving TN is lacking [48–50]. However, a few promising studies have been conducted in small sample sizes. A case report published by Abd-Elsayed et al. in 2015 described a TN patient who was refractory to conservative medical management as well as trigeminal nerve blocks. Following implantation of a peripheral nerve stimulator with a supraorbital, infraorbital, and frontoparietal leads, the patient had complete resolution of her pain and significantly increased quality of life [51]. This case study shows that peripheral nerve stimulation could be a promising alternative treatment for refractory TN and merits further research.

Conclusion

TN continues to challenge healthcare providers. Pharmacotherapy should remain first line of defense as most patients at least temporarily respond to treatment with anticonvulsants. Recent studies have shown up to 100% pain relief in over 70% of patients, indicating that Carbamazepine still remains the gold standard in TN treatment [13]. Oxcarbazepine can be an alternative first line due to similar efficacy and fewer side effects [23]. In addition, baclofen and lamotrigine can be used as either second-line agents or as an adjunct with carbamazepine for possibly greater pain control than carbamazepine used alone [26]. Third-line agents, such as levetiracetam, topiramate, gabapentin, pregabalin, and botulinum toxin-A, may be considered; however, a systematic review by Zhang et al. showed no significant difference in the comparison of carbamazepine to non-anticonvulsants tizanidine, tocainide, or pimozide. There was insufficient evidence to support the use of non-antiepileptic therapy for the treatment of TN [28].

As previously mentioned, surgical treatment of TN has provided promising results thus far; however, such treatments should be reserved for patients with refractory disease or who fail medical management. MVD is a non-destructive, though highly invasive, surgical option with the highest rate of permanent resolution of pain and lowest risk of sensory. In addition, MVD offers the highest long-term patient benefit and lowest recurrence rate [31]. Percutaneous rhizotomy, a destructive technique, is less invasive than MVD but carries a higher risk of sensory loss of up to 50% along with dysthesias, anesthesia dolorosa, corneal numbness, and aseptic meningitis. The three surgical techniques balloon compression, glycerol rhizotomy, or thermocoagulation rhizotomy differ in approach and technique but provide similar results with up to 80–90% of pain relief and low recurrence rates [36, 37, 40]. Gamma knife radiosurgery can be used as well for poor surgical candidates due to medical comorbidities or in those refusing invasive therapy with up to 69% of patients being pain-free after 1 year and up to 52% after 3 years [23].

Although there remains a lack of full comprehension of the pathogenesis of TN, neurovascular conflict remains the most accepted theory at this time. Neuroradiological techniques have allowed for progress in both the pathogenesis and surgical treatment with promising results in pain relief. Other mechanisms, such as dysfunctions of the brainstem, peripheral compression or traction, basal ganglia dysfunction, and cortical pain modulatory dysfunction, should continue to be considered, as a complete understanding has yet to be found. Furthermore, it may be more beneficial to consider all theories, as this may lead to other alternative and successful treatment options.

Contributing genetic factors, unexplored etiological factors, neurosurgical outcomes and complications, and development of drugs with better tolerability should be further explored to better our understanding of both the pathogenesis and treatment of TN. It must also be noted that non-anticonvulsants have been poorly studied in comparison to first carbamazepine in pharmacological treatment. Neuromodulation by motor cortex stimulation and deep brain stimulation are emerging techniques with promising results in patient's refractory to pharmacological and surgical techniques. Sufficient data has yet to be obtained as the most recent study involved complex regional pain syndrome and classic TN [42, 44]. Furthermore, peripheral nerve field stimulation should also be further studied, as this approach has provided significant chronic and neuropathic pain relief for a variety of conditions, but there is currently no significant data regarding treatment of TN [48].

Compliance with Ethical Standards

Conflict of Interest Mark R. Jones, Ivan Urits, Ken P. Ehrhardt, John N. Cefalu, Julia B. Kendrick, Daniel J. Park, Elyse M. Cornett, and Omar Viswanath declare no conflict of interest. Dr. Kaye is a speaker for Depomed, Inc., and Merck, Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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